High-throughput chemistry and structure-based design: survival of the smartest

'...target rich but lead poor...'

David Bailey, Chief Executive Officer, De Novo Pharmaceuticals
David Brown, Research Director, Roche Discovery

The economic imperative behind new lead generation

Pharmaceutical industry managements are under pressure to increase the productivity of their R&D groups. Recent figures from PriceWaterhouse Coopers clearly indicate that the growth rate of the industry cannot be maintained if the current industry average of 0.5 new drugs registered per annum is not increased [Arlington, S. *Pharma R&D Directions 2000*, 26–28 June 2000, Barcelona, Spain]. Two or three new registrations per annum could be required, depending on the size of the company.

This was foreseen by the industry leaders, and their response over the past decade has been to couple R&D more closely to market needs, investing heavily in 'high-throughput' technologies in genomics, screening and chemical synthesis: the so-called 'industrialization' of drug discovery.

Medical need

In a 'double-whammy', these internal economic necessities for new products imposed on the industry are compounded by market pressures within the healthcare sector, which are increasingly emphasizing the pharmacoeconomics of medical need and patient benefit. With earlier drugs targeting 'easier' diseases and the more obvious points of pharmaceutical intervention now coming off patent, companies are being forced to work on more challenging disease areas. This often means working on hitherto unfruitful classes of targets, such as protein–protein interactions and transcription factors.

Opportunities presented by genomics

In a hypothetical sense, there has never been a greater opportunity to embark on speculative areas of research: the Human Genome Project is unearthing a plethora of potential targets. However, the potential for expensive failures at the clinical level is vast with unvalidated targets. Therefore, there is an urgent need to triage genomic information to find the best points of intervention, hence the increasing emphasis on functional genomics and population genetics to confirm the mechanisms of disease.

Technological response

The response of some corporate managements to the challenge of target validation appears to be to invest heavily in target assessment technologies, screening and combinatorial technologies or compound acquisition, to the advantage of supply companies. Although a reasonable level of investment in these areas is undoubtedly necessary, it is time to ask whether or not a change of direction is required, to introduce a more thoughtful approach to target selection and lead generation.

The effectiveness of the 'high-throughput' strategy is increasingly being questioned. There is no compelling evidence that the desired productivity increase is materializing from HTS. Comments heard at scientific conferences from industry insiders suggest that in most companies the investments in HTS and combinatorial chemistry have not reaped rewards in new lead discovery on the scale expected, and that it is too early to assess the success of high-throughput genomics and proteomics. Sir James Black (King's College London, London, UK) has suggested that these high-throughput technologies should come with a company health warning[1]! There is no doubt that companies remain 'target rich' but 'lead poor'. Moreover, the plethora of targets seeking viable leads occurred before genomics substantially increased the supply of targets, suggesting that lead discovery is now set to become an even greater bottleneck.

Chemical space and therefore creative opportunity

A more thoughtful approach would recognize that chemical space is vast, even when slimmed down to include only

1359-6446/01/$ – see front matter PII: S1359-6446(00)01596-8

structures with potential in drug development. Figures such as 10^{80} chemicals are bandied around, and however dubious the accuracy of these, they at least highlight clearly that the typical company compound collection of 10^5–10^6 chemicals represents only a minute fraction of useable chemical space.

Another approach would be to increase the probability of success in screening by obtaining more information for the preselection of compounds before screening. This would entail matching the compound to the target rather than randomly screening all available compounds against all available targets. The thinking in many companies appears to be towards this strategy. With the development of combinatorial chemistry, particularly parallel synthesis methods, it is now possible to screen in HTS desired compounds rather than only those that are available. Target-specific subsets can therefore be selected from company compound collections and supplemented by the rapid parallel synthesis of targeted libraries.

Increasing competition and diminishing patent life

Improving the probability of screening success appears to be an obvious approach; therefore why has its application been lacking? In fact, some companies have pursued this strategy and with some success. However, application has been limited to a few classes of target for which sufficient information is available. The urgent requirement of the industry is the development of methods to increase the supply of information that will guide the matching of a compound to a target. Companies are using existing data to match target classes to known active series, but there are large areas in which our knowledge is insufficient. Increasingly, computational techniques could be used to increase our knowledge.

The impact of computational techniques

Computational chemistry technology made its appearance in the industry in the early 1980s. Initial enthusiasm for structure-based ligand design (SBLD) gave way to caution when few new leads emerged from such investments. More recently, there has been recognition of the extreme subtlety of drug-binding events. Nevertheless, SBLD methods have resulted in several breakthrough classes of new drug (Table 1).

However, there have been fewer successes than originally hoped. Although the basic design of a new lead by a SBLD method might be mostly correct, small imperfections will lead to inactivity in prototype compounds. What is needed is the ability to make and screen many close analogues rapidly, hoping to overcome the remaining element of uncertainty in the design. That is now possible with the current state of development of focused combinatorial libraries. Although combinatorial chemistry can be criticized for reliance on numbers rather than design, and SBLD criticized for the opposite reason, SBLD and combinatorial chemistry are set to become partners, each compensating for the weakness of the other.

