structure within a web page that can then be manipulated and modified by the viewer. This software is currently in prototype for Mac, PC and SGI machines. A commercial version of this software, called Chemscape Chime Pro, is available from MDL and allows rendering of 2D and 3D chemical and biological structures within a Web browser. This is used in conjunction with the Chemscape Server which provides full ISIS (their proprietary integrated chemical database search) structure and text search capabilities within a Web browser.

'The 3D-world of VRML...is just now coming into its prime'

An interesting tool called WebLab Viewer was recently released by Molecular Simulations, Inc. (see Box 1). Upon filling in a tracking form, users can freely download a molecule-viewing application program that opens several popular file formats, including PDB (protein database). Interestingly, this program will convert a file into VRML format from one of the other 3D formats it supports. Using a simple macro the user could convert a whole drug library into a 3D world, viewable with a web browser. This and many other programs can be used in a less elegant fashion as 'helper applications' that work in conjunction with WWW browsers.

A comprehensive list of molecular modeling software can be found on the WWW (see Box 1).

Agreed, *for now*, some of the software available may still be a little fragile or difficult to use productively for day-to-day applications. Nevertheless, the 3D world of VRML has been thoroughly underexploited by scientists and it will soon be coming into its prime thanks to recent advances in WWW browsers.

Martin Leach

Automated discovery – faster and cheaper, but better?

About 600 scientists and automation specialists attended the *International Symposium on Laboratory Automation and Robotics (ISLAR '96)* in Boston in late October, which was opened by Dr Walter Moos (Figure 1). Dr Moos joined Chiron Technologies, a division of Chiron Corporation (Emeryville, CA, USA), as Vice President of R&D in 1991 following his pioneering work in combinatorial chemistry at Parke-Davis (Ann Arbor, MI, USA). His keynote address highlighted the drug discovery technology advances of the 1990s. He outlined the paradigm shifts in discovery from affinity chromatography and radioligand receptor binding (1970s), through biotechnology and structure-based design (1980s) to combinatorial chemistry and molecular diversity (CCMD) in the 1990s. Into the next millennium, nucleic acid therapies and the delivery and targeting of natural and unnatural molecules will lead the way.

Using illustrations from the evolution of Chiron's discovery technologies, Moos showed how CCMD had enabled drug discovery to proceed 'faster and cheaper' against a difficult background of increasing costs and regulatory controls for the industry. But is it 'better'? Moos says that only time will tell. Nevertheless, the application of CCMD in discovery is already creating bottlenecks in exploratory development; Moos suggests that this has increasingly forced many laboratories to look toward the application of combinatorial principles and automation in preclinical development.

One interesting statistic to emerge from this keynote presentation was that, on the same basis that the 20 standard amino acids could yield 8,000 tripeptides, the theoretical number of all possible organic compounds has been calculated to be 10^{250}, which apparently represents many more orders of magnitude than there are particles in the universe.

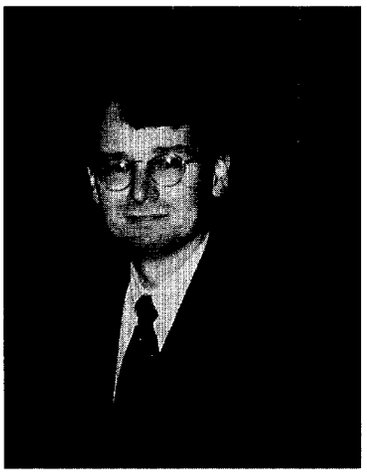

Figure 1. *Dr Walter Moos, Vice President of R&D, Chiron Technologies, gave the opening address at* ISLAR '96.

Application of 384-well plates

The main reason that scientists and automation specialists attend this meeting is to share experiences, both good and bad, and outline how they have reached solutions to their discovery problems, in terms of strategy, technology and logistics. Some companies offered 'case histories' of the theory and practice behind their approach to automated systems for HTS and combinatorial chemistry. One that attracted particular attention was that of the Glaxo Wellcome group (Stevenage, UK) represented by Dr Martyn Banks. Dr Banks argues that HTS is now entering the production era, with 'screening factories' incorporating integrated automated solid and liquid compound stores and automated combinatorial synthesis.

