Case histories in drug discovery

The Society of Medicines Research (SMR) have gained a reputation for organizing high-quality meetings, and their biannual symposium, entitled *Case Histories in Drug Discovery and Design* (held in London, UK, on 4 December 1997) was no exception. The conference offered diverse clinical interest, well-presented scientific application, humour and controversy.

Dr Anton Megens (Janssen, Beerse, Belgium) discussed the discovery of the antipsychotic risperidone (**1**) used in the treatment of schizophrenia. He explained the need for a highly potent serotonin ($5HT_2$)- and potent dopamine (D_2)-receptor antagonist to alleviate the numerous symptoms connected with schizophrenia and limit the characteristic side effects observed with many antipsychotics. The discovery of risperidone followed a medicinal chemistry programme using the neuroleptics lenperone and benperidol as the starting points. Retention of the four-atom distance between the central nitrogen and aromatic ring proved to be important for activity of several pharmacologically distinct compounds that have been developed for various clinical applications or are research tools. Risperidone possessed the desired activity for application to schizophrenia: K_i = 0.16 and 1.4 nM for $5HT_2$ and D_2, respectively. The drug is orally active, has a 24-hour duration of action, and shows marked improvement over haloperidol, a classical neuroleptic, in animal models.

The Holy Grail

The Award Lecture, given by Dr Noel Roberts (Roche, Welwyn Garden City, UK), featured the discovery and development of the HIV protease inhibitor saquinavir (**3**, Ro318959). Others have regarded an HIV protease inhibitor as the 'Holy Grail' of drug discovery. Thus, the Roche team found themselves sharing a quest with Monty Python. They were delighted, however, to report the discovery of a valuable therapeutic agent rather than a 'dead parrot'.

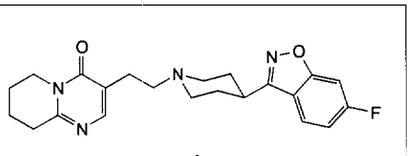
HIV encodes a retroviral protease that is essential for viral maturation and replication. The enzyme was believed to be structurally similar to human aspartic proteases and to have the rare abiliity to cleave between Phe–Pro and Tyr–Pro sites. This endopeptidase activity was an attractive feature, as inhibitors based on these cleavage sequences would be expected to be specific for the viral enzyme. A drug discovery programme was drawn up with ambitious time-scales, allowing just four years to identify a clinical candidate. Cloning, expression and purification of the protease was required, and demonstration of the putative Phe–Pro or Tyr–Pro cleavage activity was shown in synthetic oligopeptides using a novel colourimetric assay developed to detect the presence of the N-terminal proline. A hydroxyethylamine mimetic (**2**), based on the putative Asn.Phe–Pro cleavage sequence in the Pol polyprotein, was selected as the lead compound and it was systematically modified at each residue to optimize the activity of the side chains. The pleasant surprise was that the improvements were additive, and highly-potent inhibitors were prepared. These were subsequently tested in antiviral assays and examined for selectivity against a variety of human proteases. Saqinavir was shown to be a highly selective and potent inhibitor of the HIV protease (IC_{50} <0.4 nM); it had potent antiviral acitivity (IC_{50} = 2 nM) and in the mesylate form had modest solubility and oral bioavailability. Thus, saquinavir was discovered and proposed for clinical development in under three years.

It has since been shown that saquinavir is well tolerated in humans and has an exceptionally clean safety profile. Although monotherapy is not an option, it has a significant synergistic effect in combination with reverse transcriptase inhibitors. Moreover, resistance to saquinavir is relatively difficult to generate and is modest in degree. The SMR presented certificates and a cheque for £500 to Dr Roberts, Dr Sally Redshaw and Dr Ian Duncan for the development of saquinavir and its outstanding contribution to humankind. The prize money was donated to the Terrence Higgins Trust.

Unfair share of controversy

Matrix metalloproteinases (MMPs) are a family of zinc-dependent enzymes that degrade extracellular matrix components and are controlled by tissue-specific inhibitors. An imbalance in the levels of MMPs and their natural inhibitors has been implicated in several pathological processes, including tumour progression. Dr Mike Crimmin from British Biotech Pharmaceuticals (Oxford, UK) presented the development of marimastat, a broadly acting MMP inhibitor that is currently in Phase III clinical trial in Europe and the USA for the treatment of several types of cancer.

The main series of MMP inhibitors that were studied by British Biotech were succinate derivatives containing a hydroxamic acid zinc-binding group and side chains that interact with the S1′ and S2′ sub-sites. [For a review of MMP inhibitor research see Beckett, R.P. *et al.* (1996) *Drug Discovery Today* 1, 16–26.] The identification of an inhibitor with a broad spectrum of activity against the MMPs was desired as different MMPs are elevated in different types of human cancer. The first broad-spectrum inhibitor to perform well in preventing metastasis in the rat breast cancer model was batimastat, but it has poor oral bioavailability. By modification of the side chains of batimastat, marimastat was developed, which has a similar inhibition profile to MMPs (except for stromelysin) and has >2,500-fold increase in aqueous solubility. In Phase II clinical studies, response to marimastat



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Risperidone, a new antipsychotic described by Dr A. Megens.

