Fragment Based Drug Discovery: Challenges and Opportunities

Elisabetta Chiarparin and Glyn Williams

Astex Pharmaceuticals
436 Cambridge Science Park, Milton Road, Cambridge, CB4 0QA, UK
EMAIL elisabetta.chiarparin@astx.com

Over the past decade, fragment-based drug discovery (FBDD) has been successfully applied in industry and in academia to discover drug candidates with improved physicochemical properties for a wide variety of targets [1]. At Astex, we now have experience of over 30 high-throughput crystallographic and biophysical fragment screens against a broad range of protein classes, and our results in terms of hit rates, hit solubility and affinity contributed to the design of the third generation of Ro3 fragment library. Here we recount our experiences of fragment-based drug discovery with challenging protein-protein interaction targets, such as Inhibitors of Apoptosis Protein (IAP) family, key regulators of anti-apoptotic and pro-survival signalling pathways. Emphasis will be given on how at Astex structural biology and biophysical methods, such as X-ray crystallography, NMR spectroscopy and mass spectrometry and isothermal titration calorimetry (ITC) are fully integrated to identify protein constructs that are suitable for screening purposes, and subsequently to screen drug fragments and optimise them into lead and candidate drugs using structure-guided design. Highlights will be given on how NMR spectroscopy is exploited as a physical chemistry, biophysical and structural biology technique at different stages of a drug discovery programme.

[1] Chris W. Murray and David C. Rees: The rise of fragment-based drug discovery, *Nature Chemistry* **1**, 187 - 192 (2009)