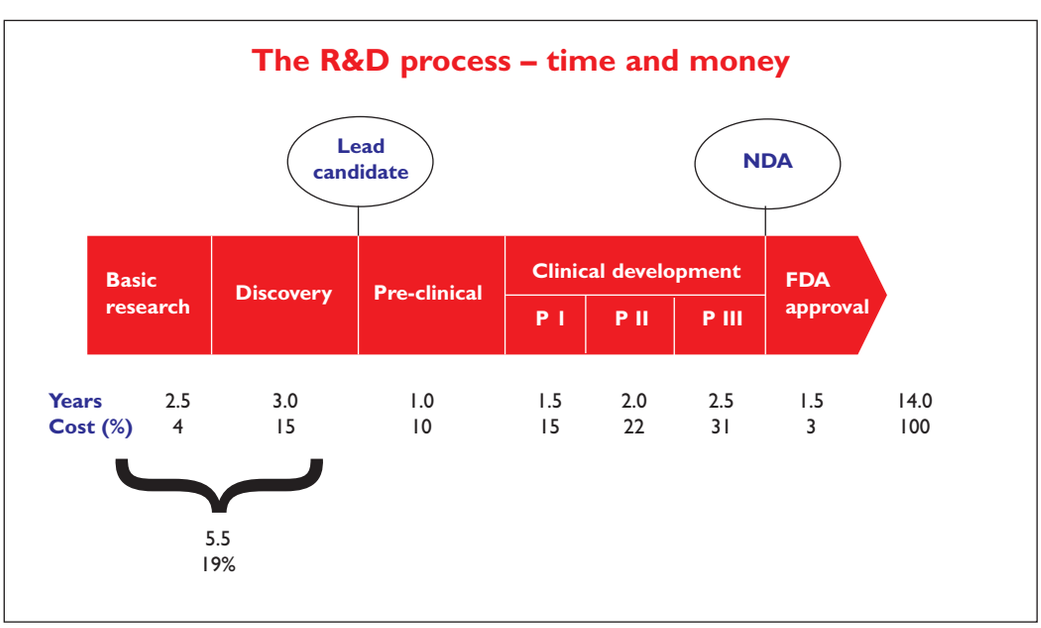
Balancing quantity and quality in drug discovery

There is a need to innovate in order to stay ahead, a need to maximise the value of the R&D engine by increasing the flow of novel drug candidates and yet, reduce the time to market. Does access to more targets mean a higher probability of success? Or will more targets increase complexity and lead to higher downstream attrition rates? Companies are faced with the dilemma of not knowing which early stage candidate will become the blockbuster that will help maintain their required growth rate.

By Eva-Lotta Allan

A pharmaceutical company now needs to spend on average $880 million to bring a drug to market[1]. This figure represents a trebling of cost over the last 10 years – the result of more complex science required to discover, develop and register new drugs, coupled with increased regulatory requirements. Close to 20% of the $880 million and approximately 5.5 years are spent in basic research and discovery (**Figure 1**). There is an urgent need to improve the efficiency of the drug discovery process providing a higher output of well validated, high quality lead molecules ready for preclinical development (**Figure 2**). The industry is faced with a new chemical entity (NCE) crisis. Historically discovery has provided five NCEs to development per thousand discovery employees. The challenge is to increase this output to 14 NCEs per thousand discovery employees in order to sustain long-term growth[2]. How can this be achieved? How can companies maximise efficiencies of internal processes to



Source: McKinsey & Co, Lehman Brothers, PhRMA, FDA

Figure 1

Figure 2

Has R&D efficiency improved?

	1991-1995	1996-2000	
NCE output/approvals (products per company)	12.3	7.2	-41% change
R&D spend (US$ billions per company)	5.9	8.5	44% change
NCE peak sales (US$ per product)	536	786	46% change
Industry-wide blockbuster launches (no of products)	15.0	12.0	

