PERSPECTIVE

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Translating cancer research into targeted therapeutics

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The emphasis in cancer drug development has shifted from cytotoxic, non-specific chemotherapies to molecularly targeted, rationally designed drugs promising greater efficacy and less side effects. Nevertheless, despite some successes drug development remains painfully slow. Here, we highlight the issues involved and suggest ways in which this process can be improved and expedited. We envision an increasing shift to integrated cancer research and biomarker-driven adaptive and hypothesis testing clinical trials. The goal is the development of specific cancer medicines to treat the individual patient, with treatment selection being driven by a detailed understanding of the genetics and biology of the patient and their cancer.

Many important advances in cancer medicine, particularly earlier diagnoses and better treatment, have led to improving outcomes from malignant diseases (http://www.cancerresearchuk.org). As a result, mortality from some common cancers such as those of the breast and prostate is decreasing in the Western world. Nevertheless, overall, despite these efforts and huge advances in our understanding of cancer genetics and biology the prognosis for a number of cancers such as pancreatic and lung remains in large part dismal.

Anticancer drug development attempts to translate understanding gained from basic research into improved clinical practice through cancer clinical trials (Box 1)[1]. These trials are rationally designed and executed research tools aimed at testing new ways of screening for, preventing or treating cancer. The specific goal of early therapeutic clinical trials is to define the safety, tolerability and pharmacological properties as well as the antitumour effects of novel agents. Later stage therapeutic trials attempt to prove that a treatment imparts clinical benefit, usually compared to standard treatment. These generally include hundreds to thousands of patients, can last several years and be very expensive; the often quoted price to generate one licensed drug is US$1 billion[2,3]. Frustratingly, the majority of cancer clinical trials have little impact on either patient benefit or understanding of cancer biology, raising major concerns about current anticancer clinical drug development processes[2,3]. Overall, this is increasing the pressure on individuals in the pharmaceutical industry to generate anticancer drugs with broad applicability in cancer patients and therefore large fiscal returns.

Clinical trials for cancer largely involve a traditional 'Evidence-based medicine' approach that currently focuses on treating patient populations with molecularly uncharacterized disease, and culminate in large, pivotal, randomized therapeutic trials aimed at regulatory approval which can take many years to complete. Usually such an approach aims to improve survival from advanced cancer by at best some months. There are major concerns, however, that this 'one size fits all' approach may not be the best or most efficient way to develop drugs[4]. Evidence for these stems from the high proportion of negative large randomized trials for common cancers as well as the very limited benefits achieved for the small proportion of positive trials that lead to drug approval. Moreover, in effect, these trials define the best treatment for the average patient whereas they may not be the best treatment for a given individual.

This traditional population-based trials paradigm pursues the accrual of large numbers of cancer patients in a statistical attempt to minimize the effects of uncharacterized heterogeneity in disease biology on clinical trial outcome. Advances in our understanding of the molecular genetics

BOX 1

Clinical trials in cancer

Traditional cancer clinical trial design

Phase 1: phase I trials are small (on average these need 20–60 patients) and largely focus on defining safety, tolerability, maximal tolerated drug dose, describing dose-limiting toxicity and evaluation of pharmacokinetic-pharmacodynamic relationships. These can take 1–2 years to complete.

Phase 2: phase II trials are larger (30 to 200 patients) and generally evaluate antitumour activity of the therapeutic strategy in question, usually in a tumour type (for example prostate cancer) with little patient selection based on disease biology. Oncology Phase II trials are often non-randomized, which is quite different to Phase II trials for other diseases. These can take 1–2 years to complete.

Phase 3: these are generally very large, expensive trials (400–2000 patients) taking many years to complete and are designed to show a statistical benefit in a clinical endpoint, commonly overall survival, in a usually unselected population with a tumour type.

Biomarker driven, hypothesis testing, cancer drug trials

Although they have the same three phases, trials will be more flexible and adaptive contingent on the acquired clinical and translational data, questioning and answering key biologic hypotheses using analytically validated biomarkers and addressing the following:

Proof of mechanism: determination of the optimal dose range and dosing schedule to achieve sufficient target blockade for long enough, as determined by analytically validated pharmacodynamic assays.

Proof of concept: evaluation of the antitumour activity of the therapeutic selected patient populations using analytically validated predictive and intermediate endpoint biomarkers.

Pharmacogenomics: assessment of inter-patient variability to achieve optimal target blockade and minimize toxicity; identification of patients most likely to benefit from strategy providing early clinical qualification of predictive biomarker.

