Fast-track approaches to selecting discovery candidates for full development

The first IBC UK conference on *Lead Identification to Candidate Selection – Discovery Strategies for Managing the Commitment to Development* was held at the Royal Society, London, UK (22–23 September 1997). For this wide-ranging topic, the discussion was divided between presentations offering project management solutions to speed up the process and technical presentations on rapid methods to filter candidates. These topics do not readily sit together, but, despite having an audience drawn from such diverse backgrounds, speakers succeeded in linking the scientific and strategic elements of the theme of the conference. Successful reduced-risk development actually depends on this fusion of innovative technology with smart business strategy.

Management strategies

The assumption was that between 10 and 20 lead compounds normally arise from high-throughput screens, combinatorial chemistry and genomics. The challenge to presenters was then to identify subsequent bottlenecks in getting the right candidate into early-stage development.

Dr Tony Causey (Covance, Harrogate, UK) suggested that the R&D phases needed to be more of a continuum than a relay race – a policy that for one particular compound had reduced the time to first administration to man to under 5 months from the expected 8 months. In theory, by concentrating on several leads of different structures, the risk can be spread even more widely. Preliminary toxicology, metabolism and formulation should begin earlier in the preclinical phase, with considerable overlap in time-lines – hence, the requirement for an experienced project management team (Dr Jerry Gennaro, Bristol-Myers Squibb, Princeton, NJ, USA). Subject to prioritized objectives, a successful team carries out rapid decision-making primarily based on experimental data. Representatives from small to medium sized enterprises (SMEs) questioned whether an entrepreneurial research culture can actually exist in 'big pharma' operating within these narrow programme management structures and that perhaps the idea of 'venture teams' could be a compromise. This discussion illustrated that management of research ('organized chaos') is quite different from that of preclinical development ('structured and predictable').

Dr Garth Rapaport (Glaxo Wellcome, Greenford, UK) felt more concerned that the quality of the Investigational New Drug (IND) Application was of more importance than an actual reduction in the lead time to man, and that 6 month timelines were atypical. For example, a positive genotoxic test means that biological testing will be required and this will double the time required to get to man. Further, the time required for the right product to be either first or 'fast-following' to the major market was the most important criterion (Dr Keith Redpath, PA Consulting, Melbourne, UK). In addition, there was agreement that there is superfluous material in current IND applications. This excess can be avoided if the R&D plan is derived from an ideal product profile, which incorporates the principle of 'retro-planning' to address a focus point (Dr Ian Skidmore, Glaxo Wellcome). Academia, Biotech and CROs are commonly employed by large pharma to cover specialized tasks to achieve the product profile. A recent development is the establishment of 'virtual' companies or integrated CROs that are capable of adopting a large portion of a company's development pipeline (Dr David Cavalla, Napp, Cambridge, UK). Dr Redpath argued that it made sense to use impartial consultants to carry out due diligence in identifying and assessing such external technology, given the current emphasis on outsourcing in order to reduce the lead optimization time.

All contributors agreed that projects should only go forward if they had good scientific rationale, had a clinical application and represented a commercial opportunity. Presumably, these decisions should be made well in advance of the lead generation stage. Addressing the business aspect, Dr Giselle Bleeker (Covance Princeton, NJ, USA) argued that commercial depts tended to overlook the aspect of actual economic response to a product, i.e. whether US insurance companies will actually pay for the products even if there is an underlying commercial basis for success.

Technical strategies

The technique of LC-MS/MS is widely used in multiple component analysis for determining drug levels in biological fluids for pharmacokinetic and toxicological study (Dr Tim Olah, Merck, Westpoint, MO, USA). This quantitative method is now being used for drug discovery, and a particular example was cited in which 22 leads were analysed in the concentration range 1–1000 ng ml^{-1} in the plasma of single animals in order to speed up candidate selection. However, Dr Jacky Vondersher (Novartis, Basel, Switzerland) argued that, while obtaining early pharmacokinetic data using the right bioanalytical test was laudable for selecting potent drugs with high bioavailability, information on the 'black box' between administration and final bioavailability was required to help the medicinal chemist address limiting factors 'in between'. Good oral formulations of cyclosporin could only have emerged by adopting this approach.

Dr Theo Liston (Pfizer, Groton, NC, USA) and Dr David Brayden (Elan, Dublin, Ireland) discussed the potential of *in vitro* systems in predicting human pharmacokinetics for lead compounds. Upon demonstration of adequate physicochemical properties, cell-based reductionist approaches are being used

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for *in vitro/in vivo* correlations at the level of intestinal permeability prescreens, such as the Caco-2 intestinal epithelial cell system, and also drug interaction and metabolism prescreens using liver microsomes. Upon obtaining *in vitro* human half-life prediction data, which provide information on bioavailability limitation factors, lead compounds are then tested *in vivo*. Thus, *in vivo* study is minimized while, at the same time, vital early-stage information is provided to formulators.