Table 1. Site-directed design: growing evidence of success

Drug	Target	Pharmaceutical company
Dorzolamid	Carbonic anhydrase	Merck Sharp and Dohme (Harlow, UK)
Saquinavir	HIV protease	Roche (Welwyn, UK)
Relenza	Neuraminidase	Biota (Melbourne, Australia)
AG85, AG337, AG331	Thymidylate synthase	Agouron (La Jolla, CA, USA)
Ro466240	Thrombin	Roche (Basel, Switzerland)

A key development in the computational world has been the arrival of *de novo* design algorithms that use all available spatial information for both target and ligand to design novel drug-like ligands. Coupling these algorithms to the rapidly growing body of information from structural genomics could provide a powerful new route to designing novel, patentable compounds for more challenging targets, such as protein–protein interactions.

Organizing for success

The close juxtaposition of computational and combinatorial chemistry resources is essential if the full benefit of these developments for lead generation is to be gained

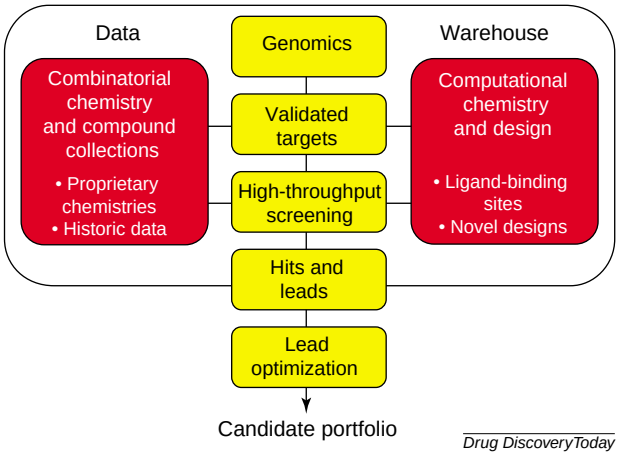

Figure 1. Integrating virtual and focused screening data.

(Fig. 1). Random screening efforts can be focused into highly productive, information-rich campaigns.

One example of this is the elegant work by GlaxoWellcome on gene family targeting within the extended nuclear-receptor gene family[2], including the peroxisome proliferator-activated receptor (PPAR) gene family. 'Data warehousing' gives the opportunity to obtain maximum benefit from these developments. The advent of high-content screening, using, for example, gene expression microarrays, promises to extend this information into the area of absorption, distribution, metabolism and excretion (ADME) toxicology profiling. Substantially *in silico* lead discovery could soon become a reality.

Conclusions

As genomic data increase the supply of potential targets, an alliance of computational chemistry with HTS and combinatorial chemistry is crucial to increase the industry's success rate in lead generation. Although most companies have made all three of these investments, the balance of investment might need review, as might the strategy with which these three technologies are used in concert.

References

1 Black, J. (1999) *SCRIP*, 2496, 12

2 Willson, T.M. *et al.* (2000) The PPARs: from orphan receptors to drug discovery . *J. Med. Chem.* 43, 527–550

David Bailey
Chief Executive Officer, De Novo Pharmaceuticals
59, St Andrews Street, Cambridge, UK, CB2 3DD
tel: +44 01223 327391
fax: +44 01223 327392
e-mail: david.bailey@denovopharma.com
and
David Brown
Research Director, Roche Discovery
Welwyn Garden City, UK

How will pharmacogenetics impact the future of research and development?

'Pharmacogenetics has the potential to radically change the pharmaceutical industry'.

Allen D. Roses, Genetics Directorate, GlaxoWellcome, Middlesex, UK

The increasing cost of drug discovery and development, and marketing of a new chemical entity, is one factor that drives large pharmaceutical companies towards blockbuster drugs. However, a narrow portfolio of medicines can expose companies to risk. If the number of patients suffering from serious adverse events is high enough, then a new wonder drug can be withdrawn from the market, leaving tens of thousands of patients who would have benefited with no access to this drug. Further, this opens up the market to other companies.

Alternatively, a drug for a common disease might only be effective in a small proportion of patients, resulting in restricted approval for use by government 'value' committees. It might also be kept off formularies on cost-effectiveness grounds because the drug might consequently be prescribed for many patients who receive no benefit.

Evolution of pharmacogenetics

Advances in pharmacogenetics will provide opportunities to resolve this problem. Let us consider pharmacogenetics and medicine response profiles (MRPs), which will be developed from these advances as tools that use information from a small fraction of patients' DNA to predict their response to a medicine[1]. It is probable that there will be a rapid evolution in the impact of this technology on research and development, and in the application of this technology to the delivery of healthcare.

First, this technology will be applied to currently marketed medicines that are associated with rare severe adverse events in a small proportion of patients. These proof-of-principle studies will evaluate the technology and potentially enhance the risk:benefit ratio of these medicines. The initial studies of this type are ongoing and will be completed over the next

1359-6446/01/$ – see front matter PII: S1359-6446(00)01598-1