OPINION

Why is cancer drug discovery so difficult?

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Abstract | Thirty-five years after the 'war on cancer' was declared, the discovery of anticancer drugs remains a highly challenging endeavour. Here, we consider the factors responsible, such as tumour heterogeneity, and suggest strategies to improve the chances of short-term success in the development of novel anticancer drugs.

Oncology has one of the poorest records for investigational drugs in clinical development, with success rates that are more than three times lower than for cardiovascular disease[1,2] (FIG. 1). The widespread, relentless and lethal nature of cancer persists, with only incremental overall improvements in treatment outcomes, despite billions of dollars of public and private investment. The few notable successes, such as imatinib (Gleevec; Novartis) in the treatment of chronic myeloid leukaemia (CML), are, so far, exceptions.

Acknowledging that drug discovery is difficult in general, here we discuss the specific obstacles that the anticancer-drug hunter must confront. We cover the two most popular therapeutic modalities: low-molecular-mass drugs and unconjugated biologicals. Although optimal drug-discovery programmes aim to integrate the different stages of the research and development process into a single coherent operation, we break the subject into three different elements: targets, drugs and patients. After assessing the impediments to oncology drug discovery, we recommend specific strategies to combat this disease.

Targets: essential versus non-essential

For anticancer drug targets, the most fundamental distinction is between those that have essential functions and those that have non-essential functions. In this context, essential means that at least one vital cell type in the human body depends on the target for survival. Inhibitors of essential functions are likely to have narrow therapeutic windows, owing to the requirement for their targets in normal cells. By contrast, drugs that target non-essential proteins (the large majority of the proteome) should be well tolerated, but their efficacy might be limited unless the proper tumour type can be defined. In mammals especially, discrimination between essential and non-essential genes is not always easy. Mouse knockout mutants provide a convenient test for genetic dispensability. Such experiments reveal that the majority of proto-oncogenes — as defined by their mutation, amplification or activation in tumours — are essential. So, drugs that target activated oncogenes run the risk of having serious side effects, although this test for viability is admittedly stringent because it assesses requirements for gene function throughout development, and not only in the adult.

Intentional inhibition of essential functions to kill cancer cells results in on-target or on-mechanism toxicity in normal cells, and clinicians rely on differences in dose–response and drug distribution within tumours and normal tissues to provide a therapeutic window. Even though normal tissue is remarkably robust, there are thresholds below which survival is not possible. For instance, humans cannot survive a 90% tissue loss in most organs. However, it is evident that if 10% of tumour cells continue to proliferate in the face of anticancer treatment, the therapeutic regime will have little effect on ultimate disease outcome. This disparity is one of the stark challenges of cancer therapy.

There are nearly 200 drugs approved for cancer, with hundreds more in development, and they represent a wide assortment of mechanisms and modalities (TABLE 1). For many decades, drug discovery focused on agents that block essential functions and kill dividing cells — the traditional cytotoxics. These drugs include compounds with pleiotropic effects, such as DNA-modifying agents (for example, cisplatin), as well as drugs that interfere very precisely with defined physiological processes such as microtubule polymerization (for example, taxol), metabolite synthesis (for example, methotrexate) and chromosome topology (for example, irinotecan). An exception to the historical focus on targeting essential functions are anti-hormonal therapies such as oestrogen-receptor modulators (for example, tamoxifen) and aromatase inhibitors (for example, letrazole). Anti-hormonals target activities that are classified as non-essential because these functions relate to the proliferation of specialized but dispensable normal tissues, such as breast epithelium, for example.

In the past few years, various novel, targeted agents have burst onto the scene. Some of these agents bind to proteins that are essential in all cells, and therefore are not easily distinguished from traditional cytotoxics. The latest agents include those that target cell division in new ways (for example, aurora-kinase inhibitors and cyclin-dependent-kinase inhibitors), as well as other processes such as protein turnover (for example, bortezomib (Velcade; Millennium) and chromatin modification (for example, histone-deacetylase inhibitors)[3–6]. These new drugs might reasonably be called 'neocytotoxics'. Although these drugs often stem from sophisticated, target-driven screening and medicinal-chemistry efforts, it is not immediately clear what advantages they offer compared with traditional cytotoxics. Nonetheless, they continue to attract interest based on the possibilities of interfering with different biochemical mechanisms and using new chemical types. In some cases, broader therapeutic windows might be ultimately achieved by refining the paralogue selectivity of the compounds, such that they avoid inhibiting essential cellular functions and target only the members of a protein family that are prominent in tumours.