He described the upgrading of their high-throughput screening automation from the existing system, which they term 'R1' (supplied by Robocon, Vienna, Austria), to a new 'R2' system, which was developed in collaboration with vendors Thurnall (Manchester, UK). The group selected this particular supplier through putting out to tender a carefully prepared user-specification document that identified key requirements associated with technical, quality assurance and project management issues. Thurnall are developers of automation across a range of industrial applications, including the nuclear industry. According to Dr Banks, 'with professional integrators around, it is now possible to build and install large and reliable turnkey systems without a huge engineering and IT resource'.

The new system is designed to meet Glaxo Wellcome's needs in their 'blitz' approach to screening, and is designed to run continuously, with fluid handling systems and detection equipment fully compatible with the 384-well microtitre plate format but back-compatible with the standard 96-well plate. The R2 system consists of two robot cells – 'hot' and 'cold' (Box 1) – and incorporates Thurnall's SPRINT software.

In addition to the benefits of increased throughput and lower costs for disposables, the group hope that by opting for the 384-well format, other HTS groups will be encouraged to adopt this platform, which in turn will drive greater involvement by suppliers in supplying the associated peripherals and disposables. Furthermore, advances in liquid-handling and imaging devices are enabling this group to investigate and actively develop 864-well technologies, and they have even prototyped a 3,456-well plate.

Liquid handling for automated combinatorial synthesis

An interesting example of how automation solutions can improve laboratory performance was the presentation of Dr Bill Neil (Bristol-Myers Squibb, Princeton, NJ, USA) describing modifications to a Hamilton Microlab 2200 liquid handler controlled using ECLIPSE v4.0 running on a Hewlett Packard Vectra 486 with 32 Mb RAM. The aim was to develop a dedicated handler for organic synthesis that could be used by a large and heterogeneous group of scientists. The team incorporated a user-friendly software interface with built-in calibration and error recovery routines, a flexible worktable with convenient carriers for different racks, and custom rack design for reagent addition. The result was a robotic handler that could be used by a range of individuals with different requirements for liquid handling, including product distribution and reagent delivery for both solid- and liquid-phase applications. The team will continue to make modifications as new needs arise and Dr Neil stressed the types of adaptation described could be applied to other liquid handlers.

Focus on core competencies

Several speakers addressed the logistic and strategic management issues associated with automated HTS. Dr Mark Lister (Sphinx Pharmaceuticals, a Division of Eli Lilly, Durham, NC, USA) described how a

Box 1. Instrumentation comprising Glaxo Wellcome's 384-well compatible R2 system. The system includes two robotic cells designed for isotopic and luminescent assays ('hot' cell) and colourimetric and fluorescence-based assays ('cold' cell)[a]

'Hot' cell

Genesis RSP 150/8 (Tecan, Reading, UK)
TopCounts (Canberra Packard, Pangbourne, UK)

Incubator (Carbolite, Sheffield, UK)
Plate sealer (Sagian, Indianapolis, IN, USA)
Plate washer (96PW; Tecan)
Lid-handling unit
Plate shaker (CAT20; Ismatec, Weston Super Mare, UK)
Bulk reagent dispenser (Hook and Tucker, New Addington, UK)
Plate turntable
Tip-rack carousel
Plate hotel
Bar code readers (DS41; Datalogic, Milton Keynes, UK)
Lid disposal unit
Tip-rack system
Plate discard system

'Cold' cell

Genesis RSP 150/8 (Tecan)
Fluorimeter (Fluorostar; SLT, Research Triangle Park, NC, USA)
Incubator (Carbolite)
Colourimeter (Spectra Image; SLT)
Plate washer (96PW; Tecan)
Lid-handling unit
Plate shaker (CAT20; Ismatec)
Bulk reagent dispenser (Hook and Tucker)
Plate turntable
Tip-rack carousel
Plate hotel
Bar code readers (DS41; Datalogic)
Lid disposal unit
Tip-rack system
Plate discard system

[a]All components supplied by Thurnall plc (Manchester, UK) except where otherwise indicated.

centralized screening group can manage screening programmes from concept to actual operation according to the α–δ paradigm that the Sphinx team have adopted (Figure 2). Key support elements for the screening team include:

- statistician to provide consultation and training in data analysis and experimental design;
- IT expertise to handle and render accessible the mass of data generated;
- support from the Biological Science group, who perform the protein expression, cell culture, molecular biology, etc.; and
- support from the compound preparation and engineering teams.

