Meeting report

Meeting the challenges of drug discovery: a multidisciplinary re-evaluation of current practices

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A report on the Keystone Symposium 'Meeting the Challenges of Drug Discovery', Vancouver, Canada, 15-19 January 2005.

With the cost of bringing a new therapeutic agent to the market now estimated at around US$1.4 billion and the disappointing pace of approvals of new therapeutics, the pharmaceutical and biotechnology industries are under increasing pressure to improve the efficiency and economics of drug discovery and development. A Keystone Symposium in January on the challenges of drug discovery brought together an eclectic group of innovators. An ambitious meeting program encompassed target validation, lead-identification strategies, novel screening approaches, early detection of toxicity, more predictive animal models, new biomarkers, molecular profiling, and new biological agents.

Leslie Brown (Pharmacopeia, Princeton, USA) in his keynote lecture gave an entertaining and wide-ranging analysis of the myriad financial and technical challenges facing the pharmaceutical and biotechnology industries. His message can be summed up as: "use the right technology to find the right drug modulating the right target in the right patient". We learned over the next four days that such advice is easy to give but more difficult to heed.

Using the right technology

Several complementary strategies for speeding up the drug-discovery process were presented. David Burns (Abbott Laboratories, Abbott Park, USA) described how he and colleagues are using high-throughput screening to accelerate the initial discovery of biologically active molecules (lead compounds) that may turn out to be potential drugs. He stressed the importance of using complementary screens for the effects of lead compounds on a target to increase the yield of *bona fide* hits. For a protein kinase target, for example, one would need enzyme assays of the kinase domain plus assays for the full-length protein, combined with screens of binding affinity, effects on the signaling pathway, and whole-cell responses. Stewart Noble (Kalypsys, San Diego, USA) also showed the power of high-throughput screening for identifying compounds that modulate particular signal transduction pathways, presenting persuasive case studies for signaling by the epidermal growth factor receptor (EGFR), the neutrophil oxidative burst, and inducible nitric oxid synthase (iNOS). One of us (S.B.) described FAST™, a novel fragment-based strategy for identifying high-quality, patentable, low molecular-weight lead compounds, with binding constants in the nanomolar range, that inhibit forms of the oncogenic protein kinase Bcr-Abl that are resistant to inhibition by the anticancer drug Gleevec™.

Gerhard Klebe (Phillips University, Marburg, Germany) provided a glimpse of the future by illustrating the potential of computerized 'virtual' ligand screening with a number of compelling case studies. Most impressive were his team's efforts at targeting tRNA transglycosylase, with the goal of developing an antibiotic against *Shigella*, a cause of dysentery. *In silico* screening successfully identified inhibitors with micromolar IC_{50} values (the concentration of inhibitor that inhibits 50% of the enzyme) that were then purchased, tested *in vitro*, and structurally validated by X-ray crystallography. Chand Khanna (National Cancer Institute, Bethesda, USA) described the importance of using a clinical trials approach with companion animals for early animal studies of possible human anti-cancer agents. The use of companion animals instead of laboratory dogs and rodents appears to be more advantageous, because results obtained with such heterogenous animal populations have proven to be more representative of human responses in subsequent clinical trials

than the more uniform laboratory populations. For example, his studies of c-Kit inhibitors in canine mast-cell tumors revealed consistently different pharmacokinetic and toxicity profiles of the inhibitors in dogs bearing natural tumors compared with laboratory beagle cancer models.

Selecting the right target
Large-scale examinations of the human genome were illustrated by three speakers, all intent on comprehensive target validation. Brian Zambrowicz and colleagues (Lexicon Genetics, The Woodlands, USA) are using mouse gene knockouts to examine the estimated 5,000 druggable targets in the mouse genome. Comprehensive evaluation of around 2,000 gene knockouts was reported to have spawned 60 new drug-discovery programs.

This heroic effort was contrasted with applications of RNA interference (RNAi) technology to produce gene knockouts (Frank Koentgen, Ozgene, Australia) and gene knockdowns (William Wishart, Novartis Institutes for Biomedical Research, Cambridge, USA). Koentgen described how the use of modified lentivirus vectors, which integrate into the genome, has proved a fast and reliable method for producing transgenic mice and rats. Related attempts to use lentiviral vectors encoding interfering RNAs to produce 'lenti-RNAi' and 'inducible lenti-RNAi' knockdown mice have also shown early promise using tyrosinase as the target gene. Wishart presented a genome-wide approach to target identification for the relief of chronic pain by using expression profiling with a P2X3 pain receptor case study. Murray Robinson (GenPath Pharmaceuticals, which is now known as AVEO Pharmaceuticals, Cambridge, USA) explained how experimentally inducible tumors can be used for both target identification and drug discovery. In such tumor models, insertional mutagenesis screens have identified new genes complementary to known oncogenes.

