Can you stand the heat of today's drug discovery?

Over the past year, the science, technology and business environment of drug discovery has progressed at remarkable speed. In the heat of Boston (MA, USA), over 2000 attendees, 200 trade exhibitors and 70 expert presenters will aggregate to form the *Drug Discovery Technology 2000* conference on 14–18 August 2000, one of the largest gatherings on this topic for this first year of the new millennium. The heart of a great conference is great speakers. The organizers have enrolled an impressive roster of expert speakers from large pharmaceutical, biotechnology and life science companies, as well as from academia. Among this year's keynote speakers will be Craig Venter (a leading pioneer of modern genomics and a continuing driver and innovator), Frank Douglas (who is leading the integration of an extensive R&D conglomerate for Aventis, one of the world's largest pharmaceutical companies) and Steven Ley (Chairman of Chemistry at the University of Cambridge, UK).

The pace and intensity in drug discovery technology is stimulated by the current revolutions in science and technology, led for the moment by the opportunities emerging from the availability of many sequenced genomes, including our own. Over the past few months, a major change has occurred as the financial and investment community appreciates the potential of what is being accomplished in biomedical technology. After years of investor apprehension and risk-aversion, the prospects of radically new and improved medicines for major diseases and for an enhanced lifestyle are attracting a new scale of investment in the biotechnology and life science sectors. This is empowering and invigorating, but it will also be challenging in terms of increased expectations and fiercer competition.

In short, the power, pace and impact of biotechnology is increasingly mimicking the high-tech and Internet sectors. Presentations in the conference will emphasize the importance of information technology on drug discovery in the established fields of bioinformatics and computational chemistry and in the challenging fields of computer simulation of tissue, organ and organism physiology and pathology.

Financial support for the industry

Compared with last year, there is a much greater inflow of capital into biotechnology. The stronger biotechnology companies can now retain more of the value of their pioneering technologies and their powerful intellectual property portfolios that could include fundamental research tools, new drug targets, large families of compounds and methods of medical use. This change will influence the relationship between the biotechnology and the pharmaceutical companies, but the top tier of pharmaceutical companies retain strong cash-flow and technical power and they will therefore continue to be major exploiters of the new technologies.

More adventurous collaborations among the established and emerging companies will be devised. There will be new types of alliances among the technology-rich and knowledge-rich biotechnology companies, perhaps with substantial outside financing. These intriguing prospects will be discussed in one of the main sessions at the Boston conference. This year's conference also contains several presentations on intellectual property issues. It can be expected that the people who see themselves mainly as inventors will engage in vigorous debates with those whose role is mainly to use and apply these inventions.

Technological advances

The conference will naturally maintain a focus on mainstream technical advances for accelerating and improving the output and quality of new compounds headed for the clinic. HTS, in particular fluorescence and cell-based assays and miniaturization, will be covered by both providers and users of the new methodologies, as will recent developments in combinatorial chemical library design and production. Several sessions will feature perspectives on target validation, with some elegant high-throughput cell biology and microbiology to examine key control points in therapeutically relevant pathways. There will be further emphasis on higher-throughput methods of 'surrogate ADME/tox'. These methods include miniaturized, *in vitro* assays, such as cytochrome P450 interactions, gene expression profiles and physical chemistry, which will be used to pre-characterize whole libraries of compounds rather than just a few leads.

Leading practitioners will discuss in parallel *in vivo* assay approaches to collate much larger quantities of data more rapidly, from fewer animal experiments. The use of predictive models of potential adverse effects, undesirable metabolism and bioavailability based on actual data and/or computer simulation, will be given more prominence than in conferences of previous years. Interestingly, these new approaches to rapid 'predevelopment' are being produced by discovery research organizations in large and small companies, not from development groups. The traditional,

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formal Good Laboratory Practice (GLP) path to the clinic will probably quickly include these new approaches instead of the traditional protocols. However, it should be expected that discovery teams will provide many more innovative, better qualified compounds with a much reduced attrition rate in development. If it is believed that the development process will be only marginally expedited and cheaper, then there must be an improved and more rapid selection of targets and compounds. This is the real payoff for innovating and applying the new discovery technologies.

Advances in research techniques

Several presentations will report on the race to find and patent disease-related single nucleotide polymorphisms (SNPs). The conference will include further debate on the promise and threat of phamacogenomic segmentation of patient populations and the move from descriptive definition of disease towards classification based on genetically defined mechanisms and subtypes. Will the anticipated cost-saving and lower attrition rate of development offset the feared reduction in the applicable patient population? Will healthcare providers pay more for more selective and potentially more beneficial therapies? As always, the audience will be persuaded more by specific examples than by speculation and conjecture. I wonder if some speakers on these topics will consider the segmentation of the antibiotic market as a useful model, even though it is based on microbial phenotype (antibiotic resistance and sensitivity) rather than genotype?

One of the new topics for this year's conference is proteomics. This has been defined as the 'phenotypic counterpart to genomics'. Gel-based and mass-spectroscopy methods for extensively parallel protein biochemistry will be discussed. An important application will be the use of proteomics as a 'phenomic' alternative to, or an adjunct to, gene expression profiling and SNP searching in target validation and patient profiling.

Some of the most attractive sessions will feature people who have pioneered the discovery of significant new compounds, presenting case histories. These case histories will include:

- Monoclonal antibodies (an overnight success story, after twenty years, possibly because of the wait to produce human or near-human molecules)
- A rationally designed anti-viral enzyme inhibitor
- A small-molecule allosteric activator of a calcium-sensing G protein-coupled receptor (GPCR) that was discovered while some scientists refuted the pharmacological evidence for a specific receptor (in this case, the compound was discovered before the receptor could be cloned)
- An analogue of a peptide hormone secreted by the cells that produce insulin
- A small-molecule inhibitor of a gut lipase.

Conclusions

I believe that none of the discovery adventures in these case histories depended on the new tools of genomics and combinatorial chemistry, as the discovery work was largely carried out before these tools were available. However, I do believe that the new technologies are accelerating and enhancing the present cohort of discovery programs. Hopefully, some presenters at the conference will describe examples of such work in progress in the intensifying heat in the kitchens of today's and tomorrow's world of discovery technology.

Information about the conference can be gained from

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