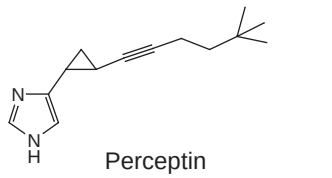

Figure 1. *The structure of Perceptin {4-[(1R,2R)-2-(5,5-dimethyl-1-hexynyl)cyclopropyl]-1*H*-imidazole}.*

ADHD sufferers are required to take medication for many years, and the adverse effects of the most commonly prescribed stimulant, Ritalin®, can include headache, insomnia and dizziness. Clark Tedford (Vice President for Product Development at Gliatech) says, 'We hope that Perceptin will fill the need for a safe, effective non-stimulant medication for ADHD'.

Narcolepsy

Narcolepsy is a disabling, incurable sleep disorder that affects 0.2–1.6 per thousand in European countries, Japan and the US. It is characterized by excessive daytime somnolence and cataplexy, which is a sudden, involuntary loss of strength in voluntary muscles and is triggered by changes in emotion. It is currently treated with stimulant and anti-depressant drugs. In a presentation at the *29th Annual Society for Neuroscience Conference* in October 1999 (Miami, FL, USA), Tedford and colleagues reported that Perceptin decreased the number and severity of cataleptic attacks in genetically induced narcoleptic dogs. Phase II clinical trials of Perceptin are therefore planned for this and other sleep disorders.

The role of H_3 receptors in learning and memory indicates that H_3-receptor antagonists could have a role in the treatment of memory disorders such as Alzheimer's disease (AD). Histamine levels in the hippocampus are significantly lower in AD sufferers compared with age-matched controls[3]. Furthermore, milder sleep and memory disorders affect millions of elderly people and, as the population ages, the occurrence of these conditions will increase. In the future, H_3-receptor antagonists might therefore play a significant role in improving the quality of life of the elderly population.

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3 Panula, P. *et al.* (1998) Neuronal histamine deficit in Alzheimer's disease. *Neuroscience* 82, 993–997

Clare Sansom

News in brief

Pharmacogenomics market to explode?

It has been forecast that, by the year 2005, the pharmaceutical R&D market for pharmacogenomics-related products and services will be worth $795 million[1]. This market was valued at $47 million in 1998, giving an expected compound growth rate of >50%. The relative contribution of the different areas of research is forecast to remain relatively constant, with the major areas in 2005 being cardiovascular disease ($139.1 million) and infectious disease ($123.3 million), followed by CNS-related disorders ($72.3 million) and cancers ($41.3 million). The field of pharmacogenomics is little more than two years old, and was created following the formation of the Abbott–Geneset Alliance in July 1997. Since then, 28 pharmacogenomic collaborations have been formed, 20 of which involve the application of pharmacogenomics to drug development (especially late-stage clinical development), at least seven are involved in drug discovery, and four involve marketed drugs.

1 Financial Times Pharmaceuticals (1999) Pharmacogenomics players.

Splicing apoptosis genes

Researchers from Isis Pharmaceuticals (Carlsbad, CA, USA) have successfully used antisense oligonucleotides to both increase and decrease the levels of two functionally antagonistic proteins encoded by the *Bcl-x* gene, one of which might trigger the development of resistance to chemotherapy in human tumours[2]. These studies have shown that alternatively spliced RNA produced by the *Bcl-x* gene produces two proteins, Bcl-xS that promotes apoptosis and Bcl-xL that inhibits apoptosis. By targeting a second-generation methoxyethyl antisense inhibitor to pre-RNA from the *Bcl-x* gene, it was possible to change the RNA splicing from one form of Bcl-x to the other, hence decreasing Bcl-xL levels and increasing Bcl-xS levels in human cancer cell lines. This then sensitized the cancer cells to apoptotic stimuli and to the cytotoxic effects of chemotherapeutic drugs. It was also suggested that this technique might enable the phenotypes of other apoptosis-regulating genes to be swapped, enabling the development of new

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therapeutic approaches that use antisense-mediated mRNA splicing to control the ability of a cell to live or defend itself[3].

2 Taylor, J.K. *et al*. (1999) Induction of endogenous Bcl-xS through the control of *Bcl-x* pre-mRNA splicing by antisense oligonucleotides. *Nat. Biotechnol.* 17, 1097–1100

3 Reed, J.C. (1999) Splicing and dicing apoptosis genes. *Nat. Biotechnol*. 17, 1064–1065

Personalizing cancer medicines

A research initiative has been launched by Bristol-Myers Squibb (BMS, Princeton, NJ, USA) to genetically identify patients that are most likely to respond favourably to the company's cancer pipeline and marketed products. This drug genotyping technique is anticipated to be an important step towards the production of personalized medicines for a broad range of cancers. The sensitivity and resistance of a patient to cancer treatments is pre-determined genetically but, at present, physicians have no method of distinguishing in advance the responders from the non-responders. Hopefully, therefore, pharmacogenomic tests will enable the design of more specific pharmaceutical agents and potentially raise the current 20–30% response rate to cancer therapies to 30–80%. The long-term goal of this project is to completely re-engineer how cancer is managed. This might lead to a new disease nomenclature, where tumours are diagnosed by their underlying genetic mutation rather than by their primary site of origin.