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of cancer, however, suggest that the complexity of the heterogeneity of human malignancy both between patients with one disease type arising at a particular site as well as between cancer cells within one patient, is such that population-based unselected approaches have major limitations for the development of novel cancer therapeutics[5]. We believe that this established drug development paradigm is proving to be a bottleneck in the delivery of benefit from our burgeoning understanding of tumour biology. We envisage that the rapid evolution, and decreasing cost, of increasingly high-throughput molecular technologies will enable a 'Personalized' or 'Stratified' medicine, hypothesis-testing, approach. This will allow us to raise the bar of what is expected from clinical and translational research, with larger benefit being delivered to patients from novel therapeutic strategies[6]. Moreover, the degree of benefit from a new treatment should preferably be recognized in early trials before larger trials are pursued. This will result in a decrease in the proportion of large, late stage, negative trials and allow a focus on delivering increased understanding of human cancer biology and the development of predictive biomarkers. This 'Perspectives' article outlines a roadmap of how we believe that improvements in cancer treatment can be accelerated by reiterative, efficient, high-fidelity translation of biological insights between laboratory and clinic.

Importance of a strong biological hypothesis

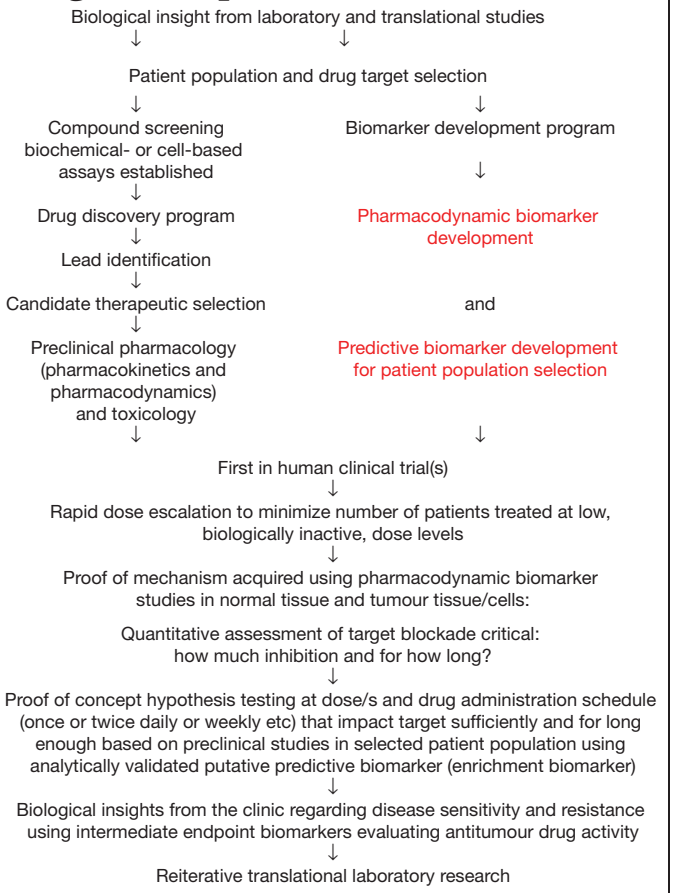
Most new cancer drug approvals are for agents against existing targets with only a small minority being novel[7]. This is less likely to be due to the lack of suitable targets but rather to the difficulty, time required, cost and attrition rate involved in anticancer drug development, as well as a lack of proper validation of novel targets and commercial pressures. We believe that the critical first step, if the process is to result in a clinically useful therapeutic approach, is a strong biological basis for the target (Box 2). Necessary for this, but not sufficient, is the identification of an altered molecular target in the cancer to provide a therapeutic window and therefore a clear basis for selective tumour cell cytotoxicity with absolute or relative sparing of normal cells[8]. Inherent in this, and an absolute requirement, is the definition of a target patient population and a practical method to identify them in a clinical context (a 'biomarker' or 'companion diagnostic')[9] (highlighted in red in Box 2). The mantra of 'no biomarker, no drug' is now heard echoing regularly in the halls of pharmaceutical companies; in practice, however, this is often neglected.