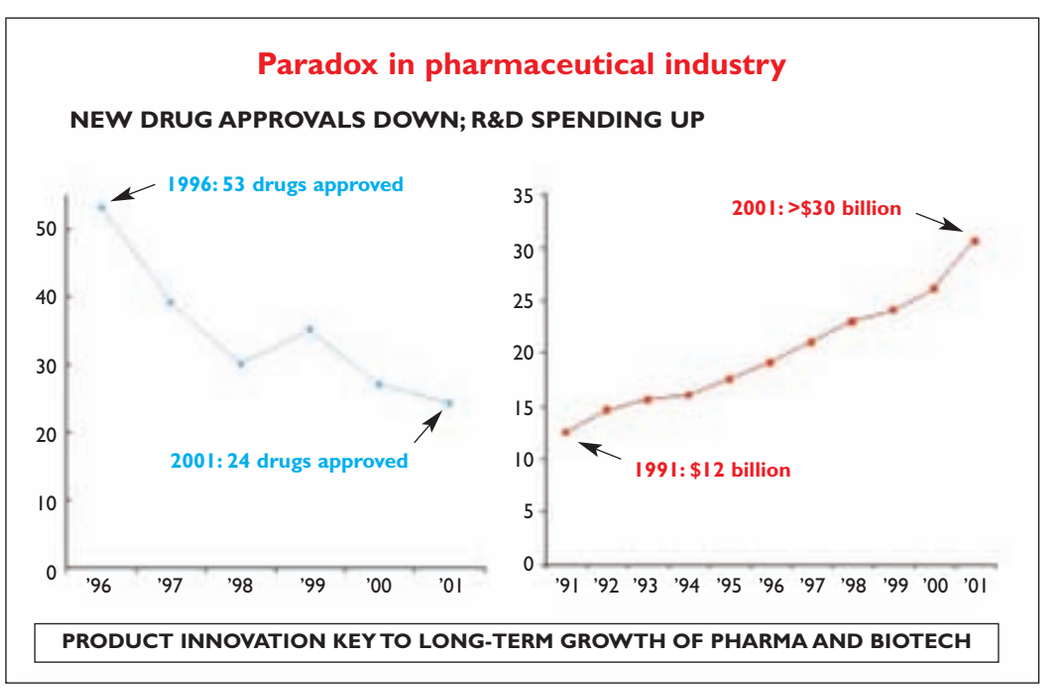
Source: E Fleming and P Maa, Nature Reviews, Vol 1 Oct 2002

ensure increased R&D expenditure bears fruit? How can they improve the efficiency of R&D processes through the use of new drug discovery technologies?

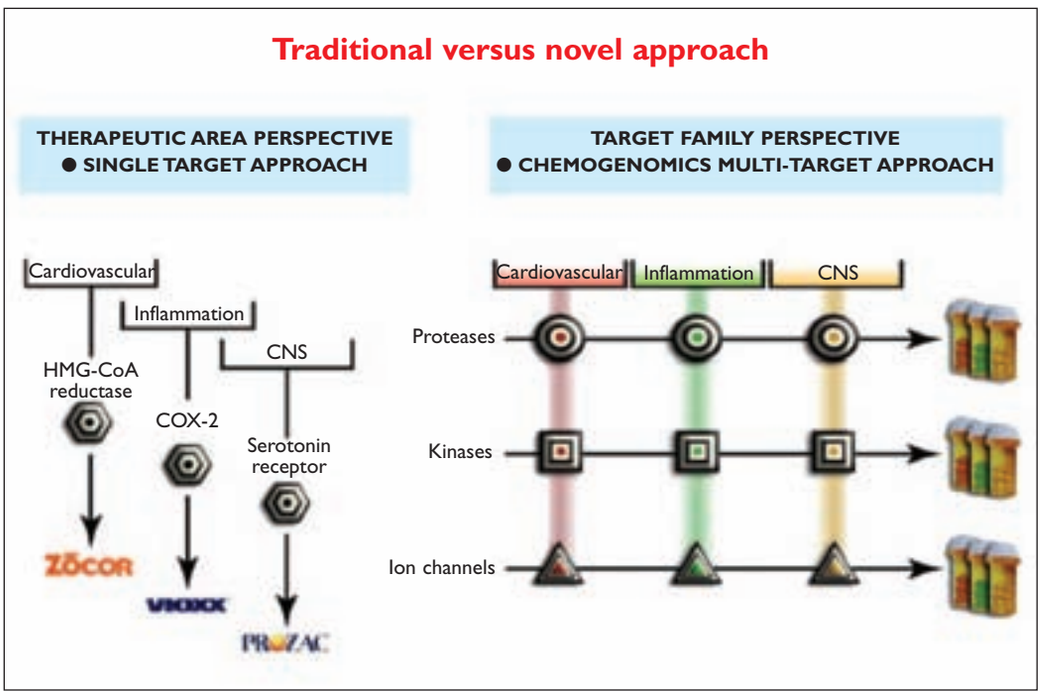
More targets = increased probability of success?

