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The quiet revolution: outsourcing in pharma

The pharmaceutical industry has always outsourced some of its activities. Perhaps 40 years ago the only activities to be outsourced were pertinent to the marketing of the products in the areas of advertising, market surveys etc. Some 30 years ago outsourcing was broadened to include aspects of formulation, clinical trials and registration. Another 10 years on most of the development and registration processes could be outsourced and this was practiced where capacity and specialist techniques were required. 10 years ago there was a jump to include the early stages of target identification and in the production of compounds to expand collections. Hit to lead and lead optimisation remained the only parts hardly touched by outsourcing but, as we now see [1], the final piece is in place. All parts of the process can and are the subject of regular outsourcing from the largest to the smallest of pharmaceutical companies. Where does the trend take us?

Philip Brown, the publisher of *Scrip*, has long maintained that major pharma has passed the point where it can, by its own research, maintain its product pipeline in a way to sustain its top and bottom lines. It could in future continue to grow only by the acquisition of

compounds, either directly by licensing or partnering or indirectly by assimilation of other companies. The recent acquisition of Pharmacia by Pfizer and the current one of Tularik by Amgen illustrate this trend. A recent survey [2] starkly brings to light another 'quiet revolution' that of in-licencing R&D projects: 44% of products in development from the top 10 companies are under licence, with a range of 36%–56%. Drugs are being in-licensed at earlier stages. Although all pharmaceutical companies avow their policy to be to licence in late stage candidates, there are few good Phase IIb compounds available and the move is to seek earlier opportunities.

So, looking at outsourcing in a broader context are these two trends one and the same? If we can outsource all stages of the process, is that any different to contracting somebody to do your R&D for you, or different to bringing in early, mid- or late-stage compounds where somebody else has taken the early risk? Is the real implication of this quiet revolution that in-licencing or partnering early projects is equivalent to outsourcing? The developments within outsourcing companies would support this view. One of the earliest companies in the sector, Arris, moved from providing chemistry services to develop protease projects internally for partnering. Following its

change to Axys it continued its own research looking to out-licence in clinical phases and was then acquired by Celera with essentially the same aim in mind. Arqule followed a similar path – moving to provide oncology compounds, Argenta have their histone deacetylase project [1] and we have developed pipelines in kinases and GPCRs.

References

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JAK kinase inhibitors

The recent *Drug Discovery Today* review *Inhibitors of JAKs/STATs and the kinases: a possible new cluster of drugs* by Luo and Laaja [1] gives a good overview of the relevance of JAK/STAT signalling as a target for therapeutic intervention in various disease states. Indeed, there are numerous disclosures in both the scientific and patent literature describing the identification of small molecules targeted to this important signaling cascade.

The authors identify several of the publicly disclosed JAK kinase inhibitors but give only brief mention to the most significant development to date, the Jak3 inhibitor CP690,550 from Pfizer [2], and neglected the selective 'pan-Jak' inhibitor reported by researchers at Merck [3]. Importantly, data presented in the Changelian *et al.* publication [2] shows that the current 'literature standard' JAK inhibitors WHI-P131, WHI-P154 and AG490 are weak ($IC_{50} > 3 \mu M$) and show quite poor

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 trials 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