interaction of cyclo-oxygenase (type 2), known to be involved in prostaglandin production, and 5-lipoxygenase, an enzyme that is involved in leukotriene biosynthesis.

According to Serhan, aspirin acetylates the 5-lipoxygenase in endothelial cells, allowing it to generate an intermediate, which is picked up by leukocytes and is rapidly converted to the new 15-epilipoxins. "This is an entirely new route, showing how aspirin can 'pirate' endogeneous biosynthetic mechanisms to trigger new mediators", says Serhan. He explains further, "In the absence of aspirin, the traditional pathway is in place; here aspirin 'pirates' by changing the enzyme's activity to generate new compounds by transcellular biosynthesis". Hence, aspirin enables the production of mediators with potential beneficial cellular actions. The finding that some of these compounds belong to the family of eicosanoids was serendipitous, according to Serhan, and the pathway that gives rise to them is totally novel.

This new interaction may contribute to the therapeutic effects of the drug and could provide a novel target for the development of nonsteroidal anti-inflammatory drugs without side-effects. "We have already synthesized analogues of these compounds that are bioactive and in some cases more potent" adds Serhan. These analogues should now serve as lead structures for drug design.

David Bradley

Modified transcriptional activators as therapeutic tools

The second annual meeting on *Drug Discovery for the Modulation of Signal Transduction and Gene Transcription*, organized by the Cambridge Healthtech Institute, was held in October in San Diego. The meeting highlighted some recent advances in the development of modified transcriptional regulators as potential therapeutic agents for selective regulation of gene expression. There is a clear need for an exquisitely specific signal transducer, or genetic switch, to control the expression of therapeutic transgenes[1]. Such a switch would respond to an otherwise physiologically inactive signal, and, when activated, would modulate the expression of a single or defined set of genes.

Three groups presented results of studies on the transcriptional activation properties of modified steroid receptors. Steroid receptors are ideally suited in many respects as prototypes for engineered signal transducers that would control the expression of transgenes. Unlike membrane receptors, where signals are transduced to components of the cell membrane and the cytoplasm, as well as the nucleus, steroid receptors are transcriptional regulators that function directly in the nucleus to modulate the transcription of a specific set of target genes[2,3].

Steroid receptors are composed of a series of conserved domains. The DNA-binding domain recognizes specific palindromic DNA sequences, known as hormone response elements, found in the vicinity of target genes. Hormone binding is controlled by a separate functional domain. Many *in vitro* studies have suggested that steroid receptors may be cytoplasmic in the absence of hormone, bound to the 90 kDa heat shock protein, HSP90. The hormone-bound receptor is dissociated from HSP90, is nuclear, and is competent for transcriptional activation. Past results have shown that steroid receptors can efficiently activate the transcription in a strictly hormone-dependent manner of transgenes whose regulatory sequences are composed solely of hormone response elements[4], indicating that they do not require other signal transduction pathways for function.

Ideally, both the DNA-binding and hormone-binding specificities of receptors would have to be engineered to generate an exquisitely specific signal transducer. Data presented in San Diego provide advances towards both of these goals. Two groups used similar approaches to generate steroid receptors with altered DNA-binding specificities. Dr V. Allgood and coworkers (GeneMedicine Inc., Woodlands, TX, USA) replaced the DNA-binding domain or the progesterone receptor with that of the yeast transcriptional activator GAL4. A McGill University group has generated a similar chimera of the estrogen receptor. GAL4 recognizes a specific DNA sequence that is distinct from those recognized by mammalian transcriptional activators.

Using gene transfer experiments in tissue culture cells, the GAL4-receptor chimeras were shown to activate transcription in a hormone-dependent manner of model transgenes whose regulatory sequences contained multiple binding sites recognized by GAL4. The GeneMedicine group went further and showed that the GAL4-progesterone receptor chimera could function *in vivo* after administration of 5 μg/kg of activator. One striking aspect of the GAL-estrogen receptor chimeras is that they failed to interact with HSP90, suggesting that the estrogen receptor–HSP90 interactions may not be important for controlling receptor activity *in vivo*. The above experiments demonstrated that modified steroid receptors could be generated that function through recognition of DNA sequences distinct from those bound by all other classes of human transcriptional activators.