An imperative for successful drug development remains the need to identify targets that cancer cells are absolutely reliant on ('mission critical') so that when these functions are blocked there is a lethal or cytostatic effect. Many of these approaches are based on concepts such as oncogene addiction[10], non-oncogene addiction[11] and synthetic lethality[12,13] that attack the 'hallmarks' of cancer[11,14] and increasingly use high-throughput genetic screens and data integration[15]. Preferably, these will be targets to which resistance is not easily gained. However, we need to recognize that our understanding of how a cancer cell is wired compared to normal cells is still remarkably rudimentary. It is now becoming apparent that what have been described as discrete pathways are likely to be complex interacting networks. It is perhaps not surprising then that the effects of inhibiting one component may have highly unpredictable consequences because of, for example, negative feedback loops or positive reinforcement. However, it seems possible that adopting 'systems'-based approaches may help to address this complexity[16,17]. Although still in their infancy, these computational methodologies coupled with deep transcriptomic, genomic, proteomic or metabolic profiling promise an integrated approach and with this, a better understanding of interacting molecular networks. This should allow us to start thinking in a more rigorous fashion about how drugs perturb networks rather than discrete pathways and to use this information to develop new 'network' therapeutic strategies.

Once an *in vitro* target has been established, the thorny issue of *in vivo* validation arises. Traditionally, this has involved treating mice xenotransplanted with human cancer cell lines. Many have questioned how valid these systems are for the preclinical assessment of anticancer agents, for a variety of reasons[18,19]. These include concerns that cancer cell lines have been adapted to grow in the laboratory, sometimes for decades, and therefore may not be indicative of the behaviour of the actual tumour they are meant to represent: they are frequently genetically very ill defined, there is a potential mismatch between human tumour cells and mouse stroma, a severely compromised immune system in the host animal, and the endpoints used in these experiments are often ill-defined and inconsistent. Although we concede that these models are useful in helping to define the potential pharmacological properties of an agent, we believe that, in general, they can be of limited value in defining the potential efficacy of an agent in treating human cancer. In part, this may be due to improper interpretation of the data—the reality is, however, that some pharmaceutical companies still use positive performance of a drug in multiple xenograft systems as an encouragement to progress a drug without consideration of what the models actually represent. A more stringent preclinical evaluation might prevent some drugs going forward that might fail later, saving money and time. Potentially, although this remains contentious, genetically defined mouse models of cancer are likely to be much more informative, even though they may be slower and more expensive to use. A compromise model might be the use of orthotopic transplantation of genetically defined mouse cancers or the use of human cancers directly transplanted into mice without *in vitro* culture. In summary, there is an urgent need for

BOX 2

Recommended schema for hypothesis testing anti-cancer drug development



models that can be used in drug development that mimic the clinical disease better.

A pervasive problem among cancer biologists is that many have little understanding of what constitutes a good or feasible therapeutic target. This could be improved by much closer communication between cancer biologists, drug developers and oncologists[20]. This we believe is critical, as it is largely academia, and to some extent focused biotechnology companies, that are best placed to define valid new therapeutic targets and patient selection markers rather than pharmaceutical companies, where pressures can lead to a short-term and milestone-driven mentality; this is fine for producing a drug but inappropriate for the truly innovative biology that propels paradigm shifts.

Testing biological hypotheses in clinical trials

The availability of an increasingly large number of novel, rationally designed, molecularly targeted anticancer drugs, and the many possible combinations of these agents, makes possible the conduct of biological hypothesis testing in clinical trials (Boxes 1 and 2)[21]. Reproducible and analytically validated biomarkers are absolutely mandatory to deliver these trials (Box 3)[22]. These trials must now not only address more traditional endpoints pertaining to drug safety, pharmacology and anti-tumour activity, but also consider addressing from the outset key biological hypotheses including the identification of the appropriate patient population (Box 2).

Early clinical trials should continue to initially focus on drug safety and tolerability and to evaluate pharmacokinetic (drug levels) and pharmacodynamic (effect of drug on target(s)) disposition. However, to minimize delay and the treatment of patients at ineffective doses in first human Phase I studies, rapid dose escalation using either accelerated titration designs or a continued reassessment method involving unselected patients should be pursued until doses modulating the target are achieved. Confirmation of the desired target effect by pharmacodynamic studies is described as proof of mechanism. The degree and duration of target modulation in tumour tissue is also very important and it is vital that early translational studies establish optimal drug dosing and dosing frequency as well as duration of drug administration for maximal antitumour activity. Pharmacodynamic studies can be conducted on normal tissue (such as blood, hair follicles and skin) but optimally involve tumour tissue analyses. As tumour biopsies can often be impracticable, there is increasing interest in using circulating tumour cells (CTC) acquired from the blood of cancer patients for such studies[23,24].

