S29-4 Fragment screening by SPR/NMR

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A first step of fragment-based lead discovery is a so-called fragment screening of dedicated library to identify fragments which can be used as a starting point for medicinal chemistry. As the interaction between fragments and target proteins is usually very weak with typical dissociation constants of 10^{-5}-10^{-3} M, screening methods has to be sensitive enough to detect such interaction and also the process has to involve the step to ensure binding specificity of the identified hit fragments.

Nuclear magnetic resonance (NMR) was the first method ever used for the fragment screening with its capability to detect very weak interaction and to give structural information of the system at the same time, but a large protein consumption and the requirement of large dedicated system for a higher throughput can be inhibiting factors. Surface plasmon resonance (SPR) optical spectroscopy is an emerging technique for the fragment screening. Protocol to detect the binding of the small molecules to the target proteins has been established and high-throughput SPR instruments are now on the market, which enables screening of several thousand compounds to be done within one week. We have used SPR as a primary method for the screening and employed NMR as a validation tool to check specificity of the hit fragments over the years. In this presentation, practical aspects of the combined use of SPR/NMR in fragment screening will be discussed.