Targeted therapeutics for cancer treatment: major progress towards personalised molecular medicine

Editorial overview
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These are exciting times for cancer research and oncology drug development. Over the past few years it has become axiomatic that a molecular understanding of the various forms of cancer provides a basis for the design and implementation of targeted molecular therapeutics [1]. We increasingly understand the genetic and epigenetic abnormalities resulting in the hijacking of key regulatory networks in the cell, culminating in malignancy [2,3]. Moreover, the sequencing of the human genome is providing the basis for the genome-wide cataloguing of the mutations, amplifications, deletions, translocations, epigenetic changes and other causes of altered expression of cancer genes, involving for example micro-RNAs [4,5]. We also now know that cancer progression is usually a result of the accumulation of such multiple molecular changes, driven by Darwinian selection. More, perhaps, than in any other area of molecular medicine, genomic understanding of cancer is resulting in the realisation of personalised medical treatments.

This success was initially exemplified by the small-molecule ABL kinase inhibitor imatinib (Gleevec) and the ERBB2-targeted antibody trastuzumab (Herceptin), followed by a whole series of other small molecule and biological therapeutics [6]. Thus there have been further important successes more recently with novel and improved agents modulating EGFR and other members of the ERBB family, angiogenic targets such as VEGF/VEGFR, and more recently IGF-1R which is involved in transformation and cell survival. Further downstream in the signal transduction cascade, inhibitors of the oncogenic PI3 kinase/AKT/mTOR and RAS/RAF/MEK pathways have great potential. Poly-ADP ribose polymerase (PARP) inhibitors are showing substantial promise for the treatment of BRCA-mutant breast, ovarian and prostate cancers. Targeting of CYP17 and androgen receptor is also proving to be promising in castration-resistant prostate cancer. Furthermore, HSP90 inhibition offers potential in breast, melanoma and other malignancies. The articles in this issue of Current Opinion in Pharmacology capture the essence of the tremendous progress being made and at the same time highlight the significant challenges of the work that remains to be done.

At the time of writing, it is almost 25 years since the first landmark papers were published showing that a single mutated oncogene may not be sufficient to turn normal cells into malignant ones, whereas co-operation between two different oncogenes can induce malignancy [7,8]. Developing this theme further, very recent studies using genome-wide expression profiling have identified a series of genes involved in the co-operation, within the process of carcinogenesis, of two classic ‘heavy hitter’ cancer genes, namely RAS and p53 [9]. Perhaps surprisingly, normalisation of the expression of individual examples of these cancer co-operation genes was shown to lead to the inhibition of tumour growth. A recent clinical
throughput genome sequencing indicates that up to 10 extensive genetic deregulation. The application of high-
a selective growth and survival advantage [10,11]. At the same time, however, we are beginning to understand that the truly sustained arrest of cancer progression, and ultimately its medical control and cure, will require combinatorial treatments.

Although two co-operating oncogenes can result in cancer [7,8,12], full malignant progression usually involves more extensive genetic deregulation. The application of high-throughput genome sequencing indicates that up to 10–20 genes may have characteristics of driver mutations in a given cancer [4,5]. Normalising any one of these may deliver therapeutic benefits because of oncogene addiction, whereby cancer cells develop a dependency upon the key oncogene abnormalities through which they gain a selective growth and survival advantage [10,11]. Oncogene addiction is one example of a series of context-dependent cancer vulnerabilities or dependencies, which provide the basis for therapeutic exploitation [13]. In some cases this can result in synthetic lethality, for example where a mutation in a particular cancer gene can result in cell killing when a second gene or gene product is inhibited [14].

Examples of exploiting oncogene addiction, synthetic lethality and other cancer vulnerabilities are provided in the series of articles in this issue. Oncogene addiction appears to explain the effectiveness of the ABL inhibitor imatinib in BCR-ABL-dependent leukaemia and Kit or PDGFRalpha mutant gastrointestinal sarcoma, of the EGFR inhibitors gefitinib and erlotinib in non-small cell lung cancer, and of the ERBB2-targeted agents trastuzumab and lapatinib in breast cancer. Halilovic and Solit discuss the various approaches to exploit dependency on oncogenic BRAF signalling, including evidence that mutant BRAF cancers are hypersensitive to MEK inhibitors [15]. Yap, Garrett et al. review strategies to take advantage of dependence on the PI3 kinase pathway, caused for example by loss of PTEN or mutation of PIK3CA [16]. Data on the reversal of trastuzumab clinical resistance in breast cancer by lapatinib and HSP90 inhibitors have bolstered the concept of ongoing ERBB2 dependency. Similar data for the continued dependence of prostate cancer on androgen receptor signalling have also recently been acquired, as described in this issue by Chen et al. The specific use of CYP17 inhibitors to block systemic androgen synthesis is also discussed by Yap, Carden et al. Moreover, the clinical antitumour activity of PARP inhibitors in homologous recombination repair deficient tumours, particularly BRCA mutant ovarian, breast and prostate cancers, provides the first example of synthetic lethality in cancer treatment as reviewed by Lord and Ashworth (see also Refs. [17,18]). After the relative disappointment in the clinic with inhibitors of cyclin-dependent kinases 1, 2 and 4, probably due at least partly to the redundancy established by genetic approaches, de Castro et al. review the challenges of targeting mitotic kinases — success here may again be dependent upon identifying the optimal genetic context in which such inhibitors should be used. The potential of modulating targets that are not themselves oncogenes per se but which support the oncogenic process is illustrated by the articles on drugs acting on IGF-1R by Pollack and on the molecular chaperone HSP90 by Taldone et al. Additional non-oncogene but nevertheless cancer-selective targets are now being revealed by high-throughput RNA interference screens [19]. Direct activation of apoptosis by the targeting of TRAIL signalling, utilizing agonistic monoclonal antibodies or TRAIL peptide, has been reported to have single agent antitumour activity in the treatment of lymphomas and chondrosarcoma and has considerable promise in combination strategies, as described by Oldenhuis et al. Agents targeting the processes of invasion and metastasis have great therapeutic potential but are challenging to evaluate in the clinic. Brunton and Frame illustrate both aspects in their discussion of the non-receptor tyrosine kinases Src and FAK as therapeutic targets.

