Fragment screening by crystallography – efficient workflow for MX users at BESSY II

Jan Wollenhaupt,[1], Tatjana Barthel[1], Elmir Jagudin[2], Dirk Wallacher[1], Thomas Hauss[1], Christian Feiler[1], Frank Lennartz[1], Uwe Müller[1], Andreas Heine[3], Tobias Krojer[2], Manfred S. Weiss[1]

[1]Macromolecular Crystallography Group, Helmholtz-Zentrum Berlin, Germany, jan.wollenhaupt@helmholtz-berlin.de, [2]FragMAX group, MAX IV Laboratory, Sweden, [3]Institute of Pharmaceutical Chemistry, Philipps-Universität Marburg, Germany

In order to develop tool compounds for biochemical assays or lead structures in drug discovery, the screening for small organic molecules called fragments became a predominant technique in the last decade. When carried out as a crystallographic screening it reveals not only the identity of the bound fragments, but also their 3D-positioning inside the binding site of the protein under study. At the macromolecular crystallography (MX) beamlines at BESSY II, a dedicated workflow was established for the user community to foster efficient and convenient screening (Fig. 1).[1] It is based on several unique developments, one being the very diverse F2X fragment libraries that deliver high hit rates, mostly in the range of 20-25%.[2] Using the EasyAccess Frame, fast and comfortable crystal soaking and harvesting is ensured.[3] After data collection at the state-of-the-art MX beamlines at BESSY II, data analysis is highly automated and conveniently interfaced via the FragMAXapp setup at HZB.[4] Beyond efficient screening and identification of fragment hits, HZB also offers methods of hit evolution to higher potency using a growing by catalog approach via Frag4Lead.[5]

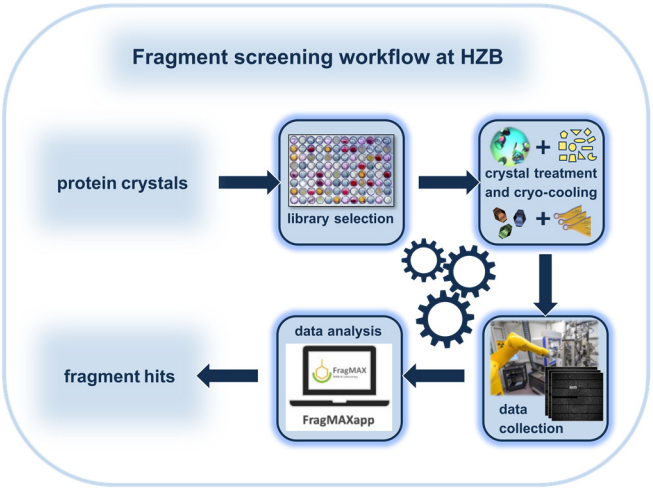

Fig. 1 - crystallographic fragment screening workflow at HZB [1]

[1] Wollenhaupt, J. *et al.* Workflow and Tools for Crystallographic Fragment Screening at the Helmholtz-Zentrum Berlin. *J. Vis. Exp.* **2021**, 62208 (2021).
[2] Wollenhaupt, J. *et al.* F2X-Universal and F2X-Entry: Structurally Diverse Compound Libraries for Crystallographic Fragment Screening. *Structure* **28**, 694-706.e5 (2020).
[3] Barthel, T. *et al.* Facilitated crystal handling using a simple device for evaporation reduction in microtiter plates. *J. Appl. Crystallogr.* **54**, 376–382 (2021).
[4] Lima, G. M. A. *et al.* FragMAXapp: Crystallographic fragment-screening data-analysis and project-management system. *Acta Crystallogr. Sect. D Struct. Biol.* **77**, 799–808 (2021).
[5] Metz, A. *et al.* Frag4Lead: growing crystallographic fragment hits by catalog using fragment-guided template docking. *Acta Crystallogr. Sect. D Struct. Biol.* **77**, 1168–1182 (2021).

J.W. and M.S.W. acknowledge support by iNEXT-Discovery, project No. 871037, funded by the Horizon 2020 program of the European Commission.