He also identified some of the core skills required within the screening team itself, notably:

- strong background in biology to enable them to perform a diversity of assays;
- operational and troubleshooting skills in automation and robotics; and
- enthusiasm to become team players: a most difficult aspect to teach.

Other staff within Eli Lilly can monitor progress of the group through access to an intranet web page, which includes details of screening programmes and targets together with the explanations of the systems and methodologies available.

Screening infrastructure

A continuing theme of the meeting was the importance of adopting an effective and appropriate infrastructure. Dr John Babiak (Wyeth Ayerst, Princeton, NJ, USA) focused on four key elements that have determined his group's infrastructure, namely sample sourcing, screen design, automation hardware and data management.

Streamlining measures for sample preparation can compromise the integrity of samples, and this risk must be balanced against the risk of sample transfer becoming a bottleneck. Bar coding (readable by man and machine) requires considerable upstream planning but ensures that sample tracking is kept simple. Dr Babiak argued that it may be necessary to lose flexibility in automated systems in order to maximize throughput. By optimizing hardware configurations for the most commonly used assays, better throughput overall is achieved. He emphasized the value of collaborating with scientist 'customers' at as early a stage as possible; although time may be wasted on projects that may never reach operational screening, the mutual exchange of information regarding core competencies will facilitate future projects.

There is often a gulf between the ideal and the reality of performance of robotic systems, and many companies can recall dramatic failings. Causes may lie in unrealistic expectations or poor software and hardware reliability. By exhaustively testing workstations before integration into a large system and documenting faults and failures, operators can identify how suitable the instrument is for use, what modifications might be necessary and whether to use it at all.

Dr Babiak highlighted three principles for success: information-intensive but standardized files should be created at the earliest possible stage; it is advisable to perform basic calculations immediately after plate processing if possible, as a check against technical errors during a screening run; and it should be remembered that there are different types of data and staff with differing data requirements, hence the most useful system will contain multiple linked databases that maintain data in the optimum form for a particular operator.

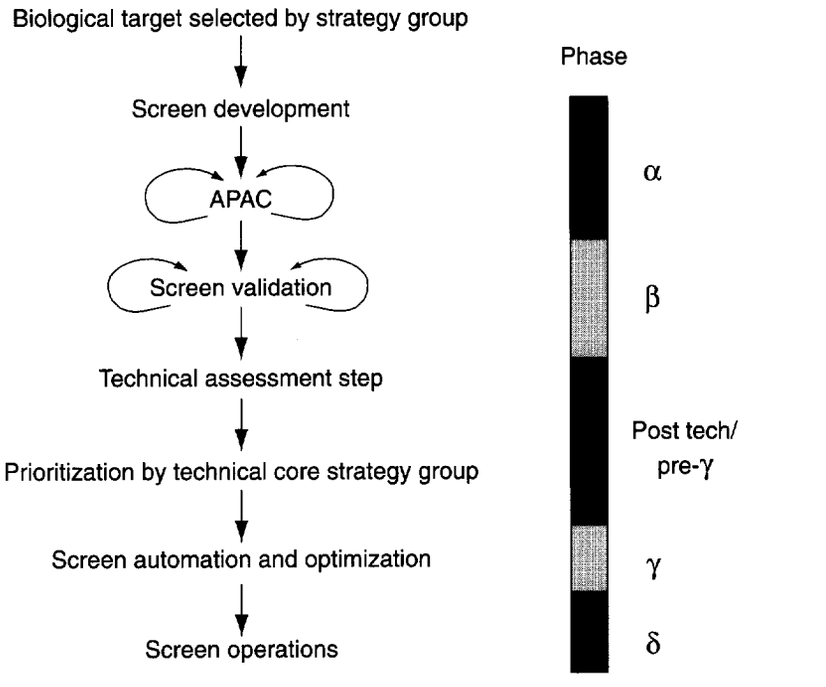

Figure 2. *Sphinx's screen approval paradigm. At each stage the screen must meet assessment criteria until the δ phase is reached when the screen becomes operational. APAC, Assay Protocol Advisory Committee.*

The Japanese experience

Dr Nihira (Nippon Roche, Kanagawa, Japan) described how his group had approached their entry into this field. The Nippon-Roche Screening Group was established as a natural-product screening centre in 1987, but geared up for HTS only in 1995. They identified data handling and analysis, sample management and

logistics, and robotics/automation as the key issues from which to derive their HTS infrastructure, and in each of these areas, support teams were set up.

