# A Boston T party

In her introductory editorial for *Drug Discovery Today (DDT)*, Debbie Tranter pointed to a 'blizzard of revolutionary novel approaches' driving the discovery process. Naturally, *DDT* aims to report and analyze this revolution and to highlight significant media events that reflect it. Two-and-a-quarter centuries after the Boston Tea Party, the city will host a 'technology party', the *Drug Discovery Technology '99 Exposition and Symposium, 16–19 August 1999* at the Boston World Trade Center.

There is an increasing, and sometimes it seems overwhelming, number of conferences devoted to aspects of novel discovery technology on such topics as automation, high-throughput screening (HTS), miniaturization, combinatorial chemistry, lead optimization and profiling, genomics, proteomics, and target identification and validation. The high attendance at such conferences attests to the importance of and rapid progress in these areas. It was a particular pleasure to find an increasingly high standard of science and technical innovation presented at these meetings; the industrialization of drug discovery processes is truly at the cutting edge of biomedical research. I have also detected a growing and productive interaction between academic and industrial science and a much-improved attitude towards appreciation of applied science and 'big biology.' Two key catalysts to these trends have been genomics (which is essentially industrialized, molecular genetics) and combinatorial chemistry (which is basically extensively parallel, automation-assisted synthesis of multiple products). These two key developments have depended not only on specific technical or scientific breakthroughs, but also on the will to instigate these paradigm shifts from the study of one gene or the making of one chemical, as well as the extraordinary advances in the power and cost effectiveness of information technology and modern computer networks. In both genomics and combinatorial chemistry, there have been crucial contributions from academia and industry. While most of the really large-scale efforts are in industry, we are increasingly seeing developments in technology and their applications forming key components of academic research, e.g. solid-phase synthesis is now a key area of basic chemistry research.

Rapid progress in target identification by genomics and chemical library production has driven the need for industrialization and miniaturization of primary and secondary screening, and increasingly of profiling or surrogate ADME (absorption distribution metabolism excretion)-toxicology. The desire to minimize the use of radioactivity and to miniaturize assays has brought a multitude of fluorescence technologies to the forefront of assay development. As with radioligand binding, many fluorescent techniques that are now widely adopted in industry have their roots as novel tools for basic pharmacology or cell biology, e.g. cytosolic $Ca^{2+}$ dyes such as Fura-2 and Indo-1 or the green fluorescent proteins. In contrast, established HTS techniques are finding their way into basic research laboratories as people realize how valuable they are in multi-variable testing, exploration of optimizing experimental conditions and more rigorous quantification of biological processes. Recently, in reviewing a large package of grant applications for facilities and equipment, I was struck by the frequency of requests for HTS equipment and fluorescence assay and detection instrumentation, which seemed comparable to the demand for rapid DNA sequencing and gene expression array systems.

Against this encouraging background of rapid progress through Debbie Tranter's 'blizzard,' Michael Keenan of IBC USA and an eclectic advisory committee have compiled the fourth in an annual series of expositions and symposia, which will produce one of the largest gatherings of drug discovery researchers worldwide. In addition to the symposium itself and the exposition, where some 150 companies will showcase their latest reagents, technologies, instruments, and informatics products, there will be specialist tutorials and workshops and a new feature: a series of short courses run by the *American Chemical Society*. This latter item reflects the links between academic and industrial research communities and will include topics such as modern synthetic methods, the organic chemistry of drug design and the chemistry of drug action.

The symposium has an excellent selection of presenters, which includes distinguished academics, as well as thought-leaders and innovators from biotechnology and major pharmaceutical companies. The plenary speakers include Leroy Hood from the University of Washington, and Stuart Schreiber of Harvard University. Hood is a pioneer in automated DNA sequencing and synthesis and also in their application to the molecular genetics of immunity. Schreiber has deployed innovative synthetic chemistry to create probes and modulators of intracellular protein signaling cascades. Both of these renowned scientists have been closely involved with successful and innovative biotechnology companies (e.g. Applied Biosystems, Vertex) and have made major contributions to drug discovery technology. From industry, the plenary speakers are George Poste (SmithKline Beecham), who led the pharmaceutical industry's first major integration of


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genomics into discovery with the Human Genome Sciences collaboration, and Michael Pavia of Millennium, who has been a pioneer in combinatorial chemistry.

