of intracellular signalling pathways from cytokine receptors [for example with inhibitors of NF-κB-inducing kinase (NIK) or FCεR1 receptors (with inhibitors of Syk or lyn) may have 'anti-inflammatory' effects. With its involvement in TNF-α and IL-1 signalling, p38 mitogen-activated protein (MAP) kinase is of particular interest. p38 MAP kinase was found to be the target of a group of SmithKline Beecham molecules, termed cytokine-suppressive anti-inflammatory drugs (CSAIDs), which although exhibiting anti-inflammatory activity, were not 'classical' anti-inflammatory drugs. Several molecules have been evaluated preclinically, including SB203580, VK19577 and L167307, but are associated with limiting side-effects, in particular hepatotoxicity. However, this does not seem to be a class effect and 'follow-up' compounds, some with potencies in the picomolar range, have been selected for potential development. Interestingly, airways remodelling may be targeted by inhibitors of receptor protein kinases for epidermal growth factor (EGF), for example CGP59326 (currently in Phase I trial; Fig. 1), and platelet-derived growth factor (PDGF), for example CGP53716 (Fig. 1).

Summary

By the end of the meeting, the impression was that remarkable progress had been made in just a year: therapeutic targets were being meticulously characterized, drug molecules were being designed specifically for those targets, and some new drugs were now not only in clinical trial but were also giving encouraging results. Although too early to tell, and with experience of many 'false dawns' in drug discovery, it is distinctly possible that there will be several new drugs aimed at conquering airway inflammation on the market early into the new millennium.

For the 1999 meeting, see http://www.nhli.ac.uk/mtgs.htm#dg

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Hunting for PPAR ligands

A crystal clear view of the peroxisome proliferator-activated receptor-γ (PPAR-γ) has been seen by US researchers, which could reveal clues to designing novel drugs for several diseases including atherosclerosis, cancer and diabetes.

The receptors for oestrogen, thyroid hormone, retinoic acid and retinoid X act as intermediaries between hormones and DNA. Drugs that act on these receptors are keenly sought. One class member, the PPAR, is crucial for normal development and gene regulation but is an 'orphan' receptor having no known ligand.

PPAR-γ is a transcription factor found in the nucleus of adipocytes and in macrophages. Although no bona fide ligand has yet been recognized, there are several compounds known to activate it. For instance, in its role in lipid regulation, several fatty acids, oxidized lipids and prostaglandin J derivatives can interact with the receptor.

Activation of PPAR-γ by a ligand causes it to bind to specific DNA sequences in the nucleus of adipocytes. It also controls differentiation of muscle cells to fat cells. Having more fat cells to respond to insulin and metabolize glucose enables better control of diabetes, so understanding the activation could lead to new drugs for this disease.

Dietary fats and cancer

Recent research on a mouse genetic model, reported in *Nature Medicine* at the beginning of September by Enrique Saez of the Salk Institute (La Jolla, CA, USA) and colleagues also suggested that PPAR-γ could be the genetic switch that allows fats to trigger colorectal cancer – at least in the mouse model [(1998) *Nat. Med.* 4, 1058–1061]. However, other laboratories [Spiegelman (Harvard) and Koeffler (UCLA)] have shown that PPAR-γ ligands halt or slow the growth of human colon tumour cells and tumour cells from other diet-related cancers such as prostate and breast cancer.

A better understanding of the site of ligand binding in PPAR-γ and discovering its natural ligands could provide clues to developing novel drugs for treating several diseases, including cancer, diabetes and atherosclerosis.

Crystal clear pocket

Now, a collaboration between Michael Milburn and his colleagues at Glaxo Wellcome (Research Triangle Park, NC, USA) and Christopher Glass and Michael Rosenfeld at UCSD Howard Hughes Medical Institute (La Jolla, CA, USA) has focused on the ligand-binding centre of the protein and built a high-resolution X-ray crystal structure to examine its interactions with a coactivator required for PPAR-γ to alter gene expression [Nolte R.T. *et al.* (1998) *Nature* 395, 137–143].