Donald Hayden, Jr, the President of BMS Worldwide Medicines Group, said 'While the era of predictive medicine is still in the early stages, the coupling of biological markers with compounds has the potential to accelerate the development of novel compounds'. BMS has formed a collaboration with Millennium Predictive Medicine (MPMx, Cambridge, MA, USA) for the development of clinical markers for drug responses. BMS is also seeking a diagnostic partner for the development of molecular-based pharmacogenomic diagnostic tests, and partnerships with cancer treatment centres for clinical research and tumour sampling.

Similar new drug approval times between Europe and the US

A report has suggested that the mean total approval time for new drugs evaluated by the European Agency for the Evaluation of Medicinal Products (EMEA) and by the Food and Drug Administration (FDA) in the US are almost identical[4]. The evaluation, carried out by the Tufts Center for the Study of Drug Development (Boston, MA, USA), analyzed the approval time for 30 new products by each agency between 1995 and June 1998, and found that the mean was 370 days for the EMEA and 366 days for the FDA. However, there was substantial variation in individual product review times, reflecting differences in submissions to each agency, in the resources and priority given to review, and in the issues raised by the two agencies concerning the applications. These variations might also reflect the different approaches to drug development and healthcare in general between Europe and the US.

The EMEA was created in 1995 by the EU to unify regulatory practices and improve market access within Europe. The EMEA segregates applications into List A (medicinal products developed using recombinant DNA technology, controlled expression of genes encoding for biologically active proteins, and hybridoma and monoclonal antibody methods) or List B products (new innovative medicinal products derived from other biotechnological processes or radioisotopes, or products that use new delivery systems or new manufacturing processes). List A products were found to take slightly longer to approve, but this is thought to be caused by more stopclock days (time used by companies to address the issues raised by the scientific reviews), suggesting more complicated questions. Of the 30 products reviewed by the FDA, 17 were assigned a priority review rating, eight were granted accelerated approval and ten were submitted as rolling new drug approvals (NDAs). Meanwhile, in the EMEA, 11 of the 30 products were granted approval under exceptional circumstances.

4 Tufts Center for the Study of Drug Development (1999) European and US approval times for new drugs are virtually identical. *Impact report: Analysis and insight into critical drug development issues*. 1, 1–4

Pharmacogenetic profiling for ADRs

The Laboratory of the Government Chemist (Middlesex, UK) and Dundee University (Dundee, UK) have launched the UK's first comprehensive genetic diagnostic service for pharmacogenetics (identifying variations in responses to drugs and the way they are metabolized). This service, GeneSolve™, has been made commercially available for the pharmaceutical industry and is expected to make a large financial impact on the industry by safer and more effective passage of drugs to market.

Many adverse drug reactions (ADRs) can be determined genetically, and Dundee University holds the license for the diagnosis of CYP2D6, thought to be one of the most crucial polymorphisms involved in drug-induced ADRs. This enzyme controls the metabolism of 25% of all prescription drugs, and approximately 10% of white northern Europeans have a serious deficiency of this enzyme. Pharmacogenetic profiling should enable the identification of individual codes in the genes that determine a personal metabolic profile. Hence, in clinical trials, the code can be used to identify whether a side effect is caused by a predictable metabolic

effect and whether the medicine dosage should be re-evaluated. The service will also provide back-up research and consultancy support to help in the identification of new genes that affect responses to medicines.

Raised β-chemokine levels and lymphocyte proliferation necessary for AIDS-free status?

It has recently been suggested that there is an association between high levels of β-chemokines (potent suppressors of HIV infection) and lymphocyte proliferation (expansion of T-cells) and a more favourable clinical status in AIDS and HIV-infected individuals[5]. Researchers at the Immune Response Corporation (Carlsbad, CA, USA) conducted a multicenter AIDS Cohort Study in collaboration with the Institute of Human Virology (University of Maryland, MD, USA) and the John Hopkins University (Baltimore, MD, USA), to examine the immune response correlates of AIDS-free status in HIV-infected patients.

The production of β-chemokines [RANTES (regulation-on-activation, normal T-cell expressed and secreted) and the macrophage inflammatory proteins, MIP-1α and MIP-1β] and lymphocyte proliferation were measured in blood samples from 100 HIV-positive patients. To test whether responses were directed specifically against HIV, the antigens HIV-1 and p24 were used to stimulate blood samples. In asymptomatic patients compared with AIDS patients, a significant increase in lymphocyte proliferation was noted to HIV-1 and p24, together with raised levels of MIP-1α and MIP-1β, but not of RANTES. These results suggest that the production of certain chemokines and lymphocyte proliferation are important in immune responses elicited by HIV-specific antigens and could play a role in controlling HIV infection. Furthermore, MIP-1α and MIP-1β production were found to correlate with increased lymphocyte proliferation and, as β-chemokines are mainly produced by activated T-cells, this suggests that enhanced chemokine production might be dependent on T-cell expansion. Hence, drugs that stimulate β-chemokine production (such as Remune™, Immune Response Corporation) could help inhibit the spread of HIV into uninfected cells.

5 Garzino-Demo, A. *et al.* (1999) Spontaneous and antigen-induced production of HIV inhibitory β-chemokines are associated with AIDS-free status. *Proc. Natl. Acad. Sci. U. S. A.* 96, 11986–11991

Rebecca N. Lawrence