

## X-ray Free Electron Laser: Opportunities for drug discovery

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### Abstract

Past decades have shown the impact of structural information derived from complexes of drug candidates with their protein targets to facilitate the discovery of safe and effective medicines. Despite recent developments in single particle cryo-electron microscopy, X-ray crystallography has been the main method to derive structural information. Recently, serial crystallography has added new opportunities for X-ray data collection of challenging systems like membrane proteins. Advances in serial crystallography are a pre-requisite to use the unique properties of X-ray Free Electron Laser (XFEL). Unmet peak brilliance and beam focus allow X-ray diffraction data recording and successful structure determination from smaller and weaker diffracting crystals shortening timelines in crystal optimization. To further capitalize on the XFEL advantage, innovations in crystal sample delivery for the X-ray experiment, data collection and processing methods are required. This development was a key contributor to serial crystallography allowing structure determination at room temperature yielding physiologically more relevant structures. Adding the time resolution provided by the femtosecond X-ray pulse will enable monitoring and capturing of dynamic processes of drug molecule binding and associated conformational changes with great impact to the design of candidate drug compounds.



Figure: Sample delivery systems for serial crystallography. The most frequently used systems at the moment are injector-based. All of them can be used for room temperature data collection, but the fixed target approach provides the option for cryo-crystallography as well.

LeadXpro is a structure based lead discovery company focusing on challenging membrane protein drug targets, including G-protein coupled receptors (GPCRs), ion channels and transporters. The company is co-located with the Paul Scherrer Institute and leverages state of the art facilities for structure determination, like the synchrotron SLS, the X-ray Free Electron Laser SwissFEL and, in collaboration with the University of Basel, single particle cryo-EM.

### Recent Publications

1. Weinert, T., et al. Serial millisecond crystallography for routine room-temperature structure determination at synchrotrons. *Nature Communication*, 8:542 (2017).
2. Cheng, K.Y.R., Abela, R., Hennig, M. X-ray Free Electron Laser: opportunities for drug discovery. *Essays in Biochemistry* (2017) 61, 529-542.