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FRAG XTAL SCREEN FOR DIRECT CRYSTALLOGRAPHIC FRAGMENT SCREENING

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A major challenge in drug discovery is the identification of chemical moieties that specifically interact with a particular protein target. Traditionally, this was addressed by High Throughput Screening (HTS) however, recently "Fragment Screening" has become increasingly popular. In a Fragment Screen a set of small molecules ("fragments"), typically with MW < 300 Da and with low affinities, are evaluated for specific interaction with a target. Crystallography/X-ray diffraction shows not only whether a fragment binds to the protein but also where and how the binding occurs and is therefore the favored screening method [1-3]. Hit-fragments are subsequently chemically modified in several optimization/screening cycles until a high affinity lead structure is obtained (figure 1). Since such a fragmented approach allows screening of broader chemical space compared to large, distinct libraries, the hit rates of Fragment Screens are believed to be 10-1000x higher than those in traditional HTS [4].

The *Frag Xtal Screen* is a unique Fragment Screen designed for direct crystallographic screening: 96 different fragments, selected for high chemical diversity, high solubility and for being validated crystallographic hits of several protein targets, are spotted onto the wells of a crystallization plate. This screening plate is ready-to-use for crystal soaking experiments and offers an easy entry to fragment-based lead discovery (FBLD) by crystallographic screening.

Figure 1: Fragment-based lead discovery takes advantage of fragment evolution and linking. Small individual fragments with inherently low affinity but high efficiency are grown according to the structural model. The efficient binding of the fragments generates a lead structure in the nanomolar affinity range.

Recent Publications

1. Huschmann F, Linnik J, Sparta K, Ühlein M, Wang X, Metz A, Schiebel J, Heine A, Klebe G, Weiss M, Mueller U (2016) Structures of endothiapepsin-fragment complexes from crystallographic fragment screening using a novel, diverse and affordable 96-compound fragment library. Acta Cryst F 72:346-355.
2. Schiebel J, Radeva N, Krimmer S, Wang X, Stieler M, Ehrmann F, Fu K, Metz A, Huschmann F, Weiss M, Mueller U, Heine A, Klebe G (2016) Six Biophysical Screening Methods Miss a Large Proportion of Crystallographic Discovered Fragment Hits: A Case Study. ACS Chem. Biol. 11:1693-1701.
3. Schiebel J, Radeva N, Köster H, Metz A, Krotzky T, Kuhnert M, Diederich W, Heine A, Neumann L, Atmanene C, Roecklin D, Vivat-Hannah V, Renaud JP, Meinecke R, Schlinck N, Sitte A, Popp F, Zeeb M, Klebe G (2015) One Question, Multiple Answers: Biochemical and Biophysical Screening Methods Retrieve Deviating Fragment Hit Lists. ChemMedChem 10:1511-1521.
4. Hajduk P, Greer J (2007) A decade of fragment-based drug design: strategic advances and lessons learned. Nature Reviews Drug Discovery 6:211-219.
5. Rees D, Congreve M, Murray C, Carr R (2004) Fragment-based lead discovery. Nature Reviews Drug Discovery 3:660-672.

Biography

Christin studied Biotechnology and joined Jena Bioscience GmbH in 2005. She was promoted Head of Macromolecular Crystallography & Cryo-EM in 2011 and works in product development ranging from classic crystallization screens to specific tools and screens for Cryo-EM

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