The crystal structure of the 'empty' PPAR-γ revealed a large binding pocket. This, says Rosenfeld, may explain the diversity of ligands for PPAR-γ. The team also examined the pocket when occupied. The ternary complex containing the PPAR-γ ligand-binding domain (LBD), the antidiabetic ligand rosiglitazone, and a stretch of human steroid receptor coactivating factor-1 (SRC-1) – a coactivator in the transcriptional

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machinery – showed that glutamate and lysine residues in the LBD form a 'charge clamp' to allow SRC-1 to bind.

According to Colin Palmer, a 'PPAR-ligand hunter' at the University of Dundee, UK, 'The binding of ligand changes the shape of the PPAR allowing SRC-1 to bind. This represents the molecular basis of how the PPAR 'switches on' transcription in response to drugs,' he explains. The charge clamp is needed for SRC-1 binding and this clamp is not in the right position unless the PPAR is bound by ligand.

Increasing interest

Palmer points out that the pharmaceutical companies are investing a lot of money on PPARs, in general. With two percent of the British population currently diagnosed as having non-insulin dependent diabetes and an increasing incidence of the disease as a result of a lack of exercise and poor diet, PPAR research is likely to become more important. Now that a crystal 'snapshot' has been taken, there is likely to be a flurry of experiments looking for its ligands and potential new drugs for the disease, he says.

In addition, Rosenfeld says that 'The data also imply there are flanking amino acids that must provide specificity and constitute a 'code' in which both receptor-specific and ligand-specific use of coactivators are likely to act.' He points out that this may underlie the diverse biological actions of nuclear receptors and act in development, regulation, and control of proliferation in all mammalian genes.

David Bradley
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Book review

Natural Products Isolation

edited by Richard J.P. Cannell, Humana Press, 1998. $89.50 (x + 473 pages, hardback) ISBN 0-89603-362-7

Nature exhibits unique structure-activity relationships and has a proven ability to produce diverse and novel chemical prototypes with drug potential. There is also an accelerated interest in the areas of herbal drugs and functional foods. However, in drug discovery the application of combinatorial chemistry together with high-throughput screening is an obvious challenge to research aimed at the discovery of new bioactive molecules from natural sources. The consequences may be that the need for natural products in lead generation will decrease, especially for compounds of low molecular weight.

If natural products should play a continuing important role in the discovery of potential and innovative leads in drug development and in the development of high quality herbal drugs with proven efficacy, improvements and development of new research strategies and in-depth studies are needed. The selection of organisms for improving diversity and increasing dereplication to avoid known molecules, and the development of faster and more efficient isolation procedures are thus routine challenges for a natural product scientist. Moreover, a broad knowledge and experience is needed to avoid the pitfalls in dealing with a complex biomass and to reach the objective of discovering novel bioactive molecules. It was therefore of great interest to have read the excellent and comprehensive book *Natural Products Isolation* edited by Richard J.P. Cannell, which summarizes this type of experience.

Consisting of 15 chapters written by experienced research scientists from both the pharmaceutical industry and academia, this book provides detailed descriptions of novel and classical methods for extraction and purification of natural products from a wide range of biological sources and discusses the potentials and limitations of these methods in drug discovery.

Strategic planning

The first, very useful, chapter of the book, written by the editor, explains how a research scientist should approach the isolation of a natural product and it provides a detailed understanding of how to build up a strategy for isolating a bioactive compound. This basic theory is supplemented with examples from the research literature and also with useful comments. Furthermore, the limitations and possibilities for extraction, isolation and assay procedures are summarized in protocols based upon the experience of the authors.

Many text books on natural product research focus on isolation and structure elucidation of natural products; however, selection and collection of starting materials and extraction from such materials are usually not discussed. It is therefore of the utmost importance that several of the chapters are focused on these details and include, for example, special problems of extraction, product capture of fermentation broths and filtration procedures together with pictures showing the set-up of necessary equipment. One section that is particularly useful is devoted to supercritical fluid extraction (SFE), which is a general extraction strategy for a wide range of bioactive compounds from plant and microbial samples. This section provides the basic theory behind SFE, the equipment required and also the pros and cons of the method compared with conventional extraction procedures and applications.

Isolation of natural products

About 150 pages of the book deal with isolation of natural products using low pressure column chromatography, ion-exchange methods, HPLC, planar chromatography and high-speed counter-current chromatography. The different techniques are introduced without a

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