Despite the undoubted therapeutic value of individual agents, however, the limited activity of most molecularly targeted cancer therapeutics and the emergence of drug resistance (e.g. by target mutation or induction of alternative signalling pathways) illustrate the need for multiple and combinatorial approaches to a formidably complex set of diseases [21]. Human cancers are typically made up of 109–1010 cells, within which heterogeneous populations are molecularly generated by genetic instability coupled by a strong selective pressure to survive. Notwithstanding the simple underlying principles of how to generate a cancer cell, the diversity and complexity of actual or potential cancer genomes urgently calls for a systems biology approach to fully understand cancer and a systems medicine approach to treating it [21]. It is probable that we will need to create ‘the perfect storm’ through combinatorial therapy targeted to the precise molecular make-up of individual cancers. This may have to be guided by, for example, whole genome sequencing or genome-wide gene expression profiling of a malignancy or its constituent subpopulations, and may not be a single one-time only diagnostic and therapeutic manoeuvre. More simple assays have been postulated, utilising, for example, a selection of one or a more limited number of known oncogenic targets. An example of this is reviewed by Raponi et al. who describe data showing that the presence of KRAS mutations can predict resistance to
EGFR inhibitors. However, concerns remain that tests involving individual or a limited number of biomarkers are very likely to miss many other key oncogenically or pharmacologically crucial alterations that as yet remain unidentified. Nevertheless, such simpler predictive assays would be a considerable advance upon what is currently being utilised in clinical practice. Importantly, however, as the cancer genome evolves and resistant populations arise such molecular profiling and targeted therapy cycles will need to be repeated in an iterative manner. Accessing tumour tissue for these studies remains a major challenge but reports on circulating tumour cell assays indicate that this technology promises to have clinical utility for such repeated profiling studies, allowing analyses by multi-colour fluorescent in situ hybridisation as well as sequencing for mutation analyses [22]. A major challenge to all such studies, however, remains the considerable tumour cell heterogeneity seen within a single cancer. Crucially, particular attention will need to be given to that rare (probably <1%), but nevertheless crucial, tumour cell population with the characteristics of clonogenic cancer stem cells [23]. In addition, minimally invasive molecular and functional imaging methods have enormous potential, as exemplified by the increasing use of FDG-PET [24].

In conclusion, it is now increasingly clear that in order to create the individualised perfect storm treatments that are required for optimal therapy, we need to build up an armamentarium of molecular therapeutics from which we can mix our lethal, cancer-selective cocktails. It is envisioned that these agents will be administered based on the assessments of suites of molecular biomarkers. These will help us give the right individualised combinatorial treatment to the right patient at the right time — true personalised molecular cancer medicine. They will also allow us to determine how the cancer responds to the challenge of treatment, for example in terms of mutations, altered gene expression, feedback loops and so on — and systems-based approaches with sophisticated bioinformatics will increasingly be needed to deal with the complexity and the vast information generated by omic technologies [21]. The emerging use of new targeted agents and corresponding biomarkers needs to be evaluated in carefully designed clinical trials that can address the key questions pertaining to cancer biology and treatment. Furthermore, it is important to stress that these new agents and biomarkers are clearly already positively impacting cancer patient care. The articles in this issue describe some of the progress made towards this exciting goal. The examples provided in these timely reviews also show that anticancer drug discovery and development is not only an impressive science involving the integrated application of many powerful technologies, but also a frustratingly perverse art form, about which we still know too little. The final and perhaps most important point to stress is the need for teamwork which remains crucial to our success in the war on cancer. Overcoming the many obstacles requires the co-operation of many different people and organisations — just as cancer requires the collaboration of many co-operating oncogene stars and support players.

Conflicts of Interest
Paul Workman and Johann de Bono are employees of The Institute of Cancer Research which has a commercial interest in the development of inhibitors of HSP90, PI3 kinase, AKT, BRAF, PARP, CYP17, CDK and chromatin-modifying enzymes. The authors have potentially relevant commercial interactions with Vernalis Ltd, Novartis, Piramed Pharma (recently acquired by Roche), Astex Therapeutics, AstraZeneca, GSK, Cougar Biotechnology Inc and Cyclacel Pharmaceuticals Inc. Paul Workman was a founder and shareholder in Piramed Pharma and is a founder and shareholder in Chroma Therapeutics.

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References
**A valuable resource within which to search for mutations present in human cancers.


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21. Workman P: Drugging the cancer genome: new challenges of infrequent and combinatorial targets. Curr Opin Invest Drugs 2007, 8:445-446. This commentary provides a perspective on the discovery (see Refs. [4,5]) that individual human cancers contain surprisingly large numbers of ‘driver’ mutations and that many cancer genes are mutated relatively rarely overall — also emphasises the need for combinatorial therapies and the importance of a systems approach to understand and treat cancer.