Perhaps the sequencing of the human genome[3] could be the solution to some of the issues. The plethora of novel targets, which can be accessed today through the human genome project and identification of more than 35,000 genes, has evidently not yet provided the same exponential increase in 'preclinical development ready' molecules. The complexity of pursuing novel proteins and the genes they encode has increased due to the lack of biological information surrounding these proteins. It is very important to understand the biological function of these unknown proteins prior to designing novel lead molecules. Pursuing unvalidated targets may lead to an increase in attrition rates, and this unfortunately may not occur until a molecule has reached proof of concept in the clinic and by then most companies have spent

Figure 3



Source: PhRMA, Pharmacy Times



Source: Vertex Pharmaceuticals Inc

Figure 4

close to half a billion US dollars. Despite the avalanche of novel targets which the human genome project has provided, companies realise that this may not increase the probability of successfully bringing a new drug to market.

A new culture

A new discovery culture has emerged requiring a repositioning of research capabilities to meet demands of novel complex technologies such as genomics, high throughput proteomics, high throughput screening and parallel synthesis. The ability to rapidly prioritise targets is changing scientists' way of thinking. It is important to discard failing targets at an early stage and to rapidly select new ones that show greater promise.

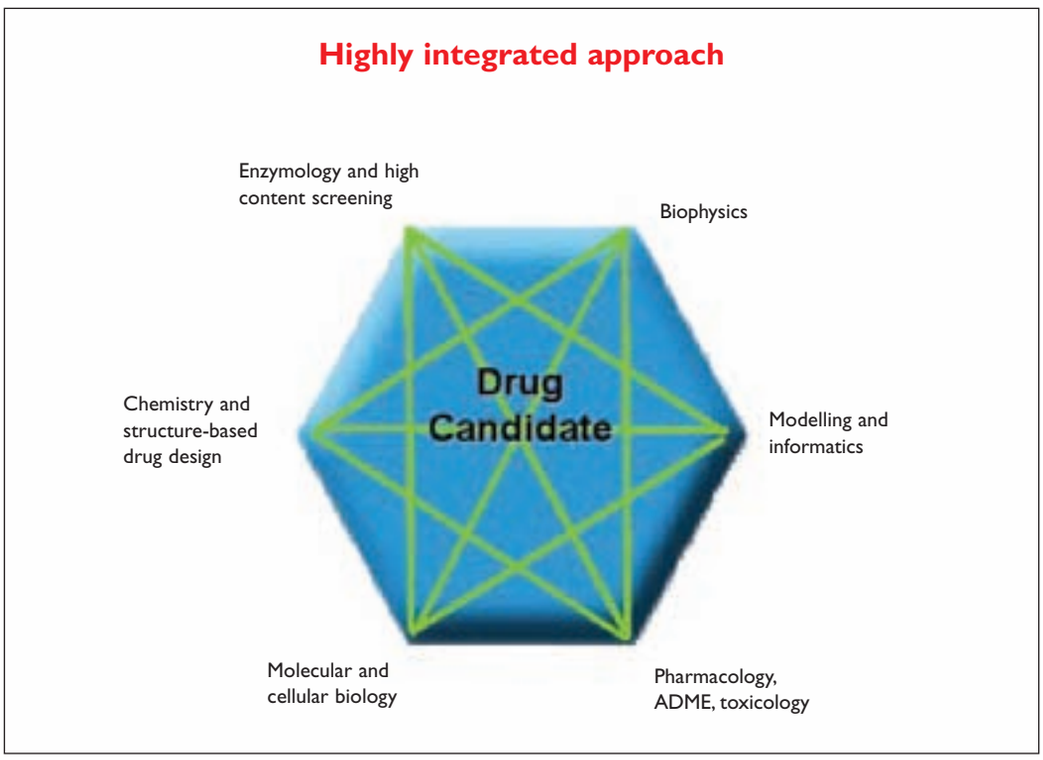
Need for innovation

A consequence of the increased expenditure of taking a drug to market and the decreasing numbers of new drugs being approved is an even greater need to capture innovation (**Figure 3**). 'Me-too' products cannot sustain the required growth and market exclusivity in new classes is rapidly declining. Pharmaceutical and biotechnology companies alike need innovative products to justify premium pricing and to gain market share. According to McKinsey & Co, by 2010 more than $200 billion in peak revenues will be at risk from patent expiration unless there are significant legal changes. In comparison, worldwide pharmaceutical sales in 2000 were just over $300 billion[4]. An average of 75% of the top 20 pharmaceutical companies' 1999 revenue will face generic competition by 2005 and 'value-added generics' will pose a serious threat to small and medium-sized companies[5].

Quantity versus quality

What does a company need to take into account when optimising its portfolio at the early stage of drug discovery? A company has to decide what it is trying to balance and what it is trying to achieve. Companies balance early-stage risk versus long-term rewards by investing in programmes, which could potentially yield the blockbusters of the future. A company also needs to strike a balance between which novel technologies to build in-house versus external alliances and outsourcing arrangements. The dilemma is not knowing which technologies to invest in or which approach to take to generate the best rewards. Furthermore, balance in drug discovery between quantity and quality of potential drug development candidates is fundamentally very important. The temptation of progressing an overabundance of poorly validated molecules into formal development which subsequently may fail, must be balanced against the time spent on carefully identifying and validating druggable targets which downstream can lead to a drug being developed and brought to market within an acceptable timeframe.

