Drug Discovery Technologies '99 conference

The Drug Discovery Technologies '99 conference was held on 26–28 April 1999 in Amsterdam and was the third such event produced by IBC in Europe attended by over 200 delegates and 26 exhibitors. The lecture programme included four workshops given by Packard Instrument (Meriden, CT, USA) ScreenTec (Leiden, The Netherlands), Biotage (Hertford, UK) and Molecular Devices (Sunnyvale, CA, USA). These workshops were invaluable for those interested in gaining more in-depth knowledge of a particular technology and provided a forum for feedback from the customer to the vendor. The administrative side of the conference was of a high standard and there were plenty of opportunities for networking.

The content of the conference reflected the ever-increasing breadth of new technologies and strategies that are currently being implemented within the pharmaceutical industry. In the sessions on strategy, little new information was presented and most speakers simply highlighted the high rate and high cost of the current attrition rate of compounds which enter clinical development but fail to survive to launch. Strategies to reduce the attrition rate were generally centred on developing a better interface between drug discovery and development, by developing more high-throughput screens (HTS) for pharmacokinetic, absorption, protein binding and toxicity factors and implementing these screens earlier on in the discovery process. John Major (AstraZeneca, Macclesfield, UK), in his presentation concerning the current status of drug discovery, warned against following a strategy driven by numbers and by the technological abilities of the industry. Additional key strategies included the outsourcing of some research and development (R&D) functions, and Peter Luke (Pfizer, Sandwich, UK) indicated that Pfizer now spend almost 25% of their R&D budget on external collaborations.

An excellent presentation from Donald Fitzgerald (Materia Medica, Meer, UK) identified various metrics and models with which to determine the effectiveness of changes to the R&D process. One of these models suggested that the effect of doubling lead-generation success rate and halving the lead-optimizing cycle time would produce an overall doubling of the discovery output for the same given input. Other scenarios, such as increasing the number of compounds available, might lead to a significant increase in the resources required to achieve the same output. The most significant, and perhaps the most difficult, factor to monitor or modify is the considerable impact of the company culture on the effectiveness of company strategies, i.e. people and their behaviours, and this issue was reinforced when identifying the reasons for the failure of compounds. Although compounds often fail due to a lack of efficacy, inappropriate kinetics or toxicity, a significant proportion (20–30%) of compounds were identified as failing for strategic reasons.

In the sessions that included presentations on ultra-high-throughput screening (UHTS), combinatorial chemistry and early absorption–distribution–metabolism–excretion studies, there was little new information, as the industry appears to be concentrating on the active phase of implementation of the known technologies. Most screening programmes are still using the 96-well plate formats, although many are now starting to use the 384-well plate formats and there is also much activity in the 1536-well plate format. Meanwhile, miniaturization continues to be developed down to the nanolitre scale and new advances in detection technologies, mainly based on fluorescent techniques, were being advertised. These advances perhaps are incremental, but indicate that many of the early technical problems seen with these instrumental technologies are being overcome. Igen International (Gaithersburg, MD, USA), for example, has now developed its electrochemiluminescence technology into 96- and 384-well plate format. Automation in the combinatorial chemistry area continues to increase and some companies (Stephan Henke, HMR, Frankfurt, Germany) are successfully developing a 24-h combinatorial chemistry approach. There is no doubt that the potential for any company to create a significant HTS–combinatorial chemistry drug discovery programme is easily within reach. It would, however, have been helpful to have had presentations concerning the application of these technologies, in terms of discovery output rather than merely numbers.

Mass spectrometry (MS), in its various forms, is beginning to make an appearance as a useful tool in many areas of the drug discovery process. Several presentations indicated the usefulness of this 'old' technology. Jan van der Greef (TNO Pharma, Amsterdam, The Netherlands) presented work combining MS with sophisticated spectra analysis (multivariate analysis) for the identification of patient-profiles from MS measurement of urine samples.