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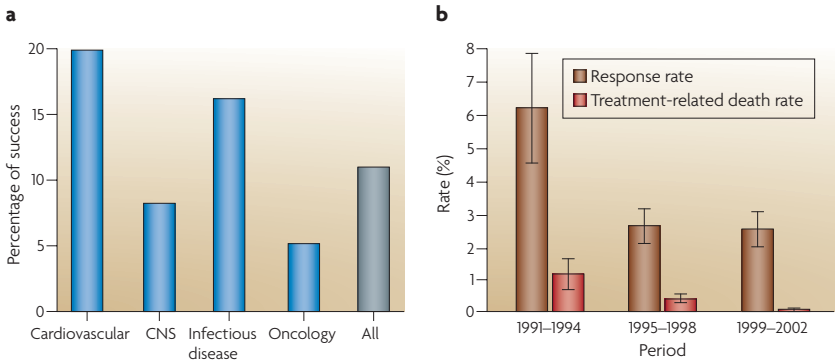

Figure 1 | **The challenge of anticancer drug development. a** | Historically, oncology compounds have had a significantly lower success rate in clinical development than compounds in other areas, such as cardiovascular disease. The rates shown are the success rates from first-in-human to registration for ten large pharmaceutical companies in the United States and Europe for the period 1991–2000. Data taken from REF. 1. **b** | Low response rates in Phase I oncology trials. Trends in response and treatment-related (toxic) death rates for studies initially submitted to Meetings of the American Society of Clinical Oncology 1991–2002 (REF. 2). The contribution of trial-level data to the period average was weighted by the number of enrollees. Error bars indicate standard error. Part **a** reproduced, with permission, from REF. 1 © (2004) Macmillan Magazine Ltd. Part **b** reproduced, with permission, from REF. 2 © (2004) American Medical Association.

Other recently developed small-molecule drugs inhibit elements in key signalling pathways, mostly kinases, which might not be essential in normal adult cells. In this way, they offer an approach to cancer therapy that is, in principle, distinct from the traditional and neocytotoxics. Imatinib is the prototype for this class of new cancer drugs. The target it was designed to hit, Ableson kinase (ABL), is activated in CML cells by a chromosomal translocation, which creates a unique dependency on this specific protein. As judged by the mouse knockout phenotype, animals have limited requirement for ABL activity. This is presumably one of the reasons that imatinib is highly effective in CML and is well tolerated as chronic therapy[7]. Both of these features are rare for cancer drugs.

It is important to note that many of the familiar protein kinases have essential functions. Proteins such as AKT, mammalian target of rapamycin (mTOR; also known as FRAP1), and extracellular signal-regulated kinase (ERK; also known as MAPK1) are embedded in crucial survival and proliferation pathways. This raises the possibility that inhibitors of these components might behave much like cytotoxic drugs, with narrow therapeutic windows. By contrast, kinases such as ABL, epidermal growth factor receptor (EGFR), and HER2/*neu* (also known as ERBB2) lie upstream in signalling networks. Therefore, they are less likely to be required in all cell types and less apt to generate broad cytotoxicity. Consistent with this view, side effects for small-molecule drugs that target ABL and EGFR generally conform with the genetic and expression data — myelosuppression and skin rash, respectively. By contrast, mitogen-activated protein kinase (MAPK)/ERK kinase (MEK; also known as MAP2K1) and mTOR inhibitors have a broader toxicity profile at their maximum tolerated doses (MTDs), along with modest efficacy at these doses[8,9].

