The following lecture on the design of the thymidylate synthase inhibitors ZD1694 (Tomudex™) and ZD9331 for the treatment of solid tumours was given by Dr F.T. Boyle (Zeneca Pharmaceuticals, Alderley Edge, UK). Dr Boyle demonstrated how clinical data could be used in drug design, together with molecular modelling, to develop more selective compounds. ZD9331 has been designed to have the same inhibitory potency as Tomudex™, without the need for polyglutamation by folylpolyglutamate synthase to overcome potential resistance problems. Dr Boyle explained that ZD9331 will shortly be entered into clinical trials.

In the final session, Dr S.B. Kadin (Pfizer Inc., Groton, CT, USA) described the design and development of tenidap, a novel oxindole derivative that acts as a nonsteroidal anti-inflammatory agent and a disease-modifying agent in the treatment of rheumatoid arthritis, through the inhibition of IL-1 biosynthesis. Finally, Dr G.T. Yarranton (Celltech Therapeutics Ltd, Slough, UK) described the development of an anti-TNF antibody for the treatment of serious inflammatory conditions. Dr Yarranton explained the rationale behind the selection of the passive antibody isotype γ_4 and described the protein engineering undertaken to produce humanized antibodies to minimize immunogenicity on patient administration. The clinical data suggest that long-term therapy with the anti-TNF antibodies may be both beneficial and well tolerated by the patients.

The Society for Medicines Research organizes one-day symposia on the discovery and development of new medicines. The next symposium, *New Technologies in Drug Discovery*, will be held on 21 March 1996 at the GlaxoWellcome Research Centre, Stevenage, Herts, UK. Further details are available from the SMR Secretariat, 20/22 Queensberry Place, London, UK SW7 2DZ. tel: + 44 171 581 8333, fax: + 44 171 823 9409.

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Novel targets for drug discovery

New paradigms for discovery were the focus of a recent two-day symposium, *Strategies for Identification of Novel Targets for Drug Discovery*, organized by Cambridge Healthtech Institute and held in La Jolla, CA, USA, in January. Recent developments in high-throughput screening (HTS), the human genome project, and 'gene knock-out' and 'gene knock-in' animal models have provided new opportunities for scientists to identify new molecular targets.

According to Dr T.R. Butt (University of Pennsylvania, Philadelphia, USA), HTS can provide a lead compound only if sufficient effort has been made at the outset to select the right target molecule. As an example, he explained that companies have been hesitant to target the area of transcriptional regulation for fear of a lack of specificity. He expressed the belief that if the right factors are targeted and sufficient research is conducted to understand how a factor works and to delineate its partners, then it is possible to discover 'robust inhibitory compounds with high specificity'.

Dr F.P. Talley (Cubist Pharmaceuticals, Cambridge, MA, USA) and Dr Gerald F. Vovis (Genome Therapeutics Corporation, Waltham, MA, USA) discussed their companies' approaches to the development of new antibiotics in the light of increasing antibiotic resistance and the recent announcement by the US Center for Disease Control and Prevention that deaths due to infectious diseases increased by 58% between 1980 and 1992 [*JAMA* (1996) 275(3), 189–193]. Cubist is focusing on the development of inhibitors for specific aminoacyl tRNA synthases from a wide spectrum of pathogens. The company believes that sufficient structural differences exist between mammalian and bacterial synthases for selective inhibitors of bacterial protein synthesis to be discovered. Biological data were provided by Talley on six compounds the company have discovered through rational design, all of which have nanomolar activity towards an *Escherichia coli* isoleucine tRNA synthase and significantly lower activities toward the mammalian enzyme. Cubist also has a major HTS operation under way to discover new compounds. However, Talley commented, "the bugs will become resistant to these compounds also – they have the advantage of numbers – that's what keeps pharmaceutical companies in business in this area".

Vovis described the different approach of Genome Therapeutics to the development of new antimicrobial agents. He pointed out that the more than 100 antibiotics currently available for use in the USA are directed towards only 15 different molecular targets. He believes that it is essential to discover new molecular targets and that this can be accomplished through sequencing the genome of selected pathogens. Sequence homology, protein motifs and structural homologies can then be used to assign function to the various gene products. Based upon what is known about the role of the gene products in other organisms, the company believe it will be possible to select novel targets and to discover selective inhibitory compounds through HTS. Three organisms of interest to Genome Therapeutics are *Chlamydia trachomatis*, *Pseudomonas* spp. and *Candida albicans*. The company has developed programs to validate and develop attractive targets in selected pathogens. They hope to form partnerships with large pharmaceutical companies to fully exploit the novel targets that are discovered.

