Hitting the chemotherapy jackpot: strategy, productivity and chemistry

'…honing a molecule against a supposed single target ignores the fact that any molecule will have a diverse and rich pharmacology…'

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The sequencing of the human genome has opened the floodgates to pharmaceutical analysts to set new standards in making unrealistic promises to a gullible population that the materialization of novel, successful clinical agents is imminent. Indeed, unsubstantiated claims about 'mining the genome for drugs' and 'cancer cures around the corner' risk bringing the cancer drug discovery community into disrepute. Today, the spiralling costs of pharmaceutical R&D [US$33 billion in 2003 according to the Pharmaceutical Research and Manufacturers of America (http://www.phrma.org/newmedicines/resources/2004-01-22.123.pdf)], accompanied by falls in productivity (number of approved drugs per unit of R&D spending), illustrate the crucial requirement for companies to identify genuine lead compounds in a time- and resource-efficient manner [1]. Novel lead compounds with appropriate properties for clinical exploitation are still the most precious entities in small-molecule drug discovery and development, irrespective of how they are discovered – from synthetic chemistry, biology or even from trawling the oceans or rain-forests for exciting new moieties.

Target-driven cancer drug discovery

Postgenomic cancer drug discovery and development, like so many other therapeutic endeavours in medicine, is now dominated by the 'target-driven' approach [2]. This prevailing strategy involves the following steps:

- identification of a validated and druggable biological target (generally a protein), which has a crucial role in tumour formation, from the wealth of possibilities emanating from basic cancer biology research and cancer genomics;
- a 'molecule hunt' that typically involves a high-throughput screen of small-molecule compound and/or natural product libraries to identify a hit;
- hit-to-lead development to identify a lead compound that is active in the cellular context and that has 'drug-like' properties;
- lead development (involving *in vivo* testing and optimisation of pharmacokinetic and pharmacodynamic properties) towards the identification of a clinical candidate molecule.

Clearly, there are variations on this theme, including the generation and synthesis of potential lead compounds using fragment-based computational approaches where the target is structurally well-characterised, and emerging target-driven chemistry techniques (dynamic combinatorial chemistry or target-accelerated chemistry) [3]. However, the model strategy that is used throughout the pharmaceutical and biotechnology world puts target selection and validation first. The idea that this approach will lead to the discovery of drugs with improved efficacy and selectivity compared with the classical DNA-targeted cytotoxic agents that still dominate the cancer clinic today is the key reason for pursuing a target-driven strategy. In recent years, the clinical success of small-molecule agents, such as Gleevec™ (Novartis; http://www.novartis.com), has given further impetus to the target-driven drug development model. Clearly, Gleevec™ (initially used in the treatment of chronic myelogenous leukaemia [4]) is good news for patients and can move stock markets, but for each success there are notable (single agent) failures – matrix metalloproteinase inhibitors, ras farnesyltransferase inhibitors and the majority of angiogenesis inhibitors, to name but a few. In addition, whatever happened to the 'differentiation strategies' that were declared some years ago as the answer to the cancer problem? Anticancer drugs with names optimistically ending in the suffix 'statin' seem particularly prone to disappoint in the clinic.

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Target-driven shortcomings

Although there have recently been significant technological advances in areas such as short interfering RNA (siRNA) technology and systems biology, the target validation and subsequent intelligent target selection phases remain time-consuming and expensive stages of the drug discovery process. But what might be considered a smart target today could be rendered irrelevant by the expansion of the biological frontier tomorrow. Furthermore, as Fojo [5] so rightly declared: 'Until proven effective in the clinic a novel target is just a target wannabe'. Agents that selectively block single targets or pathways in cancer cells might be insufficient because of the inherent ability of heterogenous tumour populations to activate alternative or redundant pathways to overcome target inhibition, thus necessitating the use of combination regimes that include those much-derided established agents in the hope of yielding clinical benefit. Also, an obsession with honing a molecule against a supposed single target ignores the fact that any molecule will have a diverse and rich pharmacology that is triggered by the perturbation of other targets that were not identified in the project plan. This oversight will manifest itself as collateral damage and the emergence of unexpected side effects in the clinic. An alternative approach that is yet to reach clinical fruition is to assault a target with multiple intracellular effects that are implicated in cancer progression, as exemplified by histone deacetylases or Hsp90 inhibitors.

