MEDICINAL CHEMISTRY

progress through innovation

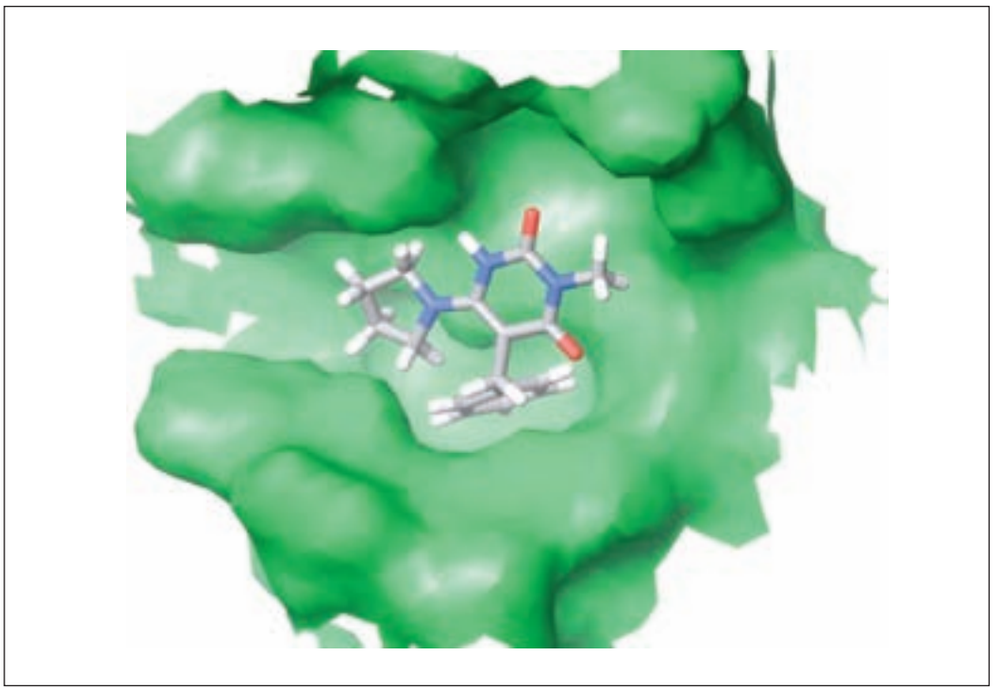
Medicinal chemistry is a specialised science that has evolved to encompass a broad range of disciplines concerned with the identification, synthesis and development of drug-like compounds for therapeutic use. It needs a wide range of expertise, developed through years of training, dedication and learning from best practices in order to produce drugs that are good enough to enter clinical trials in patients.

By Dr Terry Hart

In the early days of drug discovery, medicinal chemists often optimised and developed compounds without much knowledge of the drug target or pathway in mind. It was a largely subjective process where chemistry-driven elaboration of chemical structures was undertaken and these compounds were often tested directly *in vivo* to optimise the biological response without much thought of ADMET properties. New technologies have had a huge impact on drug discovery since the mid 20th century. The early influence of experimental pharmacology, which was first employed to study drug side-effects, coupled with advances in cell biochemistry led to the identification of many enzymes and receptors as new drug targets, thus enabling medicinal chemists to develop compounds to interact selectively with targets for a wide range of therapeutic areas.

The advent of molecular biology and functional genomics shifted the focus to tackling disease through an understanding of pathway analysis and through this, the identification of drugable targets. Novel drugs were therefore developed, especially the original HIV protease inhibitors, using structure-based drug design. To most chemists this is by far the most intellectually satisfying part of drug discovery, but good structural knowledge of the drug target is essential since drugs are developed within the confines of an accurate binding site model and optimised through precise iterative chemical synthesis.

The high-throughput era of genomic sciences heralded an alternative, more empirically random approach for drug discovery based upon a numbers game. The generation of large high-throughput screening (HTS) libraries, created by combinatorial chemistry was based upon the concept of fewer structural variations across a large number of drug-like scaffolds. However, the original templates of the early 1990s were anything but drug-like, and the Lipinski rules evolved as a response to understanding their limitations. Many drug companies are now spending considerable time and effort ridding their compound collections of these particular molecules. In general, the early combichem libraries did not produce the success that



Computer-aided drug design: a virtual screening hit

was expected due to the lack of design in their construction resulting in extremely high attrition rates during pre-clinical stages.