Bevacizumab (Avastin; Genentech), a monoclonal antibody against vascular endothelial growth factor (VEGF), targets activities — vascular genesis and physiology — which some predicted would be essential in normal adults. However, the drug has acceptable side effects and, depending on the perspective, its performance in the clinic has been either phenomenal or mildly disappointing[10]. In several studies where the antibody is administered in combination with chemotherapeutics, bevacizumab extends survival by a few months in patients that have historically been refractory to all new treatments. From an efficacy standpoint, it seems to behave as a useful chemotherapeutic and is active in a broad array of cancers, with statistically significant, yet limited, effectiveness in end-stage tumours[11].

Rituximab (Rituxan; Genentech) and trastuzumab (Herceptin; Genentech) are monoclonal antibodies that bind non-essential proteins that have restricted expression in adult tissues. The basis for the efficacy of these drugs is still a matter of debate. Rituximab relies on expression of CD20 (also known as MS4A1), a B-cell marker, to bind and destroy non-Hodgkin's lymphoma cells. This effect improves two-year survival from about 85% with chemotherapy alone, to 95% (REF. 12). Trastuzumab is effective in breast tumours that overexpress HER2/*neu* protein through DNA amplification. The subset of patients that express HER2/*neu* (about a third of those with node-positive breast cancer) experience a 50% reduction in disease recurrence over a period of 20 months[13]. This is a substantial improvement, but it also illustrates that some breast cancers might have pre-existing resistance to a useful drug, whereas others might acquire resistance and progress.

Drugs: selective versus multi-targeted

A good target is useless without a correspondingly good cognate drug. Apart from favourable pharmaceutical properties, the goal of many drug-optimization efforts is a molecule that inhibits its target in a selective or carefully crafted way. Many traditional cytotoxic drugs, although demonized with epithets such as 'slash and burn' agents, make highly specific interactions with their molecular targets. Methotrexate, for instance, binds at picomolar concentrations to dihydrofolate reductase (DHFR) and has a multi-log-fold preference for DHFR over its secondary target, thymidylate synthase. From the chemistry and pharmacology perspectives, these are excellent compounds. The collateral damage they produce is strictly on-mechanism, a result of the biological roles of their targets.

Toxicity can also be off-target, derived from the inhibition of unintended or unknown functions. In most cases, clinical effects are probably a blend of on-target and off-target activities. As clinicians escalate dose, the possibility for off-target effects increases, adding to toxicity, but possibly to efficacy as well. With more physiological functions compromised by the drug, side effects inevitably arise, but the increased stress in the tumours might offset the burden of toxicity to a point. Off-target side effects are common for small-molecule drugs and are likely to have a larger role for inhibitors that target sites that are conserved among a family of proteins such as kinases. One of the clear distinguishing features of biologicals, including antibodies, is the reduced likelihood of unknown off-target interactions. Proteins generally make highly selective contacts with their targets, and clinical failures due to unpredicted off-target toxic effects ought to be minimal. Rather, efficacy and on-target toxicity are the principal concerns.

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Table 1 | **Therapeutic mechanisms of action of anticancer drugs**

Therapeutic target or modality	Targeted process	Mechanism of action of therapeutics	Target example (drug)
Transformation	Apoptosis	Activation of apoptosis pathways	BCL2
	Signalling	Interference with signal transduction, response	ABL (Gleevec; Novartis)
	Invasion/metastasis	Inhibition of tumour spread	Cathepsin K
Immortalization	Senescence	Induction of senescence	Telomerase
Host	Angiogenesis	Interference with blood supply of tumour	VEGF (Avastin; Genentech/Roche)
	Tumour-associated membrane proteins	Antibody-directed cytotoxicity	CD20 (Rituxan; Biogen Idec/ Genentech)
Traditional cytotoxics	Replication/ cytokinesis	Interference with DNA synthesis, cell division	Microtubules (Taxol)
	Metabolism	Reduction of essential metabolite	Thymidylate synthase (5-FU)
Neocytotoxics	Protein turnover	Inhibition of acceleration of protein degradation	Proteasome (Velcade; Millennium Pharmaceuticals)
	Epigenetics	Remodelling chromatin, DNA methylation	HDAC interactions
	Stress response	Interference with cellular stress buffering	ATPase/chaperone superfamily

ABL, Ableson kinase; BCL2; B-cell lymphoma 2; HDAC, histone deacetylase; VEGF, vascular endothelial growth factor.