Despite the prevalence of the target-driven approach in strategic approaches to anticancer drug discovery, there is an alternative approach that has recently received some overdue recognition as a valuable method used to uncover lead compounds. This alternative approach can be summarised as 'chemistry-driven drug discovery'. Chemists are by nature typically more circumspect about making wild claims about their science. In addition, chemists are not inclined to be remotely jealous at the godly status of their biologist colleagues. Stuart Schreiber (categorically a chemist) illustrated this admirably when he said: 'There should be no problem with biology driving science unless perhaps you happen to be a chemist' [6]. Thus, to make the alternative paradigm more palatable to the biological community, it might be tactically rebranded as reverse drug discovery, chemical genomics and/or proteomics or chemogenomics. A more detailed description of such approaches to lead generation can be found in the recent review by Brown and Superti-Furga [7].

Chemistry to the fore

The essential idea behind the chemistry-driven drug discovery strategy is that the drug compound comes before the target, and lead selection is based on disease-relevant phenotypic changes in the cellular environment (modulation of the cellular state) *in vitro* or *in vivo* that are induced by exposure to a test molecule [8]. The advantages of carrying out drug discovery 'in reverse' include: (i) the drug discovery process is not biased towards any particular target, which enables a more precise understanding of the mechanism of action of the drug; (ii) any targets that are identified are by definition 'druggable' (avoiding the 'hit-to-lead' process) and are therefore likely to contribute significantly to the disease phenotype; and (iii) the approach is chemistry-driven and biased towards novel chemical structures with drug-like properties, which results in an increased probability of finding novel compounds that act against new (clinically unchallenged) targets and hence a reduced probability in the occurrence of competitor molecules that act at the same target.

Of course, this approach also has its disadvantages, including the requirement for target deconvolution for any given drug candidate; however, the now routinely employed microarray technologies significantly shorten this target discovery phase. The reverse drug discovery approach also raises the question as to where the search for lead compounds starts, and highlights the crucial requirement for creative medicinal chemists with an instinctive 'nose' for a good molecule (in the mould of the prolific drug-hunter Paul Janssen [9]). Medicinal chemists with such instincts wear molecules like they do their favourite shirts and can recognise an attractive molecule across a crowded room. In some ways, this approach heralds a return to the 'old-fashioned' principles of drug hunting through intelligent medicinal chemistry (albeit with modern higher-throughput chemical synthesis methodologies) to generate structurally diverse compounds systematically.

The cancer drug discovery process adopted within the Developmental Therapeutics Program (DTP; http://www.dtp.nci.nih.gov) arm of the National Cancer Institute (NCI; http://www.nci.nih.gov) illustrates the reverse cancer drug discovery process. The DTP *in vitro* anticancer drug cell line screen, which is a panel of 60 human tumour cells that have been derived predominantly from solid tumours, can be used to analyse phenotypic responses to a variety of chemical agents or natural product extracts to produce a characteristic 'fingerprint' of activity (e.g. GI_{50} growth inhibitory activity). Computer matching of activity patterns against the >600,000 NCI compound historical database can reveal tremendous insights into potential mechanistic targets, or indeed suggest novel targets for further exploration. The DTP hollow-fibre assay is then used to provide quantitative initial indices of *in vivo* activity [10]. Interesting and novel patterns of cell line activity can be found through the synthesis and testing of new compounds in a traditional

(low-throughput) manner. This principle was successfully applied in the development of the novel clinical candidate 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole prodrug (Phortress), which was selected from less than 100 synthesised compounds [11]. The iterative interactions between medicinal chemists and developmental pharmacologists have led to the deduction that this simple compound elicits a broad pattern of biological responses in specific tumour types: these effects determine the pharmacodynamic endpoint(s) that could be measured in a clinical trial.

Recent innovations in the area of chemical genomics include the approach known as gene expression-based high-throughput screening (GE-HTS). GE-HTS uses a gene expression signature as a surrogate for cellular states and this technology has been employed to identify agents that induce the differentiation of acute myeloid leukaemia cells [12]. In a collaboration between Iconix Pharmaceuticals (http://www.iconixpharm.com) and MDS Pharma Services (http://www.mdsps.com), the application of chemogenomics provided gene expression signature responses in tissues from rats that had been treated with approximately 600 drugs. These signature responses could then used to describe and predict the specific mechanisms of action of a particular drug in the whole animal [8].

Carrying out drug discovery in reverse might constitute a counter-intuitive approach for those cancer drug discovery practitioners that have been schooled in the target-driven arena, but this is a strategy that we believe is worthy of serious consideration as a resource- and time-efficient approach to lead discovery.

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