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Patients could be identified and differentiated from each other from the spectra obtained in various disease states and in the presence of drug therapy. Hanno Langen (Hoffmann-La Roche, Basel, Switzerland) suggested that matrix-assisted laser desorption ionization with time-of-flight (MALDI-TOF) MS in conjunction with custom software could be used in proteomics to perform automated matching of peptide fingerprints. This approach could bypass the need for the error-prone 2D-Gel spot-matching techniques. Finally, ScreenTec has developed instrumentation for the direct coupling of liquid chromatography to biological assays, such that only those samples with biological activity are analyzed in detail. This approach can be readily coupled to MS or nuclear magnetic resonance (NMR) for the analysis of mixtures, natural products and combinatorial chemistry mixtures, and trace analysis of proteins, peptides and drugs in biological fluids.

Terms being increasingly applied to the area of screening are high-resolution screening (ScreenTec), high-content screening (Cellomics, Pittsburg, PA, USA) and high-information content screening (Evotec BioSystems, Hamburg, Germany). The idea of these different screening technologies is that a significant quantity of information can be generated, rather than simply a yes or no answer. To capitalize on this information will require a change in the way data and information is analyzed. It would therefore be prudent to wait to assess the supporting informatics and the added value this information gives to drug discovery.

The conference also had some excellent presentations reviewing the current status of genomics and proteomics. Again, although not entirely new, most speakers focussed on the analysis of single nucleotide polymorphisms (SNPs). However, as this area now entertains whole conferences, this report will not review these presentations any further. There were also several presentations that highlighted the potential of pharmacogenomics in clinical applications, but with few 'real-life' examples that are not already known.

Michael Sibler (Pfizer, Groton, US) announced the formation, in late April, of the TSC (The SNP Consortium). This represents a significant step in combining the skills of various pharmaceutical companies (ten) and academic institutions (six) to identify 300,000 evenly spaced SNPs, map 150,000 evenly spaced SNPs and maximize the public accessibility of these genome-wide SNPs, all within two years. Sibler was also bold enough to forecast the future use of pharmacogenomics. He predicted that, in the next couple of years, submissions to the US Food and Drug Administration (FDA), or a similar regulatory authority, would be required to include pharmacogenomic data and related diagnostic procedures, whilst in the next five years, virtually all submissions will have to include such data. Furthermore, as a result of the sequencing of the complete genome, SNP maps, clinical experience, etc., the possibility to identify and even design potential drugs for use in defined subsets or individual patients will become a reality in the new decade. The obvious consequence of this will be a substantial reduction in current attrition rate, although this might be a rather over-optimistic viewpoint. The importance of public awareness, public education and ethical issues surrounding the development of such approaches should not be underestimated as a rate-determining step.

One presentation in the Functional Genomics session, given by Martin Hrabe de Angelis (GSF Research Centre, Munich, Germany) deserves special mention, as he discussed the mouse as an animal model to determine gene function, which is an unusual topic to include in a conference of this type. The main theme was that the study of the phenotype could reveal unexpected gene function. The selection of the phenotype in mouse mutation has identified many gene functions with similarities to human diseases. Various new mutants were described including a deaf mouse, curly tail mouse (spina bifida), long nails (correlating to changes in chromosome 11 in the mouse and 17 in humans) and the kinky tail mouse as a model for skeletal defects. In an eight-year programme, this group expects to have generated 1000 mutants for study. The importance of this work, based initially at least on phenotype parameters cannot be underestimated, as it is the phenotype (i.e. the patient) that will be treated with the drugs.

