Preface

The fragment-based approach has emerged in the last decade as a highly promising component of modern drug discovery. Despite its relatively short history, it has been the subject of many research articles, reviews and books, and is responsible for several compounds currently in clinical development. Its contribution is increasingly recognized by the medicinal chemistry community, and it now forms an important part of drug discovery efforts within the pharmaceutical industry.

Despite the exponential growth of interest in this field, fragment-based drug discovery (FBDD) represents a significant paradigm shift for drug discoverers, both philosophically, and in terms of methodology and work-flow. In particular, it has required a shift away from relatively potent, drug-like hits, readily identified by enzymatic high-throughput assays, to the more challenging detection of very weakly (but efficiently) binding compounds. As such, the development and application of robust and sensitive biophysical techniques to detect and characterise the binding of simple, low molecular compounds has been a key part of enabling this approach. X-ray crystallography was one of the earliest techniques demonstrated to be capable of detecting the binding of fragments, and its additional ability to provide precise three-dimensional detail on their binding modes, and hence guide their subsequent elaboration has led to it playing a central role in this approach.

In this volume we bring together chapters by a number of practitioners in the field, drawn from both the pharmaceutical industry and academia. Our aim has been to highlight the important roles that X-ray crystallography plays in the fragment-approach: as a sensitive technique for primary screening, its use in combination with other biophysical techniques to allow robust hit validation, and its importance in providing structural information to guide progression from hit to clinical candidate.

In the first chapter, Erlanson from Carmot Therapeutics provides an introduction to the FBDD field as a whole, highlighting some of the advantages of fragments and their means of detection, and giving examples of fragment-derived compounds which have already reached the clinic. Davies and Tickle from Astex Therapeutics then provide a review of the use of X-ray crystallography for fragment screening,
and describe some of the computational developments developed at Astex that have allowed the rapid generation of protein-ligand structural data required for this approach.

In chapter 3, Roughley and colleagues from Vernalis present the first of a number of personal case studies of FBDD – in this case, the application of the fragment-approach to the development of Hsp90 inhibitors, with emphasis on the role of in silico screening, and its interplay with experimental structural information. This is followed by a chapter from Wyss et al (Merck), who describe their work on the fragment-based development of BACE inhibitors and how complementary information from both NMR and X-ray crystallography were combined to successfully prosecute a drug discovery campaign against this important target. Continuing on the theme of combining biophysical techniques, Hennig and colleagues then describe the approach to FBDD taken at Roche, and in particular how Surface Plasmon Resonance and structural information are used together in an integrated approach.

Fragment-based approaches are increasingly being applied to challenging therapeutic targets, and in particular those for which conventional drug discovery methods have failed. In chapter 6, Valkov and colleagues (University of Cambridge) provide a review of small molecule inhibition of protein-protein interactions, and the application of fragment-based methods against this class of target. Bauman et al (Rutgers) then describe the use of X-ray crystallographic fragment screening to identify novel hits against HIV targets, and highlight the growing trend for academic-based FBDD. Indeed, the close association of biophysical and structural techniques, combined with the manageable size of screening libraries make fragment-based methods increasingly appealing and accessible to academic laboratories in addition to those in the pharmaceutical industry.

In the concluding chapter, and in a departure from the predominantly experimental methods discussed above, Rognan (University of Strasbourg) provides a computational perspective on the fragment-based approach, and discusses the application and development of in silico approaches which are increasingly being applied in this area.

We hope this book will provide a useful introduction to some of the key concepts and techniques in fragment-based drug discovery, highlighting the diverse set of targets it is applied to, as well as emphasizing the importance of structural information in this field. The application of X-ray crystallography to structure-based drug discovery is now a mature discipline, but one whose potential has sometimes been under-exploited. In driving various aspects of the fragment-based approach, it clearly plays a central role.

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