CRYSTAL BASED LEAD IDENTIFICATION BY FAST FRAGMENT AND COMPOUND SCREENING AT THE SWISS LIGHT SOURCE

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Abstract: Over the last two decades, fragment-based drug discovery has emerged as an effective and efficient method to identify chemical scaffolds for the development of novel lead compounds. The inherent “start small – elaborate efficiently” approach allows issues like compound-selectivity, toxicity and efficiency to be addressed from a very early development state on, while saving time and resources compared to classical high throughput screening of larger compounds. X-ray crystallography has been used for a long time as an important orthogonal method for validating binders discovered by higher throughput screening methods and to elucidate corresponding ligand-target interactions. Advances in beamline- and crystal-harvesting-instrumentation have tremendously increased the throughput of X-ray crystallography in the last few years. This has facilitated the establishment of macromolecular crystallography as a powerful primary screening method for the identification of ligand binding. Combining fragment screening with the high information content derived from crystal-based fragment screening results in a powerful platform for structure-based drug discovery. Here, we proudly present the Fast Fragment and Compound Screening pipeline (FFCS) at the Swiss Light Source (PSI, Switzerland) and its application in the development of novel drugs 1.