Sorting woods from trees

'…we see a Viagra only once in a blue moon'

Three recent issues of *Drug Discovery Today* in particular have, for me, drawn together the current paradoxes in the progress of R&D. First, in September 1998, Alison Austin focused on the plight of today's researchers, both within corporate and academic centres [*Drug Discovery Today* (1998) 3, 419–422]. Austin pointed out that the reality in most spheres of research is an atmosphere of pressure in which creativity is being stifled. Then in November, Jürgen Drews explained how the industry continues to be blighted by an 'innovation' deficit and that in spite of some more recent positive signs, continued consolidation among pharmaceutical companies cannot be avoided [*Drug Discovery Today* (1998) 3, 491–494]. Contrast these dilemmas with the very real opportunities offered by genomics and proteomics in transforming prospects for therapies as highlighted throughout the March 1999 issue. At a time when the intellectual challenges and overall opportunities are more exciting than ever before, there is considerable dissatisfaction and much worry about lack of vision.

It is, of course, true to say that the pharmaceutical industry has been complacent in the past. For a long time the giants have lumbered. But what has this meant for the overall dynamics among the big players? Since the early 1990s, pundits have predicted that the industry will merge itself into a core of maybe only five big players. There has been something of a lull in the merger scene involving a series of extended corporate engagements leads to much playing of footsie, but no real marriages. I think we now see some real momentum though, that no amount of inter/intra boardroom squabbling can hold back. Only recently, Scrip was highlighting the strength of performance of the portfolio platform for the Zeneca–Astra merger; and the Aventis merger is due to be submitted to the General Shareholders Meeting of Rhône-Poulenc and Hoechst in mid-1999.

More big-D-little-r for the major players?

All of the large players are learning new tricks, such as collaborations, joint ventures and spin-offs, to address the opportunities offered by novel discovery technologies. Nevertheless, the industry seems to have grown used to the inevitability of this accelerating inward spiral and are learning that what they are good at is being big. Being big usually means that you are good at resourcing and scheduling process-oriented activities. They are more comfortable in outsourcing high-risk, innovative work to smaller academic biotech teams inhabited by individuals who, almost by definition, have no need to go through life playing it safe – big risk takers who are prepared to lose all (well you can always start again) in the quest for fame and fortune in drug discovery.

What we need is some clarity about what the future holds. Recently PricewaterhouseCoopers (PWC, London, UK) performed an in depth review of prospects for the industry and highlighted major challenges and changes by 2005 [PricewaterhouseCoopers (1998) *Pharma 2005: An Industrial Revolution in R&D*; Fenwick, S. (1999) *Drug Discovery Today* 4, 3]. Specifically, it was pointed out in this report that the industry needs to become yet more responsive to the discovery revolution. According to PWC's Steve Arlington, 'by the year 2005, there could be as few as 13 industry giants'. The maths is compelling. According to the report, in order to boost revenues by 7% per annum in line with consensus forecasts for global sales, the industry leaders must, on average, generate an additional $28.9 billion in sales from new products by 2005. This translates into the launch of 24–34 drugs over a seven-year period, with each drug earning $1 billion to $1.45 billion.

This is all very well, but we see a Viagra only once in a blue moon. A successful new product, in any business, needs some attractive characteristics [Davis R.E. (1993) *J. Prod. Innovation Manag.* 10, 309–317]:

- Offer entirely new benefits not offered by existing products
- Offer a secondary benefit in addition to the key new product benefit

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- Make comparative claims versus competition
- Eliminate an important negative in existing products in the market
- Offer a higher quality product than those currently available
- Tap into current/emerging trends in society
- Offer a price advantage versus currently available alternatives

A drug could do with as many of these advantages as possible, but these are huge challenges. And superimposed on this is in the pharmaceutical industry is the necessity for rigorous clinical testing and the constraints of short effective patent lives.

Arlington has thrown down a challenge for some of today's leading authorities to address these issues at a special event – *Pharma R&Direction – Pharma 2005: An Industrial Revolution in R&D* – to be held in Barcelona in June (see *Diary* for contact details). 'Those companies which fail to restructure their R&D processes, track what they are doing, implement the right IT strategies and put the right skills in place will not survive in their current form' claims Arlington. The program will feature champions from big pharma, such as George Poste, and the biotech sector, such as Chris Evans. Let's hope the great men of R&D can show us the way.

David Hughes

Pharmacokinetic and toxicology screening

Over the past decade, combinatorial chemistry techniques have led to a revolution in the practice of discovery chemistry. The number of active compounds entering the preclinical testing phase of a typical drug discovery project has increased by orders of magnitude. Pharmacokineticists and toxicologists now need to develop high-throughput technologies to screen this flood of compounds efficiently. These technical developments, and the growing importance of genomics and bioinformatics in preclinical drug development, were the twin themes of a conference on pharmacokinetic and toxicology screening that was held recently in London, UK (21–22 January 1998).

Oliver Flint (Bristol-Myers Squibb, Princeton, NJ, USA) set the scene, describing the difference between traditional and combinatorial methods of discovery chemistry. The combinatorial approach may easily produce >500 potential lead compounds in a single project. Flint summed up the 'high-throughput dilemma'. With increasing numbers of compounds to test, and no corresponding increase in resources, less information can be obtained about each compound. The objective of predictive toxicology screening is simply to estimate the risk of failure in development. The design of high-throughput toxicology screens, including the choice of cell types, endpoints and measurement techniques, should reflect this straightforward need.

New technologies

New technologies for preclinical lead optimization that are now in use in the industry were described by several speakers, including Chris Atterwill (Roche Discovery, Welwyn, UK). Cytotoxicity screening, in which the measured endpoint is simply cell death, is relatively simple to scale up, but more complex mechanistic screens are likely to be more accurate. The pattern of gene expression changes under challenge by a toxic agent. Those genes that are upregulated under stress are termed 'stress genes', and their expression can be monitored if they are fused to easily detectable 'reporter' genes. Cells containing multiple copies of oligonucleotide probes for many different genes can now be placed on microarrays. The pattern of gene expression induced by a potential drug can then be measured by using these so-called 'gene chips'.

Another use of DNA array technology was described by Tim Gant (MRC Toxicology Unit, University of Leicester, UK). As gene expression is an arbiter of phenotype, it is possible to monitor the expression of genes involved in toxicological responses and so detect differential response to toxic challenges between cell types. Microarrays of oligonucelotides are now used to detect differences in gene expression between cell types and therefore to differentiate between more and less susceptible strains.

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