Even though maximal target blockade may be achieved at lower doses, in general we believe that drug dose escalation should be pursued to as high a dose as can be safely achieved (maximum tolerated dose) whenever possible. This recommendation is based on concerns regarding the limited dynamic range of some pharmacodynamic assays and highly heterogeneous drug delivery to different sites of disease. Indeed, evidence of target modulation and proof of mechanism at one site, as determined by pharmacodynamic studies, should not be equated with achieving the desired target modulation at all sites[25,26]. High interstitial tumour pressures and tumour hypoxia are common in parts of many cancers; reversing poor drug delivery has been reported to be particularly critical to the treatment of cancers such as pancreatic cancer but is poorly studied in the clinic[26,27].

Once proof of mechanism is acquired, with target modulation achieved, patient selection using adaptive trial designs and what are best described as 'enrichment biomarkers' can be pursued. Enrichment biomarkers are essentially molecular biomarkers that enrich for patients likely to benefit from treatment, and have the potential to become predictive biomarkers through a process described as clinical qualification. Adaptive trial designs to increasingly allow patient accrual to focus on the responding population, if the hypothesis being tested increasingly appears correct, are evolving and need careful consideration[28,29]. Seamless transition in the same protocol from dose escalation to assessment of antitumour activity in initially unselected and then increasingly selected populations is initially envisaged. An example of such an evaluation is the trial we conducted with the PARP inhibitor olaparib[30], which provided proof of mechanism and concept regarding the use of PARP inhibitors and which has ignited major interest in this field (Box 4). Such clinical trial data, if significant antitumour activity is observed in the selected population, as we have documented with olaparib in BRCA carrier patients (Box 4), will provide early support for the clinical qualification of the predictive biomarker under evaluation and expedite the development of registration strategies. Other examples of biological hypothesis-testing trials to support this approach are described in Box 5 (refs 31–35). We believe that early clinical qualification

BOX 3

Biomarker acquisition for translational trials

Biomarkers are characteristics that are objectively measured and evaluated as indicators of normal biological or pathogenic processes, or of pharmacological responses to a therapeutic intervention[9]. Their successful use requires thorough analytical validation and determination of assay reproducibility and variability.

Pharmacodynamic (PD) biomarkers

- Key for proof of mechanism studies (confirmation of target blockade).
- Description of magnitude and duration of PD target blockade is essential.
- PD usually conducted initially in easily acquired normal tissue such as skin biopsies, hair follicles, whole blood, plasma, peripheral blood mononuclear cells.
- Normal tissue PD helps describe optimal time-points for evaluating tumour PD (multiple serial tumour biopsies are often difficult to acquire safely); tumour biopsies feasible in a proportion of patients. The evaluation of circulating tumour cells (CTC) in blood may also allow non-invasive tumour cell target modulation studies (but CTC PD may not reflect primary/metastatic disease target modulation).
- Can involve immunohistochemistry or immunofluorescence which allows differentiation of tumour versus stroma studies; more quantitative enzyme-linked immunosorbent assays (ELISA)-based assays preferable but may not be able to distinguish tumour from stroma (on biopsy lysates).

Predictive/putative predictive or enrichment biomarkers

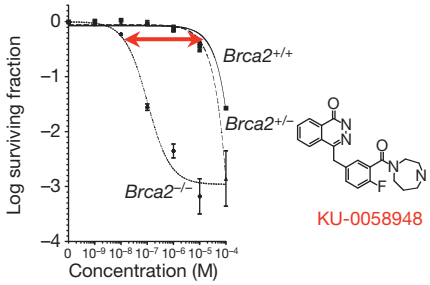
- Key for proof of concept studies to interrogate hypothesis in question.
- Allow patient selection for treatment at biologically active drug doses and schedules deemed by preclinical studies to impart antitumour effects.
- Early evaluation (described as clinical qualification) of predictive biomarkers in Phase I studies can help accelerate anticancer drug development by identifying early antitumour activity, patient population for these trials, and clinical dissection of disease biology.
- May involve DNA sequencing, fluorescent *in situ* hybridization, gene expression or genomic analysis, immunohistochemistry.