1359-6446/98/$19.00. PII: S1359-6446(97)01154-9

Dr N. Roberts (presenter), Dr S. Redshaw and Dr I. Duncan (from right to left), members of the Roche research team, receiving their SMR Awards for their work in the development of saquinavir.

was measured by the rate of increase of cancer markers (e.g. carcino embryonic antigen) and changes in histological appearance. Marimastat was shown to be well absorbed and tolerated in humans and it had a significant effect on the rise of antigenic markers of cancer in a variety of tumour types. Histology shows that tumour cells become encased in a collagen matrix, thus minimizing metastasis, local invasion and angiogenesis.

A financial analyst attending the meeting reported the following day that cumulative side effects may hinder the use of marimastat in long-term treatment, which led to a dip in British Biotech's share price of nearly 10%. Dr Crimmin says that his comment referred to higher doses of marimastat than are now being investigated in Phase III trials, and stressed that all the side effect data brought up at the meeting is in the public domain. The company say that there is no evidence to suppose that marimastat cannot be used for chronic treatment, but it appears that only the results of the Phase III trial will resolve the controversy.

Other presentations

The importance of antifungal agents was highlighted by Dr Steve Hitchcock (Eli Lilly, Indianapolis, IN, USA). Increases in the numbers of elderly and immunosuppressed individuals, and the use of antibacterial agents creating a bacterial void, has meant that fungal infections are becoming more important in disease. The development of the echinocandin class of antifungals was described. The potency, spectrum of activity and aqueous solubility of these cyclic lipopeptides has been increased, while toxicity has been reduced, to produce orally active systemic antifungals that are effective against the pathologically important *Pneumocystis*, *Candida* and *Aspergillus* species.

The clinical advantages of hirulog, a bivalent thrombin inhibitor, were presented by Dr John Maragonore (Millenium BioTherapeutics, Cambridge, MA, USA). Hirulog has application in the treatment and surgical procedures of arterial thrombotic disease and coronary artery diseases. It has been shown to be safer and easier to use than heparin in extensive clinical studies. It is due to enter a Phase II study involving 17,000 patients, where the advantages of hirulog over heparin, in combination with aspirin, will be investigated for treatment of acute myocardial infarction.

Dr Tom Boyle (Zeneca Pharmaceuticals, Alderley Edge, UK) presented the discovery of Arimidex {2,2′-[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]di(2-methyl-propionitrile)} – a potent and selective aromatase inhibitor (IC_{50} = 15 nM) – for use as a second-line therapy against breast cancer. Aromatase converts androgens into oestradiols, and this represents the primary source of mitogenic stimulus to breast tumours in postmenopausal women. In Phase III studies, a dose of 1 mg kg^{-1} effectively reduced oestrogen levels by inhibiting aromatase activity by 96.7%, and increased patient survival by 10%.

The final presentation by Dr Steve Smith (SmithKline Beecham, Harlow, UK) concerned the discovery of the peroxisome proliferator-activated receptor γ (PPARγ) agonist rosiglitazone (BRL49653) for the treatment of type 2 diabetes. He explained the use of an *in vivo* screen using the genetically obese *ob/ob* mouse strain to measure glucose tolerance (i.e. efficacy) in combination with determination of haematocrit (i.e. side effect) to select rosiglitazone as a development candidate. Rosiglitazone is the most potent PPARγ agonist known in transactivation assays and is also selective. It normalized glycaemic control in many rodent models of type 2 diabetes effectively, and in a Phase II dose-ranging study in diabetic patients, 12-week treatment of rosiglitazone produced a dose-dependent reduction in fasting hyperglycaemia. The compound is now undergoing Phase III clinical development.

Details of future SMR meetings are available from Barbara Cavilla (SMR Secretariat, 20/22 Queensbury Place, London, UK SW7 2DZ. tel: +44 171 581 8333, fax: +44 171 823 9409).

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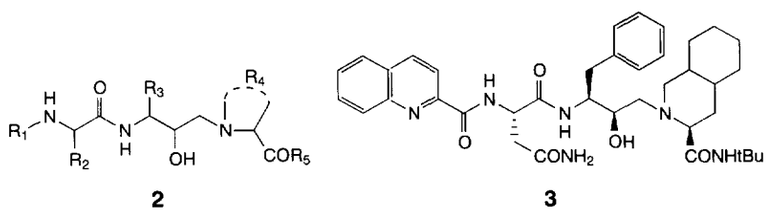

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The development of saquinavir, the first marketed HIV protease inhibitor, was described by Dr N. Roberts.