

# *Preface*

Discovering new medicines is extremely difficult, takes a long time and costs a lot of money. On average it cost over \$800 million and took 14 years from project inception for each drug that came to the market during the 1990s. It is also an activity where failure is expected and success is extremely rare. Analyses of drug development during the last decade suggest that only one in ten drugs entering clinical trials eventually is available in the market. In addition, depending on the company, therapeutic area and discovery strategy, at best only one in ten research projects that begin with a starting compound will generate an optimised candidate to enter clinical trials. Given these timescales and failure rates, it is not surprising that many people in drug-discovery research reach retirement without ever having contributed to the discovery of a marketed drug.

However, discovering new medicines is vital in providing new treatments to improve the health of the developed world's increasingly aging population as well as in combating the threats posed by emerging new diseases such as AIDS, SARS and avian influenza. There are also the continuing challenges of endemic diseases such as tuberculosis and malaria in parts of the developing world. The rapid pace of development and increased prosperity of large areas of the world will lead to increases in the incidence of various chronic conditions (such as diabetes, cancer and cardiovascular problems), but also the expectation of improved healthcare, life expectancy and quality of life.

These imperatives continue to challenge and inspire the immense scientific and financial resources of the pharmaceutical industry. Researchers in this industry have been early adopters and innovators in most of the new technologies and scientific disciplines of the past 20 years. Many companies have invested, or been created, to drive developments and attempt to harness the possibilities generated by the new areas of chemical and biological research such as genome sequencing, analysis of transcription profiles, proteomics, metabolomics, systems biology, combinatorial chemistry and molecular modelling. For each of these technologies, there has been an initial over-optimism and hype as to how they will contribute to drug discovery. Perhaps this is necessary to generate the investment and allow the methods to be assessed. However, over time, practitioners come to recognise which aspects of the methods provide real benefit and how to weave them together to provide the fabric of modern drug-discovery research.

Structure-based methods are one such technology. It is now over 45 years since the determination of the first crystal structures of proteins and the beginning of the continuing efforts to understand the structure, mechanism and biological function of the protein and nucleic acid molecules that support living organisms. The potential of such detailed structural knowledge to provide a molecular basis of disease was

first demonstrated by Max Perutz in his studies relating mutations to the structure of haemoglobin in the 1960s. By the mid-1970s, structural insights were being used not only to rationalise structure–activity relationships but also to provide guidance in the design of compounds with improved properties against such targets as dihydrofolate reductase and angiotensin converting enzyme.

It is fascinating to revisit some of these early descriptions of structure-based design. They provide a sobering reminder that there is little new in the ideas of the current wave of structure-based discovery and exemplify the two long-standing applications of structural methods in drug discovery. The first is to provide detailed understanding of the mechanism of action of the protein molecule and how this relates to its biological function. Such understanding can be important in designing the most appropriate strategy for modulating the activity of the target and the design of the *in vitro* and *in vivo* assays on which drug discovery depends. The second conventional use of structural methods is to use the structure of a lead molecule bound to the target to guide the design of modifications to improve compound affinity, selectivity or drug-like properties.

These protein crystal structures were an important driver in moving drug discovery to be more rational and target oriented. As more structural information has become available, an increasing number of drug-discovery projects use rational, target-oriented approaches that rely on either explicit or model structures of the target.

What has changed in the past decade is the availability of crystal structures of an increasing number of therapeutically important target proteins. This has led to an increasing number of structure-based methods that provide diversity in the discovery of new compounds and templates, such as *de novo* design, virtual screening and fragment-based discovery.

This book provides an introductory overview to the principles and application of structure-based methods in drug discovery. The opening chapter provides a brief overview of the whole area, charting the development of the ideas and methods. The remainder of the book is in two sections. The first is a series of chapters describing the essential features of the structure-based methods – X-ray crystallography, molecular modelling and computational chemistry and NMR spectroscopy. This section includes a chapter on fragment-based methods, which are of particular promise and excitement at this time.

The second part of the book contains comprehensive descriptions of three drug-discovery programmes, which benefited from a clear contribution from structure-based discovery and design methods. These examples are a small taste of the large number of projects (published and to be published) emerging from the pharmaceutical industry where structure-based methods have had a significant impact on the speed of discovery and/or the quality of the compound delivered into clinical trials. Although the descriptions focus on the structural aspects, they illustrate the overall drug-discovery context within which the methods are applied. The first is the story of the discovery and development of neuraminidase inhibitors as anti-influenza agents. This led to one of the first drugs on the market that could be said to have been designed by rational computational calculations on the basis of the structure of the active site. The second is an example of how a relatively small company can take a published X-ray structure and quite rapidly use computational methods to generate

ideas for inhibitors of formation of blood clots. The final example is the most recent and shows how detailed molecular calculations on the basis of protein structure led to the design of isoform specific agonists of the estrogen receptor. These compounds have not only been used to probe the biological function of this isoform but also now led to drugs going through clinical trials.

The structure of protein molecules in different activation states and in complex with DNA, RNA, other proteins or substrates and inhibitors has provided an extraordinary insight and understanding of the detailed mechanisms that underlie biological processes. As most structural biologists will agree, there is very little in science that can beat that feeling of being the first person ever to see the majesty of the structure of a particular protein, or to suddenly be able to rationalise so much mutagenic, disease, phenotype or biochemical data on the basis of the structure. For the medicinal chemist and drug discovery, these mechanistic insights provide a bedrock of understanding on which to build a rational drug-discovery programme. Overall, however, the major advantage of structure is to guide the chemistry needed to develop drug candidates – be that the discovery of distinctive chemical templates, design of increased affinity and specificity or indicating where changes can be made to the compound to modify drug-like properties. The main advantage that structure provides is the insight and confidence to embark on chemistry that will develop hopefully better drug molecules, faster.