Intermediate endpoint biomarkers

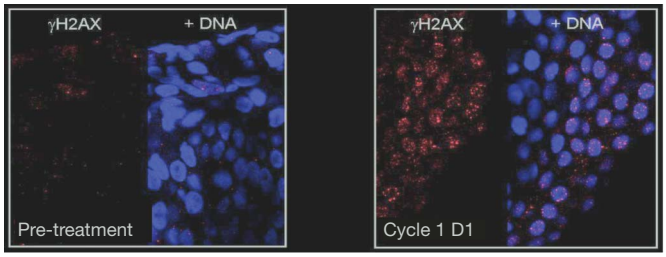
- Key to identifying antitumour activity imparted from drug effect and to acquire proof of concept.
- This can include tumour radiological measurements (by computerized tomography scans), measures of tumour cell proliferation (for example Ki67 immunostaining), apoptosis (for example cleaved caspase 3 immunostaining), evaluation of anti-angiogenic effect (for example by dynamic contrast enhanced magnetic resonance imaging), evaluation of circulating blood biomarkers such as tumour markers (prostatic surface antigen/PSA) or CTC counts.
- Imaging attractive and powerful but can be very costly (particularly if requiring positron emission tomography).

BOX 4
PARP inhibitors for BRCA-deficient cancers

1. Generation of robust hypothesis
Demonstration of activity and selective cytotoxicity
In vitro evidence for the 1,000-fold differential sensitivity of *Brca2*$^{-/-}$ cells to PARP inhibition by the PARP inhibitor Ku0058948, when compared with isogenic *Brca2*$^{+/-}$ and *Brca2*$^{+/+}$ cells, providing a potentially large therapeutic window and a robust hypothesis to test in clinical trials[66].

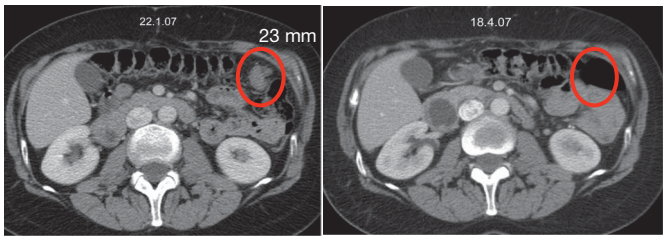


2. Biomarkers for PARP translational studies
Predictive biomarker
BRCA sequencing for loss of function mutations in patients with a strong family history of BRCA-associated cancers
Pharmacodynamic (PD) biomarker
Inhibition of poly(ADP)-ribose polymer formation (peripheral blood mononuclear cells as well as tumour biopsies taken pre- and post-treatment) and presence of γH2AX formation in normal tissues (hair follicles).



Left panel, pre-treatment samples; right panel, post-treatment assay following patient treatment with PARP inhibitor olaparib. Marker detection by immunofluorescence[30] (courtesy A. Tutt).

Intermediate endpoint biomarker of clinical benefit
Radiological and biochemical evidence of disease regression.



Computerized axial tomography (CAT) scans of *BRCA* mutation carrier ovarian cancer patients treated with olaparib taken before (left), and after (right), olaparib treatment. These scans represent clinical proof of concept for synthetic lethality by PARP inhibition in cancers with loss of BRCA function[30].

3. Biological hypothesis testing trial
Phase I trial
PARP inhibition with olaparib is safe, with drug well tolerated. Proof of mechanism acquired: PARP is inhibited in PD assays. Proof of concept generated: olaparib has significant and durable antitumour activity in cancers of BRCA carrier patients (ovary, breast and prostate) with no toxicity to somatic *BRCA*$^{+/-}$ non-tumour cells in BRCA carrier patients.

BOX 5
Other successful hypothesis-testing cancer trials

Hedgehog pathway signalling
Mutations in Hedgehog pathway genes, specifically genes encoding patched homologue 1 (PTCH1) and smoothened (SMO), occur in basal cell carcinomas and some medulloblastomas. Treatment with an oral, well tolerated, small-molecule inhibitor of SMO blocked Hedgehog pathway signalling and resulted in impressive antitumour activity in advanced basal cell carcinoma and medulloblastoma.
ABL kinase
The study of ABL kinase inhibitors for BCR-ABL driven chronic myeloid leukaemias is arguably the most important development in the treatment of haematological malignancy, transforming disease epidemiology, biological understanding and treatment.
KIT and PDGFR kinases
Small-molecule inhibitors of KIT and PDGFR for gastrointestinal stromal tumours (GIST) with mutations of these tyrosine kinases.
Mutated V600E B-Raf inhibition
The early evaluation of a V600E-mutated B-Raf inhibitor PLX4032 for cancers with this alteration that include many melanomas (>60%), some colorectal carcinomas (10%), most anaplastic and papillary thyroid carcinomas and low-grade serous ovarian carcinoma[68,69].
Targeting ALK
Oncogenic mutant or fusion variants (chromosomal rearrangements) of the anaplastic lymphoma kinase (ALK) gene have been identified in several human cancers including non-small cell lung cancer (NSCLC), anaplastic large cell lymphomas, neuroblastomas, and myofibroblastic tumours. A subset of NSCLC has a rearrangement in which the echinoderm microtubule-associated protein-like 4 (EML4) gene is fused to ALK; this can be identified by a fluorescent *in situ* hybridization (FISH) assay. This disease is highly sensitive to treatment with an ALK inhibitor[70].

of analytically validated predictive biomarkers will accelerate the drug development process and lead to a higher likelihood of successful drug development, while increasing the possibility of patient benefit from trial participation.

