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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hypersensitive to cisplatin. Of the proteins involved in NER, all but XPA have multiple cell functions, in replication, transcription and recombination. XPA only fixes DNA. Evidence for this has come from knockout mice lacking the gene for XPA. They are indistinguishable from other mice, except in their sensitivity to chemical carcinogens and ultraviolet light, which reflects the role XPA plays in DNA repair and its lack of influence on other cell processes. Antagonists of XPA should not interfere with the functioning of healthy cells and so there is a reduction in the potential for side-effects.

Cancer susceptibility

Metastatic cancers in adults are almost always terminal, with the exception of testicular cancer. Making other cancers respond in a similar manner to testicular cancer could cut mortality rates. 'Targeted inhibition of the activity of XPA in repair might be achieved, for example, by using a short peptide or small molecule inhibitor to disrupt either the critical XPA–RPA interaction or the binding of XPA to damaged DNA', explains Wood. It is probable that the inhibitor will be a small organic molecule of complex structure, selected from a combinatorial library and will have to be something that gets into cells easily and specifically affects XPA, points out Wood. 'I think that a drug development strategy based on this idea is realistic in five years' time', he adds.

One additional spin-off of the discovery could be a diagnostic test for assessing whether a particular type of cancer might respond to chemotherapy some time before the drugs are even prescribed. By measuring levels of XPA in the cancerous tissue, the physician would have a better indication of whether chemotherapy would benefit a particular patient. 'As far as a spot test for tumours, this might be possible. If one could measure the XPA level in a small sample it could give an idea of the possible efficacy of cisplatin for that tumour', explains Wood.

Reference

1 Köberle, B. *et al.* (1999) *Curr. Biol.* 9, 273–276

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High-throughput screening: new frontiers for the 21st century

IBC's 8th annual conference on high-throughput screening (HTS) was held at the Claremont Resort and Spa in Berkeley, CA from 1 to 3 March 1998, entitled *Critical evaluations of the newest technologies from big Pharma researchers*.

There have been so many advancements in HTS assay design, format and miniaturization, that the real challenge now faced by HTS managers is how to assess or incorporate new technologies that increase throughput and quality of data, while avoiding those technologies that are untested or cost ineffective. As the title suggests, the organizers made a concerted effort to produce talks regarding real case studies. As a result, this meeting was a great mix of practical improvements in screening together with new technologies in development.

In his opening remarks, Tim Rink from Aurora Biosciences (CA, USA) described the evolution of HTS. His talk could have easily been entitled *From test tubes in wooden racks to high-density plates*. The interchange between basic research and development and HTS is becoming more fluid and has fueled many new innovations including fluorescence resonance energy transfer (FRET), new reporter systems and novel fluorophores. Miniaturization is progressing and, compared to ten years ago, HTS laboratories are now routinely screening much smaller sample volumes using assays that are more sensitive and quantitative, and less radioactive. Fluorescence has emerged as the format of choice for a wide variety of assays, approaching the sensitivity of radioactive assays while offering the advantages of a mix-and-measure homogeneous format. Moreover, while there is disagreement concerning the number of compounds necessary for a useful screen, it is always preferable to have as much information as possible.

New assay technologies

The highlights of these talks included how techniques known for their quantitative nature have been transferred to higher-throughput formats. Craig Muir from Millennium (MA, USA) discussed three powerful techniques they have developed for use in HTS; these are matrix-assisted laser desorption ionization with time-of-flight detection mass spectrometry (MALDI–TOF–MS), capillary electrophoresis (CE) and Caco-2 cell monolayers. MALDI–TOF–MS is used to measure drug transport and metabolism by monitoring drug levels in the apical and basolateral media and can spot 1000 samples per square inch using robotic systems. With this technique,

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