The concept of a multi-targeted agent, or 'dirty drug', is widely discussed in oncology[14]. Many clinical-stage kinase inhibitors are fairly non-selective[15]. In our experience, clinicians tend to prefer multi-targeted drugs because they seek to maximize the chance for clinical antitumour activity. They are experts at managing attendant toxicities. Scientists, on the other hand, prefer specific drugs because their effects are more predictable. The less selective the compound, the more unreliable the conclusion about the root cause of its activity. Because cancer models are notoriously problematic, it is risky to advance compounds on the basis of suppression of tumour growth in disease models[16]. Often, only the correlation between pharmacodynamic effect and pharmacological exposure provides some comfort that the observed effects are on-target. Indeed, the mechanism of the antitumour activity of imatinib was only confirmed in the clinic when drug-resistant tumours emerged with mutations in the catalytic domain of the oncogenic fusion protein BCR–ABL[17].

Recent clinical results for two multi-targeted kinase inhibitors illustrate the pros and cons associated with such drugs. Sunitinib (Sutent; Pfizer) and sorafenib (Nexavar; Bayer/Onyx) interfere with several kinases including VEGF receptors (VEGFRs) and platelet-derived growth factor receptors (PDGFRs). Sunitinib received FDA approval on the basis of its activity against gastrointestinal stromal tumour (GIST) and renal cell carcinoma (RCC), and sorafenib has produced signs of efficacy in RCC. Although reasonable hypotheses for clinical activity in both settings have been advanced, it remains unclear which kinases are involved in the responses. In the case of RCC, the idea that VEGFR has an important role in the therapeutic effect of the drug is strengthened by the observation that bevacizumab has some activity in RCC patients as a single agent, an effect that cannot easily be attributed to antibody-dependent cellular cytotoxicity[18]. But differences among the therapeutic agents in patient progression and survival rates are mysterious[19]. A clear-cut benefit of having multiple activities in a single drug is demonstrated by imatinib which, despite being one of the most selective kinase inhibitors known, interferes with the functions of c-KIT and PDGFR as well as ABL. Imatinib is effective against GIST and hypereosinophilia, due to its inhibition of c-KIT and (presumably) PDGFR, respectively[20,21].

Patient selection: drug response as a QTL

Exceptional heterogeneity and adaptability are cardinal features of cancer. Pathologists have classified tumours into dozens of histological subtypes, and have further graded them to reflect the degree of progression of a particular subtype. This classification scheme only begins to capture the variability among cells within a tumour and among different tumours. At the molecular level, it is likely that no two cancers are identical. The range of the disease is probably wider than for any other therapeutic area. Superimposed on the germline differences that distinguish individual people at the genomic level is epigenetic variation that is derived from the cell types from which the tumours originate, as well as further genetic and epigenetic changes that accumulate as these deviant somatic cells evolve in the body.

The physical manifestation of tumour heterogeneity is reflected in observed differences in drug responses, and is the probable cause of acquired resistance. Variants in a population of tumour cells might have a selective advantage under conditions that are imposed by cancer therapy and could produce clones of drug-resistant cells[22]. Tumour heterogeneity is also a logical explanation for pre-existing drug resistance in cancer patients. Parameters that are presumably related to drug sensitivity and tumour aggressiveness display a wide range of variation among malignancies (TABLE 2). Notwithstanding imatinib and occasional idiosyncratic 'Lazarus responses' in other therapeutic settings, it seems that drug response is, in general, a continuous variable. Even a drug that is highly selective for a particular target encounters numerous mechanisms that might affect the sensitivity of a tumour. The anticancer activity of a drug might depend on the dozens of cellular efflux pumps, proliferation rate, checkpoint apparatus, repair processes and apoptotic machinery, to mention only a few possibilities. In aggregate, small differences in any of these mechanisms could produce a significant effect. Studies in cell lines and primary malignant cells support the view that drug response is a quantitative trait, much like height in the human population[23]. Most drugs that are tested against a panel of cell lines or primary tumour specimens display unimodal, continuous variation of activity[24] (FIG. 2). The extreme bimodal antiproliferation in dose–responses that are observed in some panels of cell lines and tumour types with certain therapeutics represent exceptional cases. Oncologists generally speak of 'responsive' or 'sensitive' tumours, but this

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Table 2 | **Variation in tumour biology**

Parameter	Range
Cell-cycle period	30–60 hours
Apoptotic index	0.1–4.0%
Proliferative index	1–70%
S-phase fraction	0.01–0.40

Data from REF. 22.

is misleading, a myth perpetuated by the arbitrary classification of clinical outcomes into categories such as 'stable disease' and 'partial response'. In this light, responsive tumours are those with a sensitivity to a drug that is sufficiently shifted from the MTD to generate a clinical response.