Avoiding the wrong drugs
Early detection of toxicity is critical to ensuring that only suitable drugs are put into clinical trials. Dale Johnson (Chiron Corporation, Emeryville, USA) presented computational approaches to the prediction of drug-induced toxicity. Kyle Kolaja (Iconix Pharmaceuticals, Mountain View, USA) explained the potential of the company's DrugMatrix, a proprietary chemogenomics database that incorporates information from animal studies, gene-expression profiling, *in vitro* assays and literature sources. The power of the method was illustrated by the identification and use of kidney biomarkers as early predictors of nephrotoxicity.

Stephen Durham (Bristol-Myers Squibb, Princeton, USA) and James McKim (CeeTox, Kalamazoo, USA) both described the benefits of early application of *in vitro* toxicology studies to identifying potential liabilities before substan-

tial resources are devoted in animal and human testing. Particularly impressive was McKim's use of *in vitro* cell-based toxicity screens early in the drug discovery process to predict toxicity *in vivo*. Roger Ulrich (Rosetta Inpharmatics, Seattle, USA) is applying microarray technology to toxicogenomics with the goal of reducing adverse drug reactions. After describing the power of the technique in general terms, he presented an informative case study on determining the toxicity of potential inhibitors to the chemokine receptor CCR5, a receptor used by the human immunodeficiency virus (HIV) to enter cells.

Making the right clinical decisions
There remains the challenge of matching the "right drug to the right patient". Good clinical decision-making rarely follows a straightforward path, but there are grounds for optimism. Todd Golub (Dana Farber Cancer Institute, Boston, USA) described gene-expression profiling of various human cancers combined with gene-set enrichment analyses to detect signatures of disease. In addition, he suggested that miRNA signatures could be used to evaluate the potential utility of particular compounds in treating cancer.

Samir Hanash (Fred Hutchinson Cancer Center, Seattle, USA) and colleagues are applying a host of proteomic tools to samples from human patients with the aim of establishing tissue- and serum-based markers for both diagnostics and functional classification of disease. He described the capture of cell-surface proteins via biotinylation to examine differences in expression levels and expression patterns between malignant and normal cells. Finally, Irene Tracey (Oxford University, UK) showed how functional magnetic resonance imaging (MRI) of pain processing in humans is being used to relate directly the effects of analgesic agents on neurophysiologic markers to patient perceptions of efficacy.

New types of therapeutics
Over the past two decades a number of alternative platforms for drug discovery have allowed the industry to go well beyond small-molecule and oligopeptide drugs. Recombinant proteins, monoclonal antibodies, gene therapy, antisense, RNAi, and aptamers each represent relatively unexplored frontiers for drug discovery. Antibodies, antisense and RNAi were the focus of a session entitled 'Biologics', which does not do justice to the enormous potential of these novel modalities.

Napoleone Ferrara (Genentech, San Francisco, USA) recounted the odyssey-like discovery and development of Avastin, a non-immunogenic recombinant humanized monoclonal antibody (93% human, 7% mouse) that targets vascular endothelial growth factor (VEGF) and is now used as first-line treatment for metastatic colorectal carcinoma. Frank Bennett (ISIS Pharmaceuticals, Carlsbad, USA)

summarized the relative predictability of antisense oligo-nucleotides as therapeutic agents and their potential to improve efficacy and lower costs. For the uninitiated, not to mention those skeptics who recall the checkered past of antisense approaches, he explained the multiple mechanisms by which oligonucleotides act on RNA and described how medicinal chemistry has improved their potency and pharmacokinetic properties, and lowered their cost.

Finally, John Maraganore (Alnylam Pharmaceuticals, Cambridge, USA) discussed therapeutic applications of RNAi, as exemplified by an siRNA-based agent against respiratory syncytial virus (RSV) agent, which has good cell permeability and appropriate albumin binding, plasma half-life, and tissue distribution. The painstaking development process involves choosing the right sequence, modifying the oligonucleotide backbone to avoid nuclease digestion, and then conjugating it with cholesterol to improve both plasma half-life and biodistribution. The message from these three talks was clear. Biologics can offer superior validation, better pharmacokinetic properties, and more predictable toxicity profiles, which often mean a faster path to successful proof-of-concept clinical trials.

During this meeting, we learned a great deal about how different organizations are working to implement facets of Leslie Brown's prescription to "use the right technology to find the right drug modulating the right target in the right patient". It was made clear that genomic approaches to the problem are likely to bear considerable fruit over the next five years. Integration of diagnostic tools with predictive pharmacology and toxicology should prove particularly beneficial as academic and industrial efforts drive towards more individualized clinical trials and, ultimately, more individualized medical care. The prospects for both drug-discovery and drug-development scientists and their patients look better and better. Precisely how the pharmaceutical industry is going to position itself to deal with the changing economics of personalized medicine would make an interesting addition to the program when this same group meets again in a few years.