Preparing for the new millennium

'a blizzard of revolutionary novel approaches has swept through the pharmaceutical industry'

Since being introduced to the field of drug discovery at *Zeneca Pharmaceuticals* in 1991, it has become apparent to me that a blizzard of revolutionary novel approaches has swept through the pharmaceutical industry. Now, the discovery process has become completely transformed and the race to develop commercially successful drugs is now taking place in a very different realm. Rapid advances in automation, combinatorial chemistry, high-throughput screening (HTS), genomics, proteomics and bioinformatics appear to be principally responsible for driving such a rapidly evolving discovery process. In these exciting times for pharmaceutical R&D, it is a delight for me to take over the Editor's reins of *Drug Discovery Today*.

Combinatorial chemistry and HTS: accelerating the progress of drug discovery

The most elementary of combinatorial syntheses can now yield hundreds of thousands of small-molecule compounds that are designed to target receptors or enzymatic processes. The generation of combinatorial libraries has become a highly effective technique for accelerating the progress of drug discovery; the sphere of synthetic organic chemistry has been transformed and the probability of discovering new chemical entities (NCEs) has been significantly improved. More recently, targeting the more problematic and complex protein–protein or protein–carbohydrate binding has become a goal. Natural products, such as taxol, have conventionally been used to target these interactions, however, chemical libraries have now been furnished that can mimic the action of such complex molecules. This will inevitably provide a much deeper pool from which to draw novel leads for targeting these complex binding characteristics.

Combining research endeavours

Many pharmaceutical companies have combined their HTS and combinatorial chemistry endeavours; indeed, many have made multi-million pound investments in HTS laboratories. The capacity of HTS assay techniques to decrease time and expenditure and augment information has had a great impact upon the advancement of the discovery process. The identification of compounds that are selectively active against their biological targets has been a major step. For example, assays have been developed for detecting inhibitors of basic fibroblast and vascular endothelial growth factors, which are fundamental to the growth of certain tumours and also play a major role in several other disease states. The importance of such developments has been highlighted in the work of Judah Folkman at the Boston Childrens Hospital, MA, USA. They have isolated Endostatin™ – an endogenous inhibitor of angiogenesis and tumour growth – and it is currently under clinical and commercial development. Early results in tumour models are encouraging, demonstrating both primary and metastatic tumour reduction [Cao, Y. *et al.* (1998) *J. Clin. Invest.* 101, 1055–1063].

Robotic organic synthesis has also become a dominant feature of many pharmaceutical laboratories. This technology has helped techniques such as solid-phase and combinatorial organic chemistry to become fully realized in the drug discovery process. Such versatile and efficient synthesizers have the capacity to initiate, manipulate and work-up organic reactions without supervision. They will no doubt greatly contribute to the drug discovery process in the future.

Occlusion of the development process

The considerable number of NCEs now flowing through the discovery process also require toxicity, metabolism and bioavailability evaluation. However, the lack of high-throughput techniques for such evaluation has created an occlusion or 'bottleneck' that impedes the drug development process. But are we approaching a new era in which the demands of

Debbie Tranter, Editor, *Drug Discovery Today*, Elsevier Trends Journals, 68 Hills Road, Cambridge, UK CB2 1LA. tel: +44 1223 315961, fax: +44 1223 464430, e-mail: ddt@elsevier.co.uk

 1359-6446/99/$ – see front matter © Elsevier Science. All rights reserved. PII: S1359-6446(98)01289-6

automation and combinatorial chemistry are gradually being met by the development of high-throughput evaluation techniques? A cautious 'yes' to such a question may be appropriate, as some techniques now exist that allow companies to select the most promising development candidates from the hundreds of compounds that demonstrate favourable efficacy in screening assays. Technology-based companies have developed several HTS techniques for metabolism, bioavailability and toxicity studies. Assay systems using human hepatocytes can screen expeditiously for those compounds that are rapidly or slowly metabolized, and systems using Caco-2 cells can be used to screen for compounds that readily cross the intestinal epithelium.

The data obtained from such *in vitro* evaluation models may provide a good indication of the *in vivo* parameters of compounds, but these techniques do pose some interesting problems. For example, when these processes are scaled up, the availability of the necessary human tissue may become a major obstacle. There is consequently much ground that has to be covered before it can be claimed that high-throughput evaluation techniqes are sufficiently relieving the development bottleneck.

These latest developments, however, prompt thoughts of exciting prospects for drug discovery in the new millennium, and of course, *Drug Discovery Today* will be there to cover the events as they unfold.

Objectives of *Drug Discovery Today*

This journal will continue to be a rich source of up-to-date information, especially with the assistance of and feedback from you, the readers. Your contributions to the journal are of paramount importance and therefore, we wish to encourage you to propose reviews or provide updates of the latest developments in industry or academia. We also welcome constructive comments about the content of the journal; for example, you may wish to express your views on a particular published article or draw our attention to areas that you feel have importance but have not yet been addressed.

This year, our coverage will be complemented by a new 'Products' section, which will highlight the most up-to-date equipment and services available that can maximize the effectiveness of any company's discovery programme.

As a final note, I thank David Hughes, the founder and former Editor of *Drug Discovery Today*, for his continual support and guidance, and for entrusting the journal to me.

Debbie Tranter

In the January issue of *Pharmaceutical Science & Technology Today*...

Editorial – Boosting confidence in artificial intelligence
Raymond C. Rowe

Update – latest news and views

Advances in in vitro *drug metabolism screening*
Maurice Dickins

Mechanical properties of powders for compaction and tableting: an overview
Sunil Jain

Recent developments for oral multiphase and targeted release products
William J. Bowtle

Dynamic in vitro *modelling of the blood-brain barrier: a novel tool for studies of drug delivery to the brain*
Damir Janigro, Susan Leaman and Kathe A. Stanness

Monitor – process technology, drug delivery,
analytical methodologies, legislative issues, patents