

S29-3 FBS by X-ray structure analysis

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The first step of FBDD is Fragment-based Screening. There are various analytical methods used to perform FBS : NMR, X-rays, SPR, etc. The advantage of X-ray structure analysis in FBS is that it can cope with relatively large structural changes upon a binding of a fragment and unextected events such as multiple binding.

The first thing needed to perform FBS by X-rays is a fragment library. The library currently employed at our laboratory was designed especially for X-rays and consists of ca. 400 compounds. This library was build based on Ro3 and by paying special attention to eliminating ambiguity when interpreting electron density.

FBS by X-rays requires more than 100 times of data collection and structure analysis. Recent development of basic technologies dramatically reduced time required for X-ray structure analysis. Additionally, development of software and an incorporation of an industrial robot to a laboratory system (ACTOR) enabled us to construct fully automated structure analysis system.

There also are some limitations to X-rays. It demands hundreds of quality crystals and those crystals must not only survive soaking of compounds dissolved in DMSO but also be resistant to X-ray damages.

In this talk, a practical example of FBS by X-rays will be presented by using HSP90 along with limitations of X-rays.