Quantitative traits have proved difficult to dissect, perhaps because their underlying genetic determinants are multifactorial (polygenic) and nonlinear[25]. Therefore, we might expect quantitative trait locus (QTL) interactions to pose similar analytical obstacles in somatic cells. Whatever germline differences exist between two patients' tumours are likely to be augmented during malignant growth. Therefore, the number of germline QTLs (that is, those present in the normal genome) plus somatic QTLs (that is, those that arise in malignant cells during growth) that potentially contribute to drug response is staggering. This becomes especially apparent if we expand the definition of somatic QTLs to include heritable changes other than alterations of the DNA sequence; that is, epigenetic changes in the broadest sense. Based on experiments in highly tractable model organisms, the possibility of unravelling the genetic basis of a continuously distributed drug response in tumours seems slight in the near term.

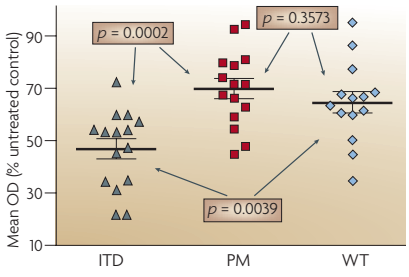

Figure 2 | **Highly variable anticancer drug response might be a quantitative trait.** Dot plot of the cytotoxic response (mean of triplicate experiments) of individual samples to CEP-701 at the 100-nM dose level, grouped by *FLT3* mutation status. Bars show the group mean ± SEM. *P* values are from Student's *t* test. ITD, internal tandem duplication; OD, optical density; PM, point mutation; WT, wild type. Figure reproduced, with permission, from REF. 24 © (2004) American Society of Hematology.

It is well known that clinical toxicity and efficacy are difficult to predict from preclinical experiments or theory. Efficacy, especially for small-molecule drugs, is nearly always dose-related, so clinicians push cancer drugs to the MTD in clinical development. This strategy deals with heterogeneity in an empirical, practical way. A Phase I trial design that includes multiple cancer types ensures a broad sampling of clinical heterogeneity. Occurrences of drug activity — for instance, with histone-deacetylase inhibitors in cutaneous T-cell lymphoma — can be followed up in subsequent focused studies[26]. Clinicians might further balance the chance of increased efficacy against the chance of increased toxicity by combining two or more drugs. This approach only makes sense if the combination maintains or widens the therapeutic window. To provide an advantage, a drug combination must enhance the effect on tumour cells without an equivalent increase in toxicity. Once again, the trade-off between efficacy and toxicity is resolved in the clinic, although it is sometimes guided by preclinical experiments. It remains to be seen how the industry and the regulatory agencies will react to strategies that hinge on advancing pairs of agents that are expected to have significant activity only in combination, and not as single agents[27]. Barring breakthroughs in patient-selection methods or a windfall of imatinibs, the 'all comers' clinical-development approach remains a valid — if frustrating and expensive — route to drug approval.

Imatinib: new standard or outlier?

The outstanding — even revolutionary — qualities of imatinib tend to obscure some clinical features that raise concerns about generality. Imatinib works substantially better in the earlier chronic phase of CML compared with the later blast-crisis phase (97% versus 49% haematological response)[7] (FIG. 3). In addition, many of the responders in blast crisis relapse within months. This behaviour raises the possibility that targeted agents might run into some of the same obstacles that have plagued cytotoxics: low responsiveness of advanced cancers and acquired resistance.

