Rational drug design — identifying and characterising a target

Structure-based drug design is now a common method used by the pharmaceutical industry to identify a lead compound and take it forward for further development. **Adam Todd**, **Roz Anderson** and **Paul W. Groundwater** describe the methods used to identify and characterise a target for structured drug design and illustrate how pharmacists can play an important role in this process

Many drugs available today were discovered by chance. Such serendipitous drug discovery has led to many drugs used commonly in pharmacy, such as glyceryl trinitrate and warfarin. Although serendipity has had a role to play in the pharmaceutical industry over the years, current drug discovery is an extraordinarily complicated, expensive and time-consuming process, with strategies involving screening natural products, mimicking biological substrates (and metabolites), and the use of structure-based drug design.

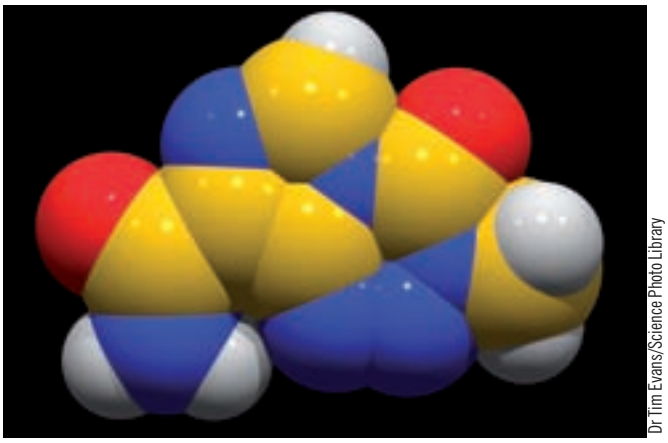
Generally, the rational development of a new drug follows a three-step process. Initially, a target, such as a receptor or enzyme, has to be identified relating to a particular disease state. This target then has to be fully characterised and, finally, a molecule must be designed that binds to it. This last part of the process can take years since, even with good structural information, it is difficult to design a drug with the desired pharmacological activity that will bind specifically to a given target.

Pharmacists can be an integral part of the drug design team because they have an almost unique understanding and knowledge base in the field of drug discovery, ranging from medicinal chemistry to pharmacokinetics and drug metabolism. Temozolomide and atracurium, both highly successful drugs on the market today, are examples of drugs discovered by research teams led by pharmacists.[1,2]

Identifying a target

Over the years, the understanding behind the molecular mechanisms of disease has significantly increased and this has allowed the identification of many biological macromolecules implicated in disease, many of which are involved in specific cellular-signalling pathways. Often, in disease states, there is a disruption or imbalance in a signalling pathway, for example, the enzyme cyclo-oxygenase (COX) is up-regulated in inflammatory disorders, leading to the production of pro-inflammatory prostaglandins.

One approach in drug design is to target and restore the normal signalling pathway by inhibiting the dysfunctional biomolecules, for example, non-steroidal anti-inflammatory drugs inhibit COX, which inhibits the synthesis of prostaglandins, thus alleviating inflammation.



Dr Tim Evans/Science Photo Library

Temozolomide molecule: temozolomide is an example of a drug discovered by research teams led by pharmacists

Proteomics

One technique that can be used to identify the biological macromolecules implicated in disease is proteomics, which can be defined as the qualitative and quantitative comparison of proteomes under different conditions to unravel biological processes.[3] The proteome is the total number of proteins expressed by a cell and can consist of more than a million proteins.

Normal healthy cells can be compared with cells from a particular disease state (eg, cancer) and proteins either up-regulated or down-regulated can be identified using proteomics, which involves the use of the hyphenated analytical technique liquid chromatography–mass spectroscopy (LC–MS). This is an extremely powerful technique and can play a significant role in the identification of impaired signalling pathways in disease pathology. Once a target has been found to play a role in disease pathology, the next step is to characterise it.

The protein databank

The recent advances in nuclear magnetic resonance spectroscopy and X-ray crystallography have allowed characterisation of numerous biological macromolecules, such as receptors, nucleic acids and enzymes. X-ray crystallography is used to generate the structure of a molecule by the diffraction of X-rays through a crystal. The analysis of the diffraction patterns gives an electron density map from which the structure of a molecule can be determined.

Once characterised, the structures of these molecules are stored in a large database, known as the protein databank,[4] which currently contains the structures of more than 52,000 molecules. The structures provided by this database are in the public domain and are easily accessible through the internet. Once the structures have been characterised and deposited into the protein databank, they can be used as a starting point for rational drug design.

DNA

Over the years, nucleic acids, enzymes and receptors have all been identified as targets for various different diseases and this has led to the development of drug molecules targeting these specific biological macromolecules. Indeed, most drugs on the market today act on either a receptor, DNA or an enzyme. For example, the anthracycline antibiotic, doxorubicin, intercalates with DNA and inhibits cell replication by interfering with transcription. Doxorubicin can be used as part of a chemotherapeutic regimen to treat acute leukaemias, Hodgkin's lymphoma, non-Hodgkin's lymphoma and some solid tumours.[5]

Enzyme inhibitors

Enzyme inhibitors account for many of the drugs on today's market and cover many different therapeutic areas. One enzyme that has had a great deal of attention over the years is angiotensin-converting enzyme (ACE), which is a key enzyme in the renin-angiotensin-aldosterone system and converts angiotensin-I into angiotensin-II. Angiotensin-II causes blood vessels to constrict, resulting in an increase in blood pressure.

Adam Todd, MRPharmS, is senior lecturer in pharmacy practice, and **Roz Anderson** is professor of pharmaceutical chemistry and MPharm programme leader, both at Sunderland Pharmacy School, University of Sunderland. **Paul W. Groundwater** is professor of medicinal chemistry at the faculty of pharmacy at the University of Sydney, Australia