Figure 5



Source: Vertex Pharmaceuticals Inc

Maximising drug discovery efficiency

It is important to recognise that it is not sufficient to establish the novel discovery technologies available today, in-house or through collaboration with enabling technology companies. The key is 'technology integration'. Only a highly integrated multi-disciplinary approach, integrating disciplines such as genomics, biology, chemistry, structural biology, modelling and pharmacology can maximise the flow of novel drug candidates to meet the challenging goals.

One approach, which has the potential to increase the flow of NCE into development, is to establish a technology platform in discovery focusing on gene families as opposed to the traditional therapeutic area approach (**Figure 4**). One of the key attributes of such a platform is that it is highly integrated and allows a massive parallel drug design to be performed. Whereas many large pharmaceutical companies have the individual disciplines in place, they are often not integrated (**Figure 5**). Many may have difficulty reorganising the entire infrastructure of a research department from the traditional therapeutic area focused approach to a gene family approach. At the same time it is tough for a young biotech company to afford the investment in the technologies required to successfully establish a highly integrated approach.

This integrated technology platform, referred to as chemogenomics (**Figure 6**), can leverage similarities among members within gene families to allow a rapid transfer of activities from one sub-class of targets to another, 'target hopping'. Target validation is performed using a variety of appropriate technologies. Additionally, compounds are morphed from one chemical class to another, 'scaffold morphing'. The chemogenomics approach allows the generation of focused libraries with drug-like properties by library teams focused on a particular gene family, eg kinases. Moreover it allows the systematic capture of vast quantities of chemical intellectual property at a very early stage. Other disciplines including protein expression and purification, X-ray crystallography and computational chemistry form part of this highly efficient drug discovery engine, with the goal to maximise the production of new chemical entities.

What lies ahead?

As the pharmaceutical industry evolves and efficiencies are gained, ensuring long-term growth targets are met, we will continue to see novel technologies become an integral part of drug discovery and development. Ways of lowering the attrition rate will include screening *in silico*, high throughput genomics, early ADME (Absorption, Distribution, Metabolism, and Excretion) and tox-

icity prediction to filter out unwanted properties at an early stage. Longer term, biomarkers and SNPs (single nucleotide polymorphism) will routinely be used as part of clinical trials.

