Chiral Europe '95

International scientists gathered at *Chiral Europe '95*, held in London in late September, to hear the very latest developments in the field of chiral technology. A wide range of speakers from industry and academia discussed the very latest advances in the production of new chiral compounds and in the 'scale up' of important syntheses to industrial production scale.

A strong theme was the increasingly important role of biological enzymes in the production of chiral intermediates. The value of lipases has been acknowledged for some time, but it is increasingly apparent that nature has supplied many similar enzymes that can prove invaluable in overcoming complex problems in chemical synthesis. Dr D.R. Dodds (Schering-Plough Research Institute, Union, NJ, USA) described the benefits of systematic screening of the hundreds of known enzymes, and Dr A.R.StG. Bowen (Celgene Corporation, Warren, NJ, USA) demonstrated how manipulation of the DNA encoding enzymes can change their properties in a controlled manner to achieve a required activity.

Enzyme stability in large-scale biotransformations is a recognized problem. Two very different approaches to overcome stability problems were discussed. The first strategy, described by Dr G.N. Sheldrake (The Queens University of Belfast, UK) involves the screening of whole microorganisms for the ability to carry out a particular biotransformation; such approaches overcome the need for complex and expensive enzyme purification. Dr R.A. Holt (Zeneca Bioproducts, Billingham, UK) highlighted the benefit of using whole organisms, which enables the *in vivo* regeneration of expensive cofactors, such as nicotinamides, that may be involved in the biotransformation. The second strategy, outlined by Dr A.L. Margolin (Altus Biologics Inc., Cambridge, MA, USA), involves the use of stable cross-linked enzyme crystals; these are reusable, stable in organic solvents and easily disposed of, unlike many inorganic catalysts. The increasing variety of enzymes that can be stabilized in this form suggests considerable potential for this type of technology.

Different chemical approaches to chiral intermediates were discussed, including the impressive work of Dr J. Brown (Oxford University, UK) on catalytic asymmetric addition to alkenes. The problem of separating chiral compounds on a large scale was addressed by Dr E. Küsters (Sandoz Pharma, Basel, Switzerland) who provided examples of method development, on a pilot scale, of preparative chromatographic separations. Dr J.N. Kinkel (E. Merck, Darmstadt, Germany) described how the new technique of simulated moving-bed chromatography provides a useful tool in the large-scale separation of enantiomers. Other presenters discussed the latest developments in the field of chiral stationary phases, including the application of modified cellulose and amylose materials (Dr K. Tachibana, Chiral Technologies Inc., Exton, PA, USA) and immobilized α1-acid glycoprotein and cellobiohydrolase as chiral selectors (Prof. J. Hermansson, ChromTech AB, Hägersten, Sweden).

Chiral Europe '95 delivered presentations of a high standard and provided an opportunity for attendees to exchange new and innovative ideas in the fields of chiral synthesis and separations. *Chiral Europe '96* will be held next autumn; details are available from Spring Innovations Ltd, 185A Moss Lane, Bramhall, Stockport, UK SK7 1BA. tel: +44 (0)161 440 0082.

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ISLAR '95 'More for less'

There was a record attendance of some 500 scientists at the 13th International Symposium on Laboratory Automation and Robotics (*ISLAR '95*), held in Boston, USA, last October. In contrast, there were 33 attendees at the inaugural meeting. This year, a considerable portion of the program was dedicated to applications in drug discovery, and included oral presentations, posters and a discussion group.

Speakers addressed both technical issues and the philosophy and strategy behind the adoption of such new systems, and the recurrent theme was the pressure to achieve 'more for less'. In the opening plenary session, Dr P.B. Fernandes (Bristol-Myers Squibb, Princeton, NJ, USA) spoke on the new face of drug discovery in the light of rapid technological advances and changing external pressures. She highlighted the enabling contributions of biotechnology and genomics to high-throughput screening in drug discovery and emphasized the urgency of unlocking the great diversity of molecules, both natural and synthetic, available for new lead generation. Applications for automation continue to grow, and some of the repetitive tasks in molecular biology, such as colony picking, purification of DNA or RNA, centrifugation and incubation, and some aspects of isolation chemistry are candidates for future consideration.