The group were able to report dramatic increases in throughput after one year, although there were areas where automation did not offer the complete solution. Early experience determined that the SPA-, ELISA- and photometry-based screens could readily be adapted to automated formats. Other assays, such as those based on electrophoresis or morphological change required manual operation, although this could be enhanced through the use of semi-automated instrumentation, such as 96-channel pipetters. The extent to which assays are now automated depends on assay type and ranges from zero to 100%, but overall improvements in productivity of up to fivefold have been observed, with a consequent increase in output of lead compounds. One problem, however, has been that screening biologists have been slow to 'buy in' to new systems and working practices.

Summary

The above is, by necessity, a very selective discussion of presentations; there were many interesting talks, lively panel sessions and workshops in the discovery field and also an equal number of (parallel) sessions for those interested in the automation of procedures associated with testing and analysis in pharmaceutical development. It was also possible to visit the headquarters of the organizers, Zymark, to view some examples of their own products in action. *ISLAR '97* will take place in Boston on 19–22 October; full details of the meeting and the Proceedings of *ISLAR '96* 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, e-mail: islar@islar.com, web site: http://www.islar.com.

David Hughes

Advanced technologies for information extraction

IBC's second European forum for IT specialists and drug discovery scientists was held in London in November. Entitled *Advanced Technologies for Information Extraction: Analysis of Complex Data Sets to Aid Drug Discovery*, the two-day meeting was a largely stimulating attempt to approach the problem of extraction, handling and optimizing the use of information from three angles:

- development of computing solutions, specifically aimed at the pharmaceutical industry;
- existing techniques employed by the pharmaceutical companies themselves; and
- commercial and academic uses of advanced technologies outside the pharmaceutical industry, and their possible application in drug discovery.

Representatives from these three areas gave examples of the application of emerging techniques that combine computing methods, such as neuronetworking and fuzzy logic ('neurofuzzy' technology), with expert systems to quiz very large databases, achieving the object of obtaining useful and easily visualized information. These can provide a company with the competitive edge, be it in lead discovery, patenting strategy or process control.

It's easy if you try

Dr William Bains (Merlin Ventures, London, UK) opened the proceedings by expounding his view that the 'problem' faced by companies in making bioinformatics a high-value component of their drug discovery programmes is not one of too much data, or acquiring the means with which to visualize and analyse it, but essentially one of 'science and scientists'. Because of the increase in automation, the data generated by established drug discovery techniques is increasing at an exponential rate. Newer technologies, such as genomics and combinatorial chemistry, have created a new class of data with its own inherent problems, and emerging and future technologies, such as proteome, functional genetics and ultra-HTS, will generate gigabytes of data per week.

Engineering approach

Dr Bains estimates that, by the year 2016, companies will be searching public-domain databases of the order of 6.5 terabytes for information, but points out that data sets of this size, and larger, are already being dealt with productively by organizations such as the super/hypermarket chain J. Sainsbury's (transaction database) and the Hubble space telescope team (already a 25 terabyte data set), using robust data mining and analysis software. Dr Bains also argues that browsing and sifting this information should not be a problem; current and developing web-based tools offer sophisticated and interactive interfaces with such databases, and they are becoming increasingly interoperable and powerful. He proposes that, for data-rich subjects, biological research must adopt an engineering approach to bioinformatics, instead of remaining 'largely a cottage industry, with data generation being carried out in an intellectually idiosyncratic and geographically distributed mode' (see Ref. 1).

Pharmaceutical companies must look at analogous data problems outside their industry for robust, proven solutions, and apply these in a rational way to their bioinformatics programmes.