With the pressure to increase the number of drugs receiving market approval, the science of medicinal chemistry needed to change in order to address the high attrition rates in pre-clinical and early clinical earlier on in development. It is worth specifying that medicinal chemists are responsible for designing and synthesising drugs that are robust enough to enter Phase II clinical trials to test proof of concept in patients. If this is not achieved then we have failed, because we have used precious time and resources but learnt nothing of value in curing disease. However, although the predictive tools that medicinal chemists use in drug discovery have improved dramatically during the past 10 years, small molecule drug discovery is getting far more difficult to do. One of the main reasons for this paradox is that medicinal chemists now need to have early stage strategies to solve not just the typical potency, selectivity and exposure problems we encounter, but also the theoretical and idiosyncratic toxicological hazards that can potentially occur in man once the drug goes into a wider patient population.

Medicinal chemistry has, therefore, grown to encompass a greater range of scientific disciplines in the drug discovery process in order to minimise the cost, time and risk of development. The arrival of newer high powered computational capabilities was one catalyst for this approach. Improved computational methods for reducing the attrition rate of compounds, due to, for example, bioavailability or toxicity issues, can be aided by virtual design and screening using specialised capabilities early in the developmental process. These capabilities mean that medicinal chemists can produce compounds with a superior starting point, providing significant cost savings during later optimisation as they have a reduced chance of failure.

Many of the design strategies and tactics that we routinely employ today in drug discovery would not be recognised by scientists 10 years ago, and I think that it is safe to say that what we will be doing in 10 years' time will have little resemblance to today's science. Accessing new drug discovery tools and technologies, especially for predictive ADMET, can therefore provide a company with a significant advantage in today's highly competitive environment.

Sophisticated models

True lead optimisation, with the target product profile of the clinical candidate in mind, in order to design a robust drug that is both effective and safe in a wider patient population, is one of mankind's greatest scientific challenges. An alternative approach to the large combichem libraries (10,000 plus molecules) are smaller focused arrays

of molecules (100-500 molecules) with a lower level of compound diversity but high specificity towards a drug target family. These 'chemogenetic' arrays are designed and developed within the confines of a particular pharmacophore model for the particular target family of interest, but with drug-like and ADMET properties in mind. This high level, knowledge-based approach to medicinal chemistry is based upon a marriage between expertise in computer-aided drug design that can propose chemical structures based upon an accurate pharmacophore and the expertise of the medicinal chemist to know what can be made. The process involves understanding how a particular ligand interacts with a diverse number of multiple receptors and then involves designing focused compound arrays to achieve drug selectivity within different but closely related families of targets. The focused arrays can be targeted towards traditional drug targets, eg enzymes, GPCRs, ion channels and nuclear receptors, however the current challenge is to develop focused arrays for particular subtypes of these broad families.

The compound arrays must be synthetically feasible and, to minimise the attrition rate in preclinical testing, must also conform to specific properties regarding adsorption, distribution, metabolism, elimination and toxicity (ADMET). Designing focused arrays to encompass a diverse range of chemical space within the boundaries of the ADMET model and synthetic capabilities is now an essential first stage in compound development. The ADMET constraints established from literature mining, *in vitro* and *in vivo* studies are often compiled into computational packages to enable chemists to predict the drug-likeness of a compound.

Suitable compounds are developed using a variety of methods including ligand and structure-based design, combinatorial docking and pharmacophore screening. These are developed further using lead docking analysis, induced fit docking, QM-MM methods, free-energy simulations and QSAR analysis. Many companies also now use real time *in silico* visualisation tools to help medicinal chemists optimise the drug like properties that are thought necessary for having optimum ADME properties.

