selectivity. We have independently obtained similar data in our internal screening program, and kinase-screening providers, such as ProQinase GmbH (http://www.proqinase.com) and Upstate Biotechnology (http://www.upstatebiotech.com) have also reported the lack of selectivity of numerous literature standards [4].

As in any endeavour, the quality of the work is related to the quality of the tools, and such a truism is most pertinent in the field of signal transduction research. We would strongly caution researchers in this area against using weak, non-selective ligands as 'inhibitors' of particular enzymes or signalling cascades, such as those described above, to underpin conclusions about the fundamental involvement of specific proteins in disease processes. Fortunately, given the interest in both academia and industry in the discovery of kinase inhibitors, particularly using rational drug-design principles, potent and selective inhibitors for many kinases are continually being identified, and over time these might enable the correction of some of the erroneous data that has emerged from the use of poorly specific kinase inhibitors.

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Mastering medicinal chemistry: strategies, issues and success stories

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Cambridge Healthtech Institute's (CHI) 11th Annual *Molecular Medicine Tri-Conference* (http://www.chiMolecularMed.com) was held 23–26 March 2004, in San Francisco, CA, USA. The conference featured four tracks (*Genomic Drug Discovery*, *Business Strategies*, *Mastering Medicinal Chemistry* and *Molecular Diagnostics*) and attracted an audience of ~1000 scientists along with 75 exhibitors.

The *Mastering Medicinal Chemistry* track was sub-divided into four sections: Organizing Discovery Teams, Medicinal Chemistry at an Emerging Company, Optimizing Leads and Success Studies in Medicinal Chemistry. Each section featured insight from industry leaders through keynote presentations, spotlight talks as well as interactive 'think-tank' sessions that elicited comments from the attendees, leading to lively discussions and debates.

The business of drug discovery is risky, challenging and expensive. In 2003, only 35 new medicines were approved by the FDA (21 small molecules and 14 biologics) from the hundreds that reach clinical trails each year [1]. When considering the number of compounds that fail, both preclinical and clinical, the cost to produce one new drug is estimated at 1 billion US dollars with an overall attrition rate, from target to IND, of 76% [2]. In light of this, industry leaders are bringing to bare the latest technology in order to meet the challenges of modern drug discovery. For instance, Ismail Kola, Senior Vice President, Basic Research at Merck & Co. (http://www.merck.com) delivered a keynote presentation on the use of genomic technologies in drug discovery. He discussed how Merck is applying an integrated battery of modern genetic and molecular profiling technologies (including bioinformatics, human and mouse genetics and transcriptional profiling) to assess target viability and prioritization. A similar approach, relying on chemical biology and gene family-oriented research, was described by H. Peter Nester, Head of Chemical Biology – Proteases, from Aventis Pharma (http://www.aventis.com).

Organizing effective drug discovery teams

One of the think-tank sessions focused on how the pharmaceutical and biotech industries can organize more effective drug discovery teams. Christopher Lipinski (Adjunct Senior Research Fellow, Pfizer; http://www.pfizer.com) pointed out that the interplay of the disciplines of chemistry and biology ultimately lead to the success of a drug discovery program; however, there are several disconnects between the two disciplines. The most fundamental disconnect concerns the definition, or

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perception, of 'what is a good target?' On this question, chemists and biologists have distinctly different views. To the medicinal chemist, a 'good' target is a biological pathway that can be intercepted in a useful sense by an orally active small organic molecule; by contrast, a biologist views a 'good' target as a biological pathway that can be intercepted in some way to provide a useful therapeutic outcome. Clearly, chemists and biologists in the drug discovery industry struggle with these mis-matched concepts of what constitutes a 'good' target in battling for chemistry support for new programs, and bridging this gap in ideology is an important step in organizing more effective drug discovery teams.

Li Chen (High Throughput Chemistry, Hoffamn-LaRoche; http://www.Roche.com) and Christoph Huwe (Automated Medicinal Chemistry, Schering AG; http://www.Schering.com) both stressed the importance of integrating new technologies into the laboratories of medicinal chemists to enable them to keep up with increasing expectations and pressures to produce. Key to the success of this approach was the presence of a core group with expert knowledge of the technologies; significantly, only robust, proven technologies, such as liquid-handling robots, microwave synthesizers and automated purification equipment, were disseminated across medicinal chemistry departments.

Medicinal chemistry at emerging companies

John Montana, CEO of Amedis Pharmaceuticals (http://www.amedis-pharma.com) delivered an intriguing talk on 'silicon switch projects'. Amedis synthesizes silicon analogs of known drugs or failed development compounds and employs the benefits of silicon to overcome a deficit in the original 'all carbon' drug. Due to the increased atomic size, electronegativity and lipophilicity of silicon (relative to carbon), 'silicon switching' can provide many benefits: altered potency/selectivty, reduced metabolism, improved pharmacokinetics and solid intellectual property position. Numerous examples were described wherein the 'silicon switch' analog provided (relative to the known 'carbon-based drug') increased potency and selectivity for a given target, while also having a dramatic effect on pharmacokinetic parameters, such as improved half-life and lower clearance. Employing this model, Amedis required only 10 months to advance SI-162, for emesis, from the hit to preclinical development stage; importantly, SI-162 had a clean toxicology profile. Another facet to their discovery model is the concept of 'fast followers', illustrated by siloxanes as biosteres in aspartyl and metalloproteases, which provided potent HIV and ACE inhibitors.

Jeffery Stafford described the approach of Syrrx (http://www.syrrx.com) to accelerate lead generation and development by the application of high-speed, structure-based design. The Syrrx platform employs a novel, high-throughput (HT) strategy for protein expression, purification, crystallization, imaging, data collection and structure determination. For example, Syrxx initiated a DP4 program (for Type II diabetes) in the spring of 2002 and rapidly generated >60 high-resolution DP4-inhibitor complexes in seven structural series. Due to their lead generation strategy, the DP4 program advanced from hit generation through lead optimization with a team of ~ five chemists, allowed for the selection of three candidates for GLP toxicology by October 2003 and facilitated Phase I clinical trials to begin in the second half of 2004. Syrrx has additional programs under development using this high speed, structure-based design strategy. Overall, this novel approach has the potential to compress the timeline for the drug discovery process from 12 to <8 years, by expediting the lead generation and optimization phase of the R&D timeline.

Optimizing leads

All of the speakers for the think-tank session shared a similar vision for optimizing leads. Terrence Kelly from Boehringer Ingelheim (http://www.boehringer-ingelheim.com), Craig Lindsley (Merck & Co.) and Nicholas Leadbeater (University of Connecticut; http://www.uconn.edu) described how the industry-wide paradigm shift away from combinatorial chemistry (solid phase chemistry, large libraries) and towards solution phase parallel synthesis (small, iterative libraries) was having a significant impact and dramatically expediting lead optimization. Notably, microwave-assisted organic synthesis (http://www.personalchemistry.com and http://www.CEM.com) was revolutionizing reaction optimization and library synthesis by enabling the entire optimization and synthesis process to be conducted in a single afternoon and also enabling chemistry to be conducted in a library format that could not be done by traditional means. Notably, Leadbeater demonstrated how losartan, marketed by Merck as Cozar, could be constructed in minutes using a series of microwave-assisted reactions. Higher quality library compounds, with purity levels in excess of 95%, was another unifying theme among the panelists. Again, a general trend towards employing mass-guided HPLC (http://www.agilent.com) for library purification, coupled with complete compound charaterization, was sweeping the industry and providing reliable screening data and solid SAR.

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