Using predictive biomarkers to select patients for specific treatments is not new in cancer medicine. The biochemical evaluation of oestrogen receptor and HER2 receptor (also known as ERBB2) expression are now well established as predictors of benefit from endocrine therapies and trastuzumab (Herceptin, Genentech) in breast cancer[36,37]. RAS and EGFR mutations are negative and positive predictors, respectively, of benefit from epidermal growth factor receptor (EGFR)-targeting antibodies and small molecules[38,39]. Nevertheless, most predictive biomarker studies continue to be mainly pursued very late in the drug development process. While a large number of molecular targeted anticancer agents are now in clinical development, few are being co-developed with corollary predictive biomarkers to identify patient subpopulations, although this concept remains inherent to evaluating targeted therapeutics. For many molecularly targeted and rationally designed agents, patient selection will be essential to successful drug development. Moreover, we believe it is important that patient selection is commenced as early as possible in the drug development process. A significant challenge to implementing this strategy remains the lack of resources invested in the analytical validation of predictive biomarkers to ensure they meet mandatory standards such as Clinical Laboratory Improvement Amendments (CLIA) requirements before their use in clinical trials.

Accessing tumour tissue and tumour tissue banks

Access to optimally preserved and stored tumour tissues linked to clinical outcomes data is vital to successful biological hypothesis-testing

translational research. This is critically important for biomarker and robust biological hypothesis development as well as for prospective patient selection for these trials. Necessary for this is the establishment of prospective and comprehensive tissue banks in Cancer Centres. These require considerable resource allocation, procedure standardization and dedicated personnel. Importantly, we must move to the situation whereby tumour collection and biomarker assessment occurs in real time in trials, to allow the rapid selection of cancer patients for participation in the relevant hypothesis-testing therapeutic trials. Moreover, repeated access to tumour material to evaluate any genetic evolution in the disease, which can happen either spontaneously or due to therapeutic selective pressures, needs to be considered. Such changes, which are inherent to the genomic instability seen in many cancers, can result in drug resistance and need to be recognized. Repeated biopsy of tumour tissue remains a major challenge but may be, at least in part, addressed by the molecular characterization of circulating tumour DNA and circulating tumour cells[23,24].

Reiterative translation

Even with a strong biological hypothesis, translation into the clinic remains a major bottleneck. Careful consideration of how to implement this must occur early, and requires a critical mass of integrated investigators and the infrastructure to maximize the likelihood of success. Modern drug development requires expertise in molecular and cellular biology, molecular pathology and medical oncology and input from medicinal chemists, structural biologists, pharmacokinetic-pharmacodynamic modellers and biomarker teams. A critical aspect of this is reiterative cycles of interrogation between the laboratory and the clinic and back to the laboratory. These reiterative studies should be designed as early as possible in clinical trial development to allow the acquisition of samples such as tumour tissue to investigate, for example, mechanisms of drug resistance (primary and acquired). This would allow the development of further hypotheses for evaluation in future clinical trials such as studies to reverse drug resistance. Trials must be designed to continue to drive the dissection of tumour biology and our understanding of why certain hypotheses are rejected by trial results. Such reiterative research led to the demonstration that chronic myelogenous leukaemia (CML) can remain driven by the *BCR–ABL* translocation in patients with CML resistant to the first-generation ABL inhibitor imatinib, and to the successful clinical development of the second-generation inhibitors dasatinib and nilotinib[40–42]. This was enabled by molecular dissection of the resistance mechanism.