Pioneer awards

Each year, awards are made to those who are considered to be 'Pioneers in Laboratory Automation' through the development of an important new application or the design of a novel solution to a technical problem. There were nine winners this year: Dr M.E. Dodds (Environmental Research Institute of Michigan, Ann Arbor, MI, USA), Dr W. Haller (Ortho McNeil, Raritan, NJ, USA), Dr S.H. DeWitt (Parke-Davis, Ann Arbor, MI, USA), Dr S.W. Swieck, Jr (Bristol-Myers Squibb, Syracuse, NY, USA), Drs D.J. Hook, J. Guss and J. Yacobucci (Bristol-Myers Squibb, Wallingford, CT, USA), Dr M. Rountree (Alcon Laboratories, Fort Worth, TX, USA) and Dr J. Sigeura (Applied Biosystems, Foster City, CA, USA).

High-throughput screening

Speakers outlined their experiences with new and experimental systems for high-throughput screening (HTS) and reflected a common theme; namely, that the current technological and commercial environment ensures that companies will process more compounds through more assays with minimal growth of staffing. Dr J. Babiak (Wyeth-Ayerst, Princeton, NJ, USA) characterized the old approaches to drug discovery in the following ways:

- Serendipity (luck)
- Random screening (dumb luck)
- Copying someone else's patent (bad luck)
- Copying someone else's drug (very bad luck)

His message was that modern technologies had returned to the second category, albeit in different clothing. He described a system for compound weighing and distribution which incorporates a robotic arm (HP ORCA) on a 3 m track, Tecan 8051 and 5051 diluters, two barcode printers/applicators (Zebra 105), three barcode readers (Symbol), two syringe pumps (Hamilton) and a Mettler AT200 balance. Custom components included a microtiter plate elevator, a vial rack elevator and microtiter plate sealer (Sagian). Communication is maintained with a Sagian IID, the robot is controlled with HP-MDS, and data management uses Microsoft Access. This single system enables weighing, dilution, dissolution and distribution of compounds to microtiter plates with minimal human involvement. The system applies barcodes to, and tares, vials into which compounds are automatically added at a remote log-in station. Automatic steps then accommodate weighing, solvent addition and transfer to 'mother' and 'daughter' plates. Dr Babiak claims that this flexible system has substantially increased capacity for compound handling before screening, without any increase in staffing, and predicts that it will have an enormous impact on the Wyeth-Ayerst screening program.

Dr Sheila Hobbs DeWitt receives a 'Pioneer' award for her contribution to the development of the integrated package of technologies for solid-phase organic synthesis in use at Parke-Davis (Diversomer™ Technology).

Team building

Dr D.J. Hook (Bristol-Myers Squibb, Wallingford, CT, USA), put the hardware to one side to discuss team building and leadership. Team leaders in HTS face pressure to screen more, with a faster turnaround of library decks. Continuous operation is now mandatory for an effective program. He characterized the constraints on HTS programs as follows: chemical library diversity (proprietary libraries being constrained by the focus of past programs), cost of assays, speed and specificity of assays, numbers of compounds to screen, and selection of compounds for screening (for example, natural products vs new synthetic libraries).

According to Dr Hook, the key to building a good team lies in ensuring that members 'buy in' to the program and its new technology. Planning for the future is also important; for example, predicting the numbers of compounds to be screened in the future, ensuring adequate reagent supplies (briefing of support teams) and ensuring the investment in infrastructure (acceptance by management of forecast requirements). He concluded by summarizing the requirements for managing a successful program in a changing environment as follows:

- Commitment from all parties
- Vision
- Wide skills base ('in house' or 'buy in')
- Management support
- Informed support services
- Ongoing training
- Acceptance of change

Cost–benefit issues

Dr J.J. Zieman described a spreadsheet used at the Dow Chemical Company (Midland, MI, USA) to enable cost-benefit decisions to be made as to which systems to automate. The spreadsheet uses the 5-year zero net present value (NPV) model to evaluate potential automation systems. The model predicts, in simple terms, how much money one would need to put in a bank to equal the value of a project after a specified time (5 years in this model). Dr Zieman then outlined several case histories in chemical synthesis and analysis where the spreadsheet had been successfully applied. In certain cases, even when the 5-year NPV is negative, there may be overriding pressures for automation, such as the avoidance of contact with toxic materials by laboratory workers.