The emerging story of erlotinib, another clinically successful signal-transduction inhibitor, also raises this concern. Erlotinib (Tarceva; OSI/Genentech), which targets the EGFR kinase, prolongs survival of non-small-cell lung cancer patients[28]. Early clinical studies with this inhibitor and its cousin, gefitinib, also an EGFR inhibitor, indicated that it might work far better in patients whose tumours have activating EGFR mutations[29]. However, subsequent studies have revealed that responses linked to these mutations are not durable, and that tumours with such mutations seem to be generally more sensitive to chemotherapeutics, not only to erlotinib/gefitinib[30] (FIG. 4). Therefore, the link to EGFR inhibition might be misleading.

It is perhaps too early to draw firm conclusions, but the current data indicate that imatinib, rather than being a new paradigm, might be an exception. The clinical successes of imatinib, erlotinib and trastuzumab inspired the idea that genetic mutations or amplifications signified a dependency of the tumour on a particular protein. Drugs that targeted a mutant or overexpressed protein were considered likely to produce impressive single-agent responses. However, evidence is accumulating that, at least in the advanced and more lethal stages of cancer, tumours might have already abrogated this dependency, or can easily do so. Blast-crisis CML is a case in point. The chronic-phase tumours are overwhelmingly sensitive, whereas the late-stage blast-crisis cells are often resistant. Those tumours that respond often subsequently develop variations in the target that result in resistance or circumvent inhibition of the target. Although a substantial fraction of this acquired resistance can be reversed by drugs such as the second-generation BCR–ABL inhibitor dasatinib (Sprycel; Bristol-Myers Squibb), which has broader activity against clones of BCR–ABL mutants that are insensitive to imatinib, remissions are transitory[31]. It is unlikely that a single BCR–ABL inhibitor can simultaneously possess sufficient breadth of activity to inhibit all mutant enzymes that arise, and also have adequate selectivity to be safe. Whether these properties can be mimicked by particular combinations of drugs, as in the current standard of care for HIV infection, is an open question. Yet even if such broad coverage can be achieved, the addiction of a tumour to BCR–ABL might diminish as the malignancy evolves. Experiments in mouse genetic models of cancer support this view[32]. Mice that are engineered with controllable oncogenes reveal that, in several situations, tumours arise that initially depend on the oncogene, but gradually lose this reliance.

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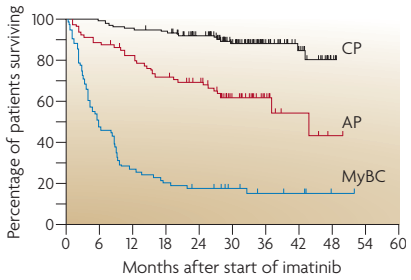

Figure 3 | **The value of early detection, the right drug and the right patient population.** Overall survival after the start of imatinib for patients in chronic phase (CP), accelerated phase (AP) and myeloid blast crisis (MyBC)[7]. In CP, the estimated overall survival rate was 88% at 30 months. Median overall survival for patients in AP was 44 months (range 0.4–50 months), with a survival rate of 62% at 30 months. Median overall survival for patients in MyBC was 6 months (range 0.1–52 months), with survival rates of 27% at 12 months and 17% at 24 months. Figure reproduced, with permission, from REF. 7 © (2005) Wiley Interscience.

Therefore, experience in the clinic and with mouse models indicates that metastatic cancers of epithelial origin — such as those of the breast, lung, prostate and colon — might require a different approach. Tumours might possess a single motive force that propels their early evolutionary destiny. Indeed, mouse models that incorporate transgenic oncogenes support the view that a single genetic alteration can produce a hyperproliferative phenotype. However, to gain further advantages in growth, additional changes accumulate. Some of these might bypass the need for the initiating event; others might simply add to it. It is easy to see why a tumour might ultimately adopt a strategy of multi-pathway versus single-pathway signalling. Reliance on a single function can be dangerous, especially if that function is subject to vicissitudes that cannot be controlled, or is insufficient to enable growth in broader environmental contexts. Tumours that are sensitive to inhibitors of specific signal-transduction components might concentrate signalling through that component. By contrast, tumours that distribute signal flux through multiple pathways might not respond because the target is, in essence, a minor somatic QTL. The most successful tumours — the metastatic ones — might evolve compensatory growth mechanisms and stress resistance that also render them less responsive to drugs. Chronic-phase CML and imatinib comprise a story in which all the key ingredients for success, some controllable but many not, come together: first, a proliferative disorder with dependency on a single target that is non-essential in most normal cells; second, a relatively selective kinase inhibitor; and third, a clear way to select patients who will respond to the drug.