Expediting regulatory targeted drug approval

Overall, although we have emphasized biomarker-driven approaches, broader approaches may need to be considered with some novel agents. Moreover, pursuing both broader and more selective approaches at the same time may be a reasonable compromise for some agents. For example, drugs targeting the PI3K/AKT pathway should be evaluated in tumour types with evidence of pathway activation (p110α, also known as *PIK3CA* mutation or amplification); *AKT* mutation or amplification; or PTEN loss)[43,44]. Furthermore, there is significant evidence that these agents may also affect the tumour stroma and inhibit angiogenesis. If proof of concept evidence for this can be acquired in clinical trials evaluating biomarkers of the anti-angiogenic process, then broader approaches may be indicated. Pursuing broader and selective strategies concurrently may also decrease risk for anticancer drugs if the evaluated predicted biomarker has limited sensitivity or specificity. Unselected patient evaluation, however, has a higher risk of failure in late-stage trials because of disease molecular heterogeneity unless the sensitive subtype is very common in the disease overall. Indeed, the development of the oestrogen-receptor antagonist tamoxifen was successful despite the lack of molecular patient selection because oestrogen receptor positive breast is very common in postmenopausal women[45].

Conversely, most therapeutic trials in patients with advanced castration-resistant prostate cancer (CRPC) have failed to show clinical benefit, probably due to the high molecular inter-patient heterogeneity of this disease[46,47]. In view of this, when we pursued hypothesis-testing studies of the CYP17 inhibitor abiraterone, which inhibits androgen and oestrogen synthesis, we elected to attempt to dissect this heterogeneity[23]. This trial tested the hypothesis that CRPC commonly remains hormone driven[48]. We showed that abiraterone inhibits CYP17 in patients and decreased downstream hormone levels while upstream hormones increased, acquiring proof of mechanism[49]. We also established robust proof of concept by showing that this agent had a high level of durable antitumour activity in CRPC patients[50]. Preliminary single-centre studies have indicated that this agent has higher antitumour activity in cancers with a TMPRSS2/ERG rearrangement than those that do not[23]; this rearrangement results in a potent ETS oncogene becoming driven by a promoter containing androgen and oestrogen response elements (see Fig. 1)[51,52]. Since antitumour activity with this agent in both ERG rearranged and unrearranged subgroups has, however, been reported, this agent is being evaluated more broadly in unselected patients with multi-centre data being prospectively collected in a large late-stage trial to evaluate this more extensively.

The evaluation of novel agents for the treatment of advanced prostate cancer is not only challenged by undissected disease heterogeneity, but also by the lack of intermediate endpoint biomarkers to measure antitumour activity[53]. These patients usually do not have radiologically

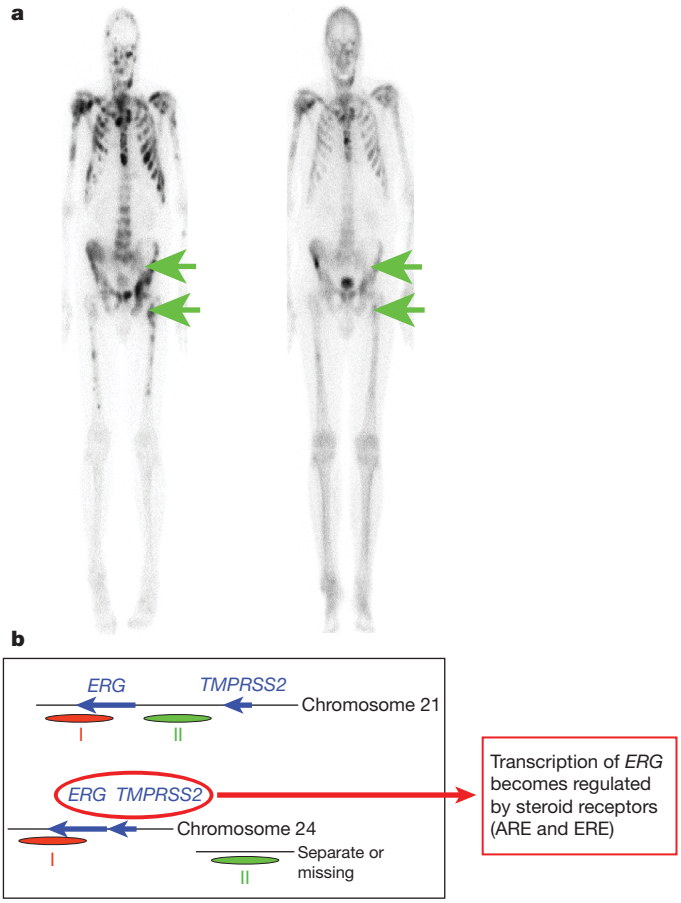


Figure 1 | Proof of concept studies: castration resistant prostate cancer remains hormone driven and is highly sensitive to CYP17 blockade by abiraterone. **a**, Bone scans depicting metastatic prostate cancer responding to treatment with abiraterone[67]. Left before treatment, right after treatment. **b**, *TMPRSS2/ERG* rearrangements in prostate cancer. *TMPRSS2/ERG* rearrangements result in *ERG* becoming driven by a promoter that is regulated by androgen and oestrogen response elements (ARE and ERE). This may explain why CYP17 blockade by abiraterone, which inhibits androgen and oestrogen synthesis, is most active in *ERG*-rearranged cancers[52,23].