Combinatorial chemistry

Dr J. Cargill (Ontogen Corporation, Carlsbad, CA, USA) reviewed the OntoBLOCK and OntoCODE proprietary systems for high-speed synthesis on nonpeptide small organic molecule libraries. The OntoBLOCK system provides for the introduction and removal of reagents, agitation, an inert atmosphere, temperature and pressure control and vacuum drying. Reaction blocks incorporating 96 reaction vessels are processed at task-specific workstations, and compounds are cleaved from vessels into the individual wells of 96-well plates compatible with HTS systems. Client/server database software for inventory control, experimental design, instrumentation control, HTS data analysis and SAR studies is written in Visual Basic and Oracle7. The OntoCODE system involves the use of a radio-frequency programmable microchip to replace the need for chemical tagging;

miniature reaction capsules are electronically coded with a solid-state radio-frequency tag, which is electronically read after each of a sequence of split-and-recombine synthetic steps to maintain a reaction histogram. Combinatorial libraries are characterized using a proprietary automated mass spectroscopy system to produce spectra for all compounds.

Discussion group

The drug discovery discussion group, chaired by Dr D. France (Sandoz, E. Hannover, NJ, USA), was well attended. The seemingly eternal debate regarding the future of the 96-well plate as the standard format for HTS resurfaced. Although it was felt that the 96-well format would continue to hold off the challenge from 384-well or other formats for some time, the big leap may come with a transition to unformatted 'plates' – perhaps even incorporating ink-jet technologies. In discussing detection technologies, some panel members felt that the scintillation proximity assay had not lived up to expectations and can yield unacceptably high 'hit' rates, although this experience was far from universal among the attendees. Interest was expressed in non-radioactive assays, such as dye-based systems, as promising future options.

Discussions on data handling and cell-based assays followed, and there was a final discussion on the manufacture of the 96-well plate because variable footprints remain a problem. The Society for Biomolecular Screening is attempting to resolve this through the development of new standards.

ISLAR '96

ISLAR is greeted with increasing enthusiasm each year, and the ongoing rapid technological advances and the importance for companies to adopt the correct strategies, both in terms of the cost and the success of discovery programs, will ensure that this continues. ISLAR '96 will take place in Boston on 20–23 October; full details are available from Christine O'Neil, Zymark Corporation, Zymark Center, Hopkinton, MA 10748, USA. tel: +1 508 435 9500 (ext 2224), fax: +1 508 435 3439.

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G protein-coupled receptors by Tiina P. Iismaa, Trevor J. Biden and John Shine, Springer-Verlag 1995. £67.00 (181 pages; hard cover). ISBN 1 57059 058 3

This book describes in five chapters many different aspects of this superfamily of membrane proteins, which encompasses hundreds of receptors for many chemical messengers. G protein-coupled receptors are structurally and functionally characterized and compared to other cell-surface receptors. Three subfamilies are distinguished, and the most successful techniques that have been used to determine the sequences of new members are shown. Special attention is given to the gene structure, the phylogenetic tree and the chromosomal localization of the receptors.

In the second chapter, *Signalling through G protein-coupled receptors*, the biochemical cycle and mammalian G-protein subunits and subtypes are characterized. Effector systems are described and correlated with the G protein α-subtypes, as are receptor regulation, desensitization, specificity of effector systems and receptor cross-talk. The structural determinants of receptor function, including ligand binding and signal transduction, are the main topics of the third chapter. The theories of the binding of agonists and antagonists are discussed on a molecular level according to the different subtype of receptor families. The role of post-translational modification and the mechanism of G-protein coupling, receptor sequestration and downregulation are explained.

Pathology and therapeutic strategies of G protein-coupled receptors are important topics addressed in the penultimate chapter. Some known receptor mutations of G protein-coupled receptors are summarized, and systems that are known to be involved in diseases but have not yet been characterized on a molecular level are presented. Receptor subtype-specific agents and novel therapeutic strategies are also included. In the final chapter, prospects for this protein family are discussed.

The book provides an excellent overview of this very important topic. Modern techniques and very recent results are included, and the reference sections of each chapter include full titles and relate to very recent work. The figures, some in colour, are very helpful to the reader.

A section is included in which the authors explore some questions and topics of current debate and research, such as the physiological significance of subtypes and diversification and integration of signalling pathways. Hence, the book summarizes recent research results and offers perspectives on future directions within the field.

The book is recommended not only to senior students and research fellows of biochemistry, medicine, pharmacy and pharmacology, but also to senior researchers from related fields who need to keep up to date with the projects of their colleagues or collaborators.

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