Prescriptions

If hope for the emergence of further drugs like imatinib is misplaced, at least in the short term, what angle should scientists working in oncology drug discovery take? We suggest that a merger of thoughtful innovation with practical experimental plans is most realistic. With regard to target selection, a balance between essential and non-essential functions seems prudent. It is probable that continued efforts to inhibit essential proteins might only produce incremental benefits to patients. Exclusive focus on non-essential targets, however, will produce more failures through lack of efficacy, but successful drugs will have wider therapeutic windows. The identification of non-essential targets that tumours have come to rely on requires better computational and experimental models — no simple task. The possibility of finding so-called synthetic-lethal drug targets, which are only essential in cancer cells that carry mutations in specific tumour-suppressor genes or oncogenes, is attractive in theory[33]. However, the search for such genes — if they exist — might be frustrated by tumour heterogeneity and awkward tools for somatic-cell genetics. In the meantime, it seems sensible to use cancer models in conservative ways; that is, to study cell-autonomous functions with robust phenotypes, or use the models purely to test the pharmaceutical properties of candidate drugs. Non-autonomous functions that involve multiple cell types are, in general, too complex to model in a reliable way. Tests of compelling biological rationales should be reserved for the clinic.

With regard to drug development, we favour the philosophy of high chemical selectivity. With few clearly defined interactions, preclinical and clinical data are more easily interpreted, and the possibility of observing bimodal responses that are amenable to genetic analysis is higher. If single-agent activity is not observed in experimental models, a rapid search for combination partners should be undertaken. When synergies are identified, immediate assessment of potential toxicities is compulsory.

With respect to patient stratification — the area where the most significant advances will ultimately be achieved — we believe that the challenges of quantitative traits are sufficiently great to preclude significant progress in the cases of continuous response distributions. Rather, it is advisable to concentrate on drugs for which there is evidence in cell lines or tumours of bimodal sensitivity. We consider the analogy between simple Mendelian traits and normal height variation in a population on the one hand, and CML and the bulk of epithelial cancers on the other, as instructive. The underlying basis for dwarfism is accessible, while the molecular origins of quantitative differences in height remain obscure. When clear qualitative differences in tumour response to drugs exist, the underlying molecular cause might reveal itself, as for CML and the BCR–ABL translocation.

We emphasize that our proposals are not a prescription for basic cancer research, which can afford to take a long-term view. Rather, we seek feasible, short-term solutions to the problems of cancer drug discovery. Although immensely challenging, the impediments to predictable cancer therapy are not insuperable, nor are the molecular underpinnings of drug response and cell survival unknowable. Ultimately, cancer must yield to a systematic and sustained assault.

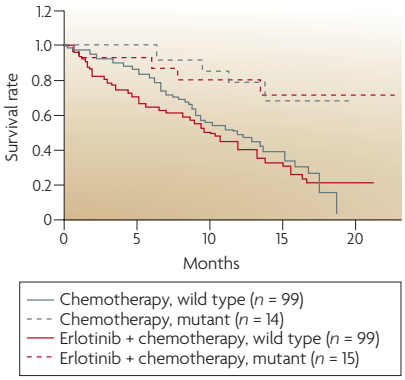

Figure 4 | **Target-based stratification might prove inadequate.** Kaplan-Meier curves by treatment received and epidermal growth factor receptor (EGFR) mutation status[30]. $P = 0.958$ for erlotinib plus chemotherapy versus chemotherapy alone among patients with EGFR-mutant tumours (dashed lines) and $P = 0.294$ for erlotinib plus chemotherapy versus chemotherapy alone among patients with wild-type tumours (solid lines). All P values refer to log-rank tests. Adapted, with permission, from REF. 30 © (2005) American Society of Clinical Oncology.

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