The GeneMedicine group and Dr J. Carlstedt-Duke and coworkers (Karolinska Institute, Stockholm, Sweden) presented studies of steroid receptors with altered ligand-binding specificities. The GeneMedicine group exploited the observation that a modified progesterone receptor lacking the C-terminal 42 amino acids of the protein can be strongly activated by compounds that are antagonists of the wild-type receptor[5]. Carlstedt-Duke and coworkers used affinity labelling techniques to identify key residues in the glucocorticoid and progesterone receptor–ligand binding domain. Based

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on these results, they have performed site-directed mutagenesis experiments and have been able to isolate a mutant receptor with increased sensitivity to triamcinolone acetonide and reduced sensitivity to other glucocorticoids.

In summary, significant advances in the development of transcriptional activators as therapeutic agents were reported in San Diego. Functional steroid receptor chimeras with specific DNA specificities have already been generated, and we are well on the way to developing receptors with altered and specific ligand binding affinity. This technology should prove to be extremely versatile because several parameters of receptor function can be readily manipulated. In addition to controlling the specificity of receptor function, the potency of transcriptional activation can be modulated by altering the number of receptor DNA binding sites in transgene regulatory regions and/or addition of transactivation domains from other classes of activators. In the longer term, receptors specific for ligands with different stabilities and clearance times can be generated to control the extent and du-ration of transgene activation. Thus, the future looks bright for the use of steroid receptors as exquisitely specific signal transducers for gene therapy experiments.

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People

An increasing number of people involved in drug research are leaving established companies to strike out on their own or else are retiring from relatively secure university posts to pursue more challenging careers in industry, free from the restrictions imposed by academic life. Two good examples of this new breed have recently been in the news.

In June 1995, Dr David Barry, then President of The Wellcome Research Laboratories and member of the board of Wellcome plc, left after 18 years' service to set up Triangle Pharmaceuticals in Chapel Hill, NC, USA. Dr Barry has a BA and an MD from Yale University and spent five years at the FDA before joining Wellcome.

The staff of his new company so far consists entirely of former employees of Burroughs Wellcome, and they are concentrating their efforts on antiviral drugs. This is hardly surprising because at the FDA, Dr Barry became Acting Deputy Director of the Division of Virology and progressed to play a major role in the development of Wellcome's antiherpes agent, Zovirax^{R}. He is also coinventor of Retrovir^{R}, the first and most frequently prescribed drug for the treatment of HIV infection and AIDS.

Unusually, he is not trying to discover new drugs, but to identify promising agents discovered by other companies or institutions and take them through phases II–IV of clinical testing. According to Dr Barry, "recent advances in virology and immunology indicate that the future of therapy for serious viral diseases such as HIV infection lies in combination regimens". The company is completing agreements to acquire six novel antiviral and anticancer compounds, and several more are expected to be added to their portfolio shortly.

One of the most successful British ex-academic scientists of this breed is surely Dr Denis Stanworth. After spending his entire academic life as an immunologist at Birmingham University, UK, he retired in the autumn of 1993 to establish Peptide Therapeutics, a small biopharmaceutical company devoted to the rational design of peptide drugs. He used his experience in using synthetic peptides as probes to study the molecular pathology of certain immunoglobulins in order to develop a peptide vaccine for IgE-mediated allergies and a tetrapeptide for the treatment of rheumatoid arthritis.

Peptide Therapeutics was originally based at Aston Science Park (Birmingham, UK) but the company recently moved to much larger laboratories at Cambridge Science Park. The company published a prospectus for its flotation on the London Stock Exchange in December. It was expected to raise at least £15 million and, in fact, the final figure was £24 million. The company has announced that it will issue its 1995 report in March 1996. Dr Stanworth is Scientific Director of the company and is Special Professor in Therapeutic Immunology at the University of Nottingham, UK. Like many other Directors, Dr Stanworth has agreed not to sell any ordinary shares for a period of two years after the flotation but, when he does, he is likely to join that very select band of ex-academics who have gone on to become millionaires.

David B. Jack

CAS record

The Chemical Abstracts Service (CAS) registry, a division of the American Chemical Society, reports that the number of 1995 registrations for new chemicals was nearly 50% greater than that in 1994. For the first time in the 30-year history of CAS, more than one million new substances were recorded in a single year. Dr J.E. Lohr, CAS Director of Editorial Operations, attributes this growth, in part, to a general increase in literature and patents, but he also emphasizes the contributions of biotechnology and genome research. More than one-third of the registrations resulted from human genome research, and a further one-third were the result of work on stereochemistry and chiral drugs.

David Hughes

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