measurable disease and measuring overall survival is currently the primary approvable clinical trial endpoint for this disease. The development of intermediate endpoint biomarkers is an absolute requirement for accelerating the development of novel treatments for all cancers. Intermediate (surrogate) endpoint biomarkers have been successfully used for drug approval for other diseases including human immunodeficiency virus (HIV) infection, diabetes and cardiovascular disease, where HIV viral load and CD4 cell count, blood glucose levels and blood pressure measures, respectively, have proven utility. The rapid development of ABL inhibitors for the treatment of CML and their expedited regulatory approval was also at least in part due to the availability for this disease of highly specific and sensitive biomarkers of response and clinical outcome (circulating Philadelphia-positive CML cells, cytogenetic response and molecular monitoring by real-time polymerase chain reaction of BCR-ABL transcripts), although arguably while these biomarkers are proven prognostic factors they are not yet established as statistically robust surrogates of outcome[31,42]. However, unlike CML, most other malignancies do not yet have such easily measurable biomarkers.

The most commonly used measure of antitumour activity remains tumour shrinkage as measured by radiological imaging[54,55]. This is usually taken as being meaningful of patient benefit as is durable stabilization of cancer growth for at least 6 months. However, tumour shrinkage does not necessarily equate to clinical benefit to patients and this cannot usually be the sole evidence to support regulatory drug approval. Improved biomarkers that can serve as intermediate or surrogate endpoints to acquire rapid regulatory approval are urgently needed. These could also potentially identify patient benefit from a novel therapeutic strategy earlier, assist in early discontinuation of ineffective strategies and identify active anticancer drugs more efficiently. It would be particularly advantageous if such biomarkers could be measured easily, rapidly and frequently; these requirements are probably best met by circulating multiplex assays. The study of circulating tumour cell counts, circulating tumour DNA (total DNA or tumour-specific DNA) and the caspase-cleaved cytokeratin fragment M30 have significant promise[56–60]. Other tested biomarkers include measures of tumour proliferation and programmed cell death in tumour biopsies (for example Ki67 immunohistochemistry) as well as radionuclide imaging[61,62]; although these have been proposed as potential intermediate endpoints, they are currently limited by access tissue and imaging costs, respectively. Moreover, if the hierarchical tumour stem cell model of cancer research is correct, better intermediate endpoint biomarkers of tumour stem cell eradication will also be critically important because all the other biomarkers described may not represent tumour stem cell kill[63]. Finally, the statistical complexity and rigor required to prove that any of these biomarkers is a validated and qualified intermediate endpoint remains a major challenge[64,65]. This has limited this area of research, which merits significant investment.

Implications

There is clearly an urgent need to continue to improve and accelerate the translation of preclinical research into improved therapeutic strategies for patients with cancer. Critical to future progress will be an increased understanding of tumour biology, the identification of disease 'driver' molecular targets, the discovery of rationally designed anticancer drugs and their clinical development singly or in rational combinations. The detailed mapping by deep sequencing of the cancer genome, with functional evaluation of the complex and multiple molecular perturbations generated by these changes, will expedite such future progress. Translating the results of this concerted effort into clinical utility will require the development of analytically validated biomarker assays that can be tested in the clinic as potential predictors of benefit from anticancer drugs. These biomarkers will need to be used to dissect intra-patient and inter-patient tumour molecular heterogeneity and to support the selection of the optimal anticancer treatment for the individual patient. Moreover, they should be increasingly used as intermediate end points of response. This personalized medicine approach may lead to the treatment of cancers with different sites of origin using the same therapeutic strategies. The early use of patient selection and establishment of proof of concept in drug development may help minimize the risk of late and costly drug attrition due to disease heterogeneity, accelerate patient benefit, improve drug approval registration strategies and result in more frequent and less costly anticancer drug approvals. Patient selection will also decrease morbidity and cost by decreasing the number of patients treated with ineffective agents. It is likely that the spiralling cost of new agents will mandate such an approach in the near future, if novel targeted agents are to achieve their full potential. Finally, to achieve this change will require a sustained and concerted effort from the cancer research community and must involve basic and translational scientists, clinicians, the regulatory authorities, health economists, as well as political, biotechnology, industry and funding partners.

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