Resecting the neck of the medicine bottle

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IBC's *High Throughput Screening Technologies* conference (27–29 November 2001, London, UK) brought together >100 European and American scientists representing >30 companies and several universities and covered many aspects of screening in pharmaceutical discovery. As compound screening has become miniaturized and thoroughly industrialized, the rate-limiting steps have become the crucial ones of: (1) target validation, (2) capture of data and its conversion to information, and (3) early development, especially the incorporation of good ADME properties.

In the first two days of the conference, popular topics included the use of fluorescence assays and novel systems in cellular and subcellular assays for target validation and lead identification. Innovative approaches to address bottlenecks (2) and (3) were addressed on the third day (not covered by this synopsis). Although new screening technologies were the focus of the conference, other topics ranged from novel synthetic chemistry for making natural product analogs, to *in silico* pharmacokinetics, to directed protein evolution.

Key trends

The first of the three keynote addresses, by Frank Craig, described new assay tools from Amersham Biosciences (Little Chalfont, UK). For example, the capabilities of the LeadSeeker™ system (based upon confocal charged coupled device technology acquired several years ago from Imaging Research; St Catherine's, Canada) are being expanded. The new LeadSeeker, which should become available in mid-2002, will enable assays based on luminescence, time-resolved fluorescence resonance energy transfer (TR-FRET), and fluorescence polarization (FP). Amersham Biosciences can now sub-license green fluorescent protein (GFP) variants, enabling protein translocation assays in intact cells.

Craig described a 'screenotype' (invented by Dabney Johnson of Oak Ridge National Laboratory; Oak Ridge, TN, USA) as any phenotype enabling a screening assay, and noted that screenotypes can generate the biochemical tools needed to validate drug targets. Craig also suggested six future trends: (1) structural proteomics, (2) systematic mapping of signaling networks, (3) enhanced utility of computational models, (4) selection of targets based on knowledge of their 'druggability' and disease relevance, (5) an increased number of new chemical entities (NCEs) produced annually at typical pharmaceutical companies, and (6) pharmacogenomics. These trends were indeed evident at the conference.

The second keynote speaker, Craig Muir of Millennium Pharmaceuticals (Cambridge, MA, USA), described applications of chip-based microfluidics systems, using kinase assays and transcriptional profiling as examples. Muir announced that Millennium and Biacore (Uppsala, Sweden) are developing surface plasmon resonance (SPR) detection in array format. Muir emphasized the crucial importance of high quality data in making project decisions, and noted that rapid provision of early ADME data to chemists continues to be challenging.

The third keynote address was delivered by Kurt Stoeckli of Aventis Pharmaceuticals (Frankfurt, Germany). The pivotal point of Stoeckli's presentation was a quotation from Ernst and Young (London, UK; http://www.ey.com/GLOBAL/gcr.nsf/Zimbabwe/Knowledge__-_generation_within_your_organisation), 'The basis of competition comes always down to the ability to acquire, share, and use information wisely.' Stoeckli discussed how Aventis is using diverse subsets of compound libraries as a screening tool, as well as targeted libraries. (The use of target-biased libraries had also been mentioned by keynote speakers from ArQule and Millennium.) The information to generate such libraries requires robust data generation and capture processes. To this end, a knowledge-driven and quality-oriented scientific culture is crucial for the successful creation of these processes.

Post-genomic technologies

Cell-based assays

Several speakers addressed the challenge of 'winnowing the wheat from the chaff' in the 'haystacks' of post-genomics targets. John Harrington of Athersys (Cleveland, OH, USA) told participants that his company has developed proprietary vectors to enable random activation of gene expression (RAGE) from endogenous genes in many cell types. These vectors enable cell lines to be developed, based upon phenotype screening or functional selection, that are useful for genome-wide protein expression [1], target identification and HTS.

An alternative approach to create similar cell lines using versatile adenovirus vectors with cDNAs (from Incyte Pharmaceuticals; Palo Alto, CA, USA) was described by Onno Van de Stolpe of Galapagos Genomics (Leiden, The Netherlands).

1359-6446/02/$ – see front matter PII: S1359-6446(02)02213-4

Reza Halse of Xcellsyz (London, UK) described the use of conditional immortalization vectors to create human cell lines that can be reverted to a more tissue-like phenotype in culture. Such cell lines could find use in target identification, pharmacogenomics, and *in vitro* toxicity screening.

Fluorescence imaging approaches, such as those described by Jeff Paslay of Cellomics (Pittsburgh, PA, USA) and by Stefan Prechtl of Schering-Plough (Kenilworth, NJ, USA), enable cell-based assays with specialized cell lines to be highly multiplexed. Galapagos Genomics has validated several microscopic imaging assays with cell lines they have created. The high information content that image-based techniques provide makes rapid screening of cell line collections feasible, although the software and memory requirements are high.

Whole organism approaches

The expedited identification of drug targets using intact animal models, rather than cell-based systems, was described by several speakers. Alex Turner described how Lexicon Genetics (The Woodlands, TX, USA) is validating drug targets by generating and characterizing thousands of mouse mutants, created by genetically manipulating embryonic murine stem-cell lines. The detailed phenotypic data, captured in a database, is used to choose a few targets for mechanism-driven discovery projects in several therapeutic areas.

The use of *Caenorhabditis elegans* for genomics and compound screening to identify candidate drug targets and small molecules that will affect them *in vivo* was discussed by Benoit Deprez from Devgen (Ghent, Belgium). Although nematodes are invertebrates, they share 70% of the metabolic and signaling pathways found in humans, according to Deprez. The tiny worms have the advantage of being almost transparent to ultraviolet and visible radiation, making target assays on whole organisms feasible, and can also be grown in 96-well plates, unlike mice or humans! Devgen has patented technology that enables small molecules to penetrate nematodes effectively.

Lead identification

Not all of the presentations had a post-genomics focus. For example, Michael Hann GlaxoSmithKline (Stevenage, UK), whose presentation was provocatively entitled 'Making lead discovery less complex?' had the premise that a compound library that is optimal for lead identification must balance the structural complexity of the component molecules required for potency with simplicity. Otherwise, if 'drug-like' molecules are too complex, the probability that any library member will actually bind is extremely small. Hann enforced his statistical arguments with data from the published literature and his own experience [2]. Similar analyses have been published by scientists at AstraZeneca [3].

The take-home message was that Chris Lipinski's 'rule of five' does not go far enough. The solution that Hann recommended was to screen smaller molecules at higher concentrations, using biophysical methods to illuminate specific structural interactions at sufficient resolution to guide optimization. Hann concluded his presentation by recalling Albert Einstein's proposition that 'Everything should be made as simple as possible but no simpler'.

In summary, the conference provided an excellent balance of overview and technical detail about new directions for HTS in pharmaceutical discovery. Although many of the topics involved issues directly relevant to HTS, it was also obvious from the breadth of topics presented that screening *per se* is often not the bottleneck. There are many new bottlenecks that constrict the pace of drug discovery, both up- and downstream in the process from HTS. The conference informed the attendees about novel tools that can be used to resect these new bottlenecks, and provided a context for HTS within the industry.

References

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