The hot topic of gene chips was addressed by Dr David Bailey (Incyte, Palo Alto, CA, USA) and Dr Gordon Smith-Baxter (Pharmagene, Oxford, UK). In theory, chip technology allows the simultaneous display of expression data from thousands of genes and has a resolution that can detect single base polymorphisms. Ideally, the large genomic databases that are available allow companies to target specific gene families, followed by application to human isolated tissue for functional assay and screen of potential discovery compounds. Many participants did not yet trust the gene expression end point, given that some data showed a nonlinear relationship between protein expression and RNA production. Beyond the hype, the technology is not yet at the stage where the chips can give quantifiable data that relate to real biological consequences. Also, multiple gene diseases may not be adaptable to this technology given the role of environmental factors. Nonetheless, this exciting technology has potential as part of early-stage discovery programmes, perhaps more immediately to screen ligand binding for single gene conditions in animal models.

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Society for Biomolecular Screening – highlights

The *3rd Annual Conference of the Society for Biomolecular Screening* (SBS) held in San Diego, CA, USA attracted 546 registrants and 180 exhibitors (77 exhibits). The increased attendance over last year's meeting demonstrates the greater emphasis placed on 'screening' in the pharmaceutical and biotechnology industries. At the annual conference of this society, short, but highly informative, courses were held prior to the proceedings (e.g. 'Genomics in Drug Discovery'), and tutorials were given by the manufacturers of screening equipment and reagents. Moreover, these technology-oriented meetings are useful for learning about existing methods and for introducing new instrumentation.

Assay platforms

This first session included talks ranging from functional cell-based assays to screens based on affinity selection, fluorescence polarization (FP) and electrochemical detection. Dr Daniel Gil (Allergan, Irvine, CA, USA) described the advantages of functional high-throughput screening (HTS) using receptor selection and amplification assay technology (RSAT). In this method, mixed populations of cells expressing different receptors are engineered to proliferate in response to ligands. Screening for α-adrenoceptor subtype selective compounds was also described using RSAT. For most receptor screens, the particular pathway used in a given therapeutic target is not known, and the functional screen provides a variety of conformational possibilities. Receptors signal through multiple biochemical pathways, and the conformation of the receptor varies depending upon the pathway selected. Although a compound must bind to the receptor to be active, it was noted that binding assays might actually be misleading because the activity in functional assays may be less than in binding assays. The activity of ligands selected from the functional assay was shown to correlate with the therapeutic effect in cornea reflex studies. Partial agonists could also be identified by RSAT.

Dr Dennis Church (Glaxo Wellcome Research, Geneva, Switzerland) discussed cell-based functional assays as alternatives to electrophysiological methods for measuring activation of the purinergic receptors P2X, P2X2/3 and P2X4. These receptors are a family of ATP-gated channels that are permeable to both Ca^{2+} and Na^{+}. HEK cells expressing P2X7 receptors are made permeable by the activation of P2X7 receptors. The increased permeability was measured using Yo-Pro-1 iodide; this complexes with DNA, and the fluorescence produced can be measured using a cytofluorometer and a fluorescence imaging plate reader (FLIPR). The calcium-sensitive indicator, Fluo-3, and the membrane-potential-sensitive dye, DIBAC, were used for measuring P2X2/3 and P2X4 activation, respectively. These methods allowed a throughput of 2,000 samples per day.

The Raf kinase pathway has several component kinases, each of which is a good drug target for oncology. Dr Brad McDonald (Glaxo Wellcome, Research Triangle, NC, USA) described the use of a single scintillation proximity assay (SPA) to identify inhibitors of Raf/MEK/ERK. This screen requires His-tagged c-Raf-1 to be expressed in the activated form and the other kinases expressed, in an inactive form, as glutathione-*S*-transferase (GST) fusion proteins in *Escherichia coli*. Phosphorylation of a biotinylated peptide substrate by ERK-2 was detected by binding to scintillant beads.

Dr John Wang (Chiron, San Francisco, CA, USA) described mini-spin affinity columns and mass spectrometry to deconvolute and identify structures of hits from pools of compounds. The mini-columns can be parallel-processed and a throughput of 200 samples per day was described.

The use of electrochemistry as a real-time method for measuring inhibitors

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