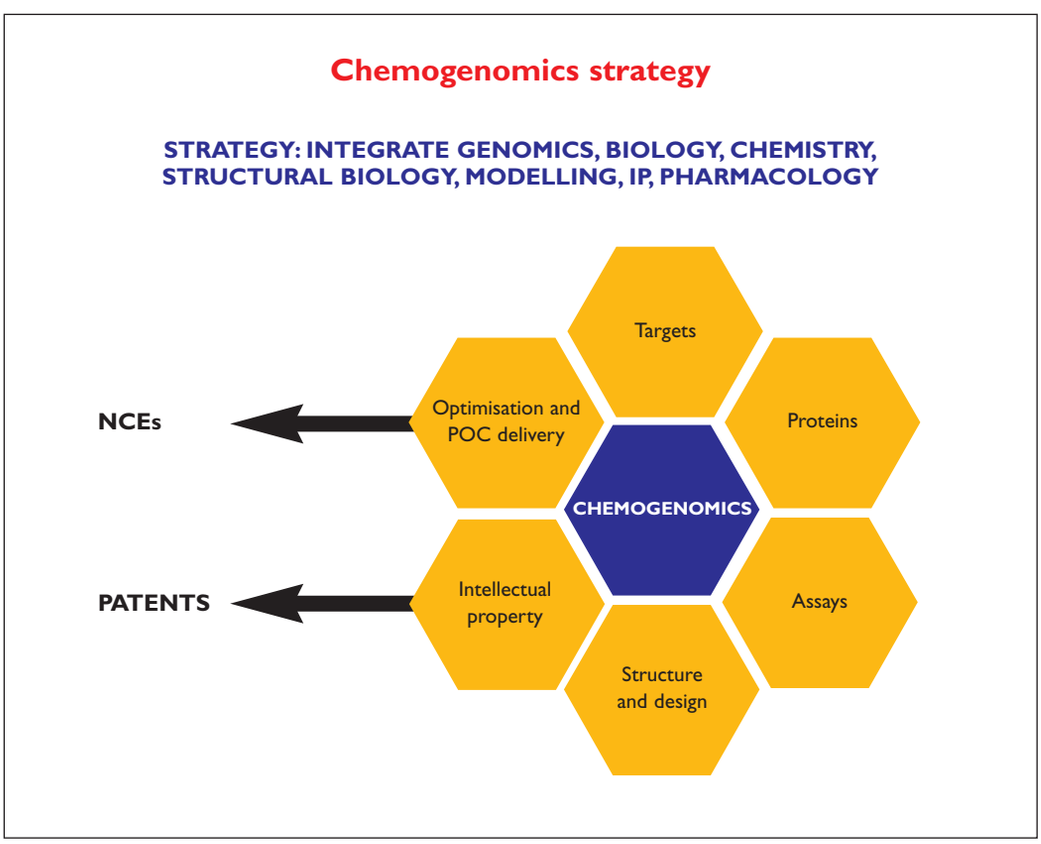
Gene family research is one drug discovery approach which has the capabilities of improving the efficiency in discovery, generating a sustainable growth for pharmaceutical and biotechnology companies alike. This approach balances quantity and quality of lead molecules progressing into development. Chemogenomics combines diverse technology disciplines and an integrated organisational philosophy allowing drug discovery timelines to be reduced while increasing success rates in early development. Gene family research and other approaches will continue to evolve as the industry remains under pressure from patent expirations, pricing pressures, intensified competition and pressure from financial and political sources. These increasing demands are all strong drivers for continued change.

There is always a desire to continuously improve. The Japanese have a word for this: KAIZEN[6]. The word was originally defined as: "KAIZEN means improvement. Moreover, KAIZEN means continuing improvement in personal life, home life, social life and working life. When applied to the workplace, KAIZEN means continuing improvement involving everyone – managers and workers alike". DDW

Eva-Lotta Allen has more than 16 years' experience in business development. She joined Vertex in 2000 from Oxford Asymmetry International and her role involves all aspects of business development including partnering Vertex's own programmes, in-licensing of products and technology. Prior to Oxford Asymmetry International, Ms Allen held various commercial positions with OGS and Amersham International. She holds a BSc in Microbiology from the University of Stockholm and worked in the Tumour Biology department at the Karolinska Institute before moving into the commercial environment.

References

1 The Boston Consulting Group Report Nov 2001.
2 Outsourcing Industry Monitor, Pennsylvania Merchant Group, Oct 1999.
3 Venter, J et al. The sequence of the human genome. Science 291, 1304-1351, 2001.
4 Fleming, E and Maa, P. Nature Reviews Drug Discovery Vol. 1. Oct 2002.
5 SMI Publishing: The Generics Industry in 2005: A New Threat to Pharma.
6 Massaki Imai. KAIZEN, the key to Japan's Competitive Success.



Source: Vertex Pharmaceuticals Inc

Figure 6