One main session will focus on functional genomics and target validation with a panel of speakers from 'second-generation' genomics companies. Perhaps they will persuade me that there is a more relevant definition of a validated target than one that is targeted by a useful marketed medicine! Other sessions will cover HTS and miniaturization with contributions from companies at the technological leading edge, such as Aurora, EVOTEC and Scriptgen. Presentations on combinatorial library production and lead optimization include speakers from leading small and large companies such as Oxford Asymmetry, Pharmacopeia, Abbott and Pfizer.

A series of case histories of successful drug discovery should be of great interest. Biotechnological examples come from SUGEN's angiogenesis inhibitor and Immunex's soluble tumor necrosis factor receptor, while the big pharmaceutical cases are Lilly's protein kinase C inhibitor LY333531, a novel lipid lowering agent from Bristol Myers Squibb and Merck's VIOXX.

It is clear that the new 'platform' technologies are increasing the pace of lead discovery and causing concern about the next bottleneck. Pre-conference tutorials focus on some of the many current efforts to develop HTS surrogate ADME-toxicology assays for compound and library profiling, to guide the selection of candidate compounds which have reduced potential for pre-clinical toxicity and clinical adverse effects, but that have more desirable pharmacokinetic and metabolic characteristics.

Lastly, but certainly not least, there will be a number of presentations on key aspects of informatics. In future years, I suspect there will be much more emphasis on the development of information technologies to manage the processes of industrialized drug discovery and to collect, manage, analyze and make sense of the data stream, which could engulf us, but will hopefully inform us and speed the development of new medicines.

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# Single enzyme may hold key to cancer treatment

The difference between kill or cure when it comes to some types of cancer chemotherapy may boil down to a single enzyme.

A British team at the Imperial Cancer Research Fund (ICRF) believes that they now understand why one particular form of cancer is so susceptible to chemotherapy, with more than 80% of patients responding to the treatment, while other forms are inevitably fatal.

In most cancer tissues, attack by a DNA-damaging chemotherapy agent does not necessarily kill the tissues as DNA repair mechanisms revitalize the cells. This second chance can quickly lead to resistant cells as mutations occur during and after the repair process. Cancers depend on their DNA receiving this quick fix for survival.

In the mid-1990s, Beate Koberle and a team led by John Masters and John Hartley at University College London (UCL) (London, UK) discovered that testicular cancer cells are hypersensitive to cisplatin and have a low capacity to remove cisplatin-induced DNA damage from the genome, unlike other cancers.

## Testicular cells

Richard Wood and Koberle at the ICRF's Clare Hall Laboratories (South Mimms, UK) along with Cancer Research Campaign (CRC) colleagues at UCL then looked more closely at how well nucleotide excision repair (NER) was performed in cells in the well-defined 833K and GCT27 human testis (tumour cell lines). The rates of repair were much lower in these cells than in repair-proficient cells. The team used immunoblotting techniques to check for the amounts of the common proteins involved in NER.

Unusually low levels of XPA (the xeroderma pigmentosum group A protein) and the ERCC1–XPF endonuclease complex were observed in testicular cells. When XPA was added to the cell lines, however, it was possible to confer the full NER capacity of other types of cells onto them. The team says that this implies that the lack of XPA in testicular cells could be behind their poor ability to repair DNA damage and thus their susceptibility to chemotherapy. This is perhaps why even significantly advanced forms of the disease can be treated so well, whereas chemotherapy for other cancers achieves much lower success rates.

The team now believes it understands the implications of this discovery[1]. Wood suggests that drugs that inhibit XPA activity in other types of cancer cells could also make them

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