Finally, there were presentations concerning the paramount importance of the underpinning technology for the effective and efficient deployment of all the technologies, i.e. information technology (IT). Most presenters identified IT as being key to extracting the knowledge from all the data and information being generated. As such, it was good to hear the presentation by David Neilson (Synthelabo Recherche, Paris, France) on the use of Intranet, browser-based, Java-written, metadata-layer architecture in the rapid development and integration of their corporate-research IT systems. With the help of an external partner, Tripos (St Louis, MO, USA), they were able to transform their existing fragmented systems into a user-friendly information access system in the space of a few months. Although the technology to do this has been available for some time, it was good to hear presentations from companies who have actually done it. Felix Reichel (Bayer AG, Leverkusen, Germany) highlighted the application of data mining and visualization tools. In-house research at Bayer concerning the judicious use of tools from outside the industry combined with Mineset (Silicon Graphics, Mountain View, CA, USA) has enabled Bayer to build systems that can predict primary activity-relationships from screening data. The presentation also showed the

usefulness of decision trees using holographic fingerprints of chemical structures when applied to primary screening data and convincing examples were provided. This technique also required the generation of rules that can be interrogated further for their relevance, and the preparation of the input data, although details of how this was achieved were not given. This presentation indicated that virtual-screening is becoming a reality.

In summary, the conference provided a good overview of the current state-of-the-art drug discovery. Key messages were that:

- The crucial issues in the business are the attrition rate
- Earlier input of pre-clinical parameters will provide better leads earlier
- The technology to mount significant programmes is now available and 'mature'
- Informatics must play a larger role in exploiting the inputs, and pharmacogenomics (possibly based on SNPs) in optimizing the outputs.

Perhaps these conclusions are already well-known, but these conferences serve to bring all the approaches into perspective, enabling companies to benchmark their activities and perhaps to gain more insight into alternatives. Full conference proceedings can be purchased from IBC (UK).

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Enzyme links build better antibiotics

As bacterial resistance becomes more widespread, so the need for structurally and functionally novel antibiotics will increase. Synthetically engineered polyketide synthases (PKSs), which are a group of microbial enzymes that produce drugs such as erythromycin, offer hope for the development of new polyketides to combat bacterial infections. However, one problem is that synthetically engineered PKSs are usually chemically unstable, therefore producing low yields. US researchers have now found a solution to this problem of instability by using specific amino acid-linkers to boost PKS productivity.

Polyketides, from organisms such as actinomycetes, have been isolated and studied for more than a 100 years and have produced some commonly used antibiotics (such as erythromycin, oleandomycin and spiramycin), immunosuppressants (such as rapamycin and FK506), the veterinary antiparasitic, avermectin, and the antifungal drug, candicidin. The discovery of the enzyme systems responsible for their bioconstruction has led to a rejuvenation of the field. Many of the PKSs are multienzyme complexes that can be manipulated to act as 'factories' for the production of new synthetic polyketides.

Genetic manipulation of PKS genes

Novel diverse polyketides can be produced simply by manipulating and rearranging the different enzyme modules within the structure using genetic engineering techniques. Domain inactivation, substitution, or addition of modules by genetic manipulation of the PKS genes, have been used to produce artificial polyketides. Meanwhile, the gene fusion approaches, which have been developed by Peter Leadlay (Cambridge University, UK), Leonard Katz (Abbott Laboratories, Queensborough, UK) and Chaitan Khosla (Departments of Chemical Engineering, Chemistry and Biochemistry, Stanford University, CA, USA, and founding scientist and Chairman of the Scientific Advisory Board of KOSAN Biosciences, Inc., Burlingame, CA, USA) have led to the biosynthesis of diverse synthetic polyketide products. Khosla has highlighted that the manipulations usually result in decreased *in vivo* productivity of the polyketides, the reasons for this being poorly understood. However, suggestions for this reduced productivity include structural instability of the engineered protein, suboptimal chemistry within the altered module, or inefficient processing of the synthetic polyketide intermediates by downstream modules.

Combinatorial biosynthesis of polyketides

Khosla and coworkers, together with David Cane (Brown University, Providence, RI, USA), have spent the past few months trying to overcome this problem. Once these genetically modified PKSs, have been stabilized, they can be used more effectively to produce a diverse range of polyketides, some of which might have useful pharmacological properties, e.g. antibiotic activity.

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