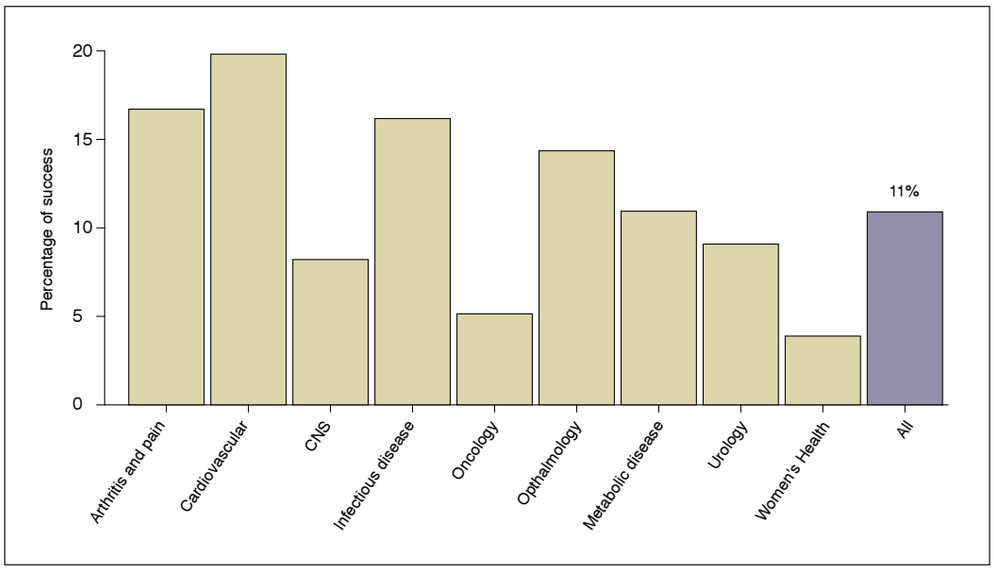
The end-point of the CADD-medicinal chemistry design process is a focused array of molecules with a superior starting point for hit to lead program. During this hit to lead phase, expertise in synthetic chemistry is critical for success. The scientific nuances and boundaries of the SAR need to be quickly understood so that informed decisions can be made as to which of the many ways forward offers the best chance of success. Most recently, newer technologies, such as microwave chemistry used in conjunction with palladium and polymer supported chemistry and parallel purification, have quickly become important methods for generating analogues. Another increasingly important skill for a medicinal chemist in the hit to lead phase is the judicious use of employing novel heterocyclic chemistry to its full advantage, as this often opens new vistas for patent novelty and offers excellent opportunities for rapid parallel synthesis while retaining drug-like properties. The greatest skill of a medicinal chemist is the ability to draw on all of these disciplines for innovative drug design and synthesis. In the race to develop novel compounds in a diverse range of therapeutic areas, highly specialised medicinal chemistry expertise is currently in great demand by biotechnology and pharmaceutical companies.

Outsourcing of medicinal chemistry

In this highly competitive, post genomic, target rich age, drug discovery research in multi-national pharmaceutical companies is often hampered by their lack of medicinal chemists. Typically the best leads will, of course, be pursued in-house, but the outsourcing of hit to lead or back-up programmes to a professional external medicinal chemistry provider should enable companies to move faster through both these stages and allow them to test proof of concept in patients more quickly.

Hit to lead, back-up chemotype and fast follower programmes have in the past been the mainstay of medicinal chemistry outsourcing of pharmaceutical companies. From a small range of lead candidates, pharmaceutical companies would often outsource a back-up chemotype to specialised medicinal chemistry providers which in many cases superseded the in-house lead candidate. Fast follower candidates (drugs that have improved properties to those first-in-class drugs which have shown proof of concept in man using the same mechanism of action) were often outsourced to medicinal chemistry providers due to resource constraints. Because of medicinal chemistry skill shortages, multinational pharmaceutical companies need to use their own medicinal chemists as drug designers and discoverers, not as pure synthetic organic chemists. Therefore, there is a growing trend for companies to outsource synthetic chemistry projects, such as array, building block and custom synthesis.

In contrast, at the other end of the scale, smaller biotechnology companies are increasingly being driven by their investors to move into drug



Clinical success rates from first clinical trial to registration
Data obtained by Datamonitor in the Pharmaceutical Benchmarking Study. The data are from the 10 biggest drug companies, 1991-2000

discovery in order to leverage their proprietary biology technology, and these same companies now represent a significant proportion of the synthetic chemistry and medicinal chemistry outsourcing market. This is because biotechnology companies usually do not have the necessary knowledge or resources to fully support their drug discovery initiatives and therefore need to outsource most, if not all, of their drug discovery research. Typical projects required by biotechnology companies are hit to lead and lead optimisation projects because the expert knowledge and synthesis capabilities offered by medicinal chemistry service providers can often overcome many of the problems that are associated with lead development to drive a compound through to market.