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Other companies outlined their use of gene sequence information to identify new targets. Dr M. Vasseur (Genset, Paris, France) described how their company is building a database of the 5'-regulatory sequences of selected human genes. The database contains about 25,000 DNA sequences and is growing rapidly using the company's highly developed sequencing capabilities. Vasseur believes that the database will prove to be very useful in identifying nuclear factors that are appropriate for drug discovery. Unfortunately, some interesting speakers were unable to attend because of the snowstorm that paralyzed the east coast of the USA. Dr G.Z. Feuerstein (Smith-Kline Beecham, King of Prussia, PA, USA) was expected to explain how his company are using differential display RT-PCR technology to identify genes that are upregulated in stroke, restenosis and renal failure; and Dr P.J. Dillon was to report on how Human Genome Sciences Inc. (Rockville, MA, USA) have already identified more than 100 different therapeutic protein candidates from sequence information.

The final area of major significance at the symposium was the use of genetically engineered animals to identify novel functions and potential targets for biomolecules. Dr S. Lira (Bristol-Myers Squibb Pharmaceutical Institute, Princeton, NJ, USA) described how 'rational animal design' can be of enormous benefit in understanding the role of particular genes in the inflammatory response. Lira described studies in which the chemokine KC, which is a homologue of the cytokine IL-8, and monocyte chemoattractant protein-1 (MCP-1) were expressed *in vivo* in mice to determine their roles in inflammatory disease. When he 'designed' a mouse that expressed KC in the thymus, the gland was heavily infiltrated with neutrophils, but there was no inflammation. Lira concluded that IL-8 alone was insufficient to trigger an inflammatory response, although it is a chemotactic factor for neutrophils. When MCP-1, a chemokine with a previously unknown function *in vivo* was expressed in various tissues, it triggered an influx of monocytes and macrophages. According to Lira, rationally designed animals are highly useful in identifying the function of such molecules, to validate a particular molecule as a target and to serve as a tertiary animal model for drug development.

Dr M. Hanks (Procter & Gamble Pharmaceuticals, Ross, OH, USA) described new technologies that allow 'gene knock-in' or incorporation based on gene targeting in embryonic stem cells to replace one gene with another. This enables insertion of the gene into an appropriate locus with a promoter that will allow it to have the desired or physiological relevant distribution of expression. The usefulness of 'knock-in' technology is that the normal gene of an animal can now be replaced with the defective gene that causes an illness. Such animals will be invaluable as models for testing the usefulness of new therapeutics.

Robert W. Wallace

NIH patent profile

A recent report by the intellectual property consultant Peter Steele [*Exp. Opin. Ther. Patents* (1996) 6(2), 117–128] profiles National Institutes of Health (NIH) patenting activity between 1992 and 1995 and includes information on the most important collaborative projects between NIH, other academic centres and the pharmaceutical industry. The NIH is a collective name that applies to more than 20 specialized healthcare research institutions in the USA, and the development and licensing activities of these organizations are centralized in the Office of Technology Transfer.

The driving force behind the report is the remarkably high ranking of NIH in the pharmaceutical R&D league of products in development. NIH occupied sixth position at the end of 1994, with 54 products of its own and 37 in development and fell to ninth position at the end of 1995, but with 58 and 37 products, respectively. The only comparable organization in the top-fifty ranking is the British Technology Group, which now occupies 26th position. The report shows that patenting activity has focused, in particular, on the anticancer and anti-infective therapeutic categories. In each year from 1992 to 1995 inclusive, these have topped the table of NIH patent categories, with 106 (anti-infectives) and 90 (anticancer) patents out of a total of 406 patents published during this period. It is interesting to note a significant number of patents in the antiparasitic category; not a priority for most commercial organizations.

In the four years studied, NIH engaged in joint patenting activities with 25 companies, 12 universities and nine other institutions. Almost all work supporting these patents was performed in the USA, with external collaborations chiefly focusing on biotechnology.

Since 1989, an average of 147 NIH patents have been published each year, of which 83% are 'pharmaceutical'. Overall, and in line with general trends in the industry, pharmaceutical patenting activity has declined during the 1990s. In real terms, overall NIH patenting now stands at 83% of the 1989 level, and pharmaceutical patenting has declined even further in this period (69%).

The full article, *National Institutes of Health: analysis of patenting 1992–1995*, deals with the level of patenting, names used, subjects patented, inventors, patenting policy and includes a final summary. The information is well supported by tabular data. *Expert Opinion on Therapeutic Patents* is published by Ashley Publications, 1st Floor The Library, 1 Shepherds Hill, Highgate, London, UK N6 5QJ. tel: +44 181 347 5030, fax: +44 181 347 5040, www: http://biomednet.com/ashley/ashley.htm

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