Concerns over retention and establishment of intellectual property (IP) can be a barrier to outsourcing, especially for the larger pharmaceutical companies, who need to protect carefully any potential blockbuster drugs. Larger pharma tend to avoid those service providers who have a high turnover of staff in companies where confidentiality agreements and patents are difficult to enforce. This is because they realise full well the financial implications of losing proprietary knowledge. To combat this, outsourcers should consider working with those providers who behave ethically to their employees and who do not undertake their own early stage drug discovery research programmes.

Value, not price, should be the main driver for companies to choose a service provider. The famous quotation from the English philosopher Ruskin remains, perhaps, even more valid today.

***John Ruskin** (1819-1900)*
Looking for value?
It's unwise to pay too much but it's unwise to pay too little.
When you pay too much you lose a little money, that is all.
When you pay too little, you sometimes lose everything, because the thing you bought was incapable of doing the thing you bought it to do.
The common law of business balance prohibits paying a little and getting a lot.
It can't be done. If you deal with the lowest bidder, it's well to add something for the risk you run.
And if you do that, you will have enough to pay for something better!

Current challenges

The greatest challenge is to reduce the number of drugs that fail in pre-clinical stages, since this is responsible for the very high cost of bringing a drug to market. The accountant's mantra of 'fail early/fail cheap' is now central to the drug discovery process, although I suspect that most medicinal chemists would prefer to succeed early and to succeed cheap, but this involves considerable early design work. Analysis of ADMET properties, especially toxicology, and establishing the boundaries for drug design is the area undergoing the largest growth, as these properties largely decide whether a compound is rejected immediately or taken forward for optimisation. Outright show stoppers include irreversible protein binding, idiosyncratic toxicity,

mutagenic toxicity, hERG, phospholipidosis, phototoxicity, while addressable problems could typically be due to oral bioavailability, weak Cyp inhibition, selectivity or minor solubility issues. Great strides have been made during the past 10 years to understand all these different drug design problems and better *in silico* predictive tools and cell-based assays are continually being developed.

It is quite evident that ADME profiling using *in silico* and cellular approaches has successfully resulted in a reduced attrition rate. Predictive toxicology remains a big problem to be solved, since this is now responsible for a large proportion of failures in the pre-clinical stages. Chemistry service providers that have developed a range of *in silico* and mathematical capabilities are now employing additional *in vitro* approaches to test and predict the efficacy of potential drug compounds. *In vitro* screening has become a critical tool for the medicinal chemist to assess potential toxicology problems, enabling them to rank clinical candidates. The results from *in vitro* studies are often fed back into the *in silico* models to further refine and predict drug-likeness.

To support their customers' drug discovery initiatives, medicinal chemistry outsourcing companies must now include state of the art *in vitro* and *in silico* approaches. These companies must be a 'one-stop-shop' that can provide the necessary expertise to enable them to maintain their competitive advantage. Medicinal chemistry providers must, therefore, draw upon a greater range of disciplines to fully support customer initiatives through an innovative approach to drug discovery and development.

Meeting the challenge

Due to the ever-changing face of the industry, outsourcing providers must not only adapt rapidly to the industry pressures and change, but must also try and predict the future direction of the industry. This requires adaptability in the business model and also flexibility to undertake strategic partnerships with other service providers to support customers' drug discovery initiatives.

The key to successful partnering is the development of good relationships between scientists of all disciplines; regular face to face contact ensures a synergistic process that complements the capabilities and knowledge of both parties to develop a clear understanding based upon trust. Empowering chemists to take an entrepreneurial approach to chemistry ensures a customer-focused, specialised service.

Medicinal chemists now, more than ever, need, in addition to their core expertise of synthetic organic chemistry and CADD, a broad range of expertise covering cell biology, pharmacology, formulation science and pharmacokinetics. We are entering a new chemogenetic age of knowledge-driven drug discovery where medicinal chemistry is driving the drug discovery process and medicinal chemists need to take the leadership role in all phases of the target identification to preclinical candidate phases. DDW

Dr Terry Hart *joined Peakdale Molecular in 2005 as Medicinal Chemistry Services Director. He has more than 20 years' experience in the pharmaceutical and biotechnology industry both in drug discovery research and in senior management roles. Prior to joining Peakdale Molecular Terry served with two of the top pharma companies: RPR (Sanofi-Aventis) and Novartis. While at Novartis Terry was the co-inventor on the patents for compounds which have entered clinical development for pain, schizophrenia and anxiety.*