Exploiting the Cancer Genome: Strategies for the Discovery and Clinical Development of Targeted Molecular Therapeutics

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Abstract

Our biological understanding of the molecular basis of cancer has benefited from advances in basic research, accelerated recently by cancer genome sequencing and other high-throughput, genome-wide profiling technologies. Given the diverse heterogeneity among tumors, the traditional cytotoxic chemotherapy and one-size-fits-all approaches to cancer discovery and development are not appropriate for molecularly targeted agents. Selection of new drug targets is based on achieving cancer selectivity through exploiting specific dependencies and vulnerabilities predicted from tumor genetics. Discovery of highly target-selective agents is enhanced by integrating multiple modern technologies, particularly structure-based design. Efficient clinical evaluation requires smart, hypothesis-testing studies using validated pharmacodynamic and predictive biomarkers. We discuss and exemplify biomarker-driven clinical development and the concept of the Pharmacologic Audit Trail. We detail the exciting approaches offered by drugging the cancer genome, focusing on blocking oncogene addiction, drugging the oncogenic lipid kinome, addressing nononcogene addiction, exploiting synthetic lethality, and overcoming apoptotic resistance, leading to personalized molecular medicine.

INTRODUCTION

Until relatively recently, the diagnosis and treatment of cancer were based on clinical evaluation, radiological assessment, and pathological appearance. This has changed dramatically over the past decade as a result of the genetic characterization and molecular understanding of the disease. We have now entered the era of personalized cancer medicine, achieved through the combined use of molecularly targeted therapeutics and companion biomarkers. At a time when we recognize the diverse heterogeneity within and among tumors, the individuality of genetic signatures, and the variability of pharmacogenomic profiles, it is clear that the traditional one-size-fits-all approach to cancer drug discovery and development that was previously employed for cytotoxic chemotherapeutics is no longer fit-for-purpose (1, 2).

Our increased biological understanding of the molecular basis of oncogenesis and malignant progression has benefited greatly from decades of basic cancer research and has been greatly accelerated by recent rapid advances in cancer genome sequencing and other high-throughput, genome-wide profiling technologies (3, 4). Defining the different genetic drivers of various cancer subtypes has led to many new molecular targets for drug discovery and development. As a result, a range of novel targeted molecular therapeutic agents have gained regulatory approval over the past decade. These include highly effective trailblazing molecular therapeutic drugs, such as the monoclonal antibody trastuzumab (Herceptin®; Roche), which was approved for the treatment of HER2-positive metastatic breast cancer in 1998 (5), and the small-molecule tyrosine kinase inhibitor imatinib (Gleevec®; Novartis), which is licensed both for chronic myelogenous leukemia (CML) though its inhibition of the kinase activity of the oncogenic driver translocation product BCR-ABL and for gastrointestinal stromal tumors owing to the blockade of the mutated oncogenic driver KIT kinase (see **Table 1**) (6, 7). An impressive range of other molecularly targeted drugs are now gaining regulatory approval, notably inhibitors of mutant BRAF and anaplastic lymphoma kinase (ALK) in melanoma and lung cancer, respectively, and many others are progressing through preclinical and clinical development.

Now that we have moved the emphasis away from the development of cytotoxic chemotherapies—which damage proliferating healthy cells as well as cancer cells—and are focusing much more on molecularly targeted agents exploiting abnormalities in the cancer genome, we have needed to switch the underlying philosophy for contemporary drug development from a drug-to-patient strategy to a more sophisticated and targeted patient-to-drug approach. This new approach starts with the unraveling of the molecular causation of cancer (**Figure 1**) (8). Selection of new drug targets is based on achieving cancer selectivity through exploiting specific dependencies and vulnerabilities predicted from tumor genetics. Discovery of highly target-selective agents is enhanced by integrating a range of modern technologies, particularly structure-based design (8a). Efficient clinical evaluation requires smart, hypothesis-testing studies using validated pharmacodynamic (PD) and predictive biomarkers.

The application of genomics to identify novel drug targets and biomarkers has put the field of oncology at the forefront of the exploitation of the genome sequence for personalized medicine (9). Our biological understanding of cancer and the discovery of these new targets and biomarkers have been facilitated by powerful new technologies, particularly genome-wide profiling methodologies such as next-generation sequencing and RNA interference (RNAi) screening (10). Thus this is a very exciting period in cancer research and targeted therapeutics.

A conventional clinical approach has traditionally been used to select safe and effective drugs across a broad patient population that is not stratified for molecular pathology. This has involved toxicity-driven Phase I studies, single-arm Phase II trials, and randomized controlled trials in an unselected patient population. Such an approach usually leads to large and costly Phase III trials,

Table 1 Examples of approved molecular cancer therapeutics

Year of approval	Drug	Trade name	Primary target(s)	Primary indication	Reference(s) for randomized trial results used for approval
1998	Trastuzumab	Herceptin®	HER2	HER2-positive metastatic breast cancer	5
2001	Imatinib	Gleevec®	ABL c-KIT	BCR-ABL translocation-driven chronic myeloid leukemia	111
2003	Gefitinib	Iressa™	EGFR	EGFR-driven non-small-cell lung cancer	36
2004	Bevacizumab	Avastin®	VEGF	Metastatic colorectal cancer	112–114
2004	Cetuximab	Erbitux®	EGFR	Head and neck squamous cell carcinoma; KRAS-wild-type colorectal cancer	115
2004	Erlotinib	Tarceva®	EGFR	Non-small-cell lung cancer; pancreatic carcinoma	37
2005	Sorafenib	Nexavar®	VEGFR	Hepatocellular carcinoma; renal cell carcinoma	116, 117
2006	Sunitinib	Sutent®	VEGFR	Renal cell carcinoma; gastrointestinal stromal tumor; PNET	118, 119, 120
2006	Panitumumab	Vectibix®	EGFR	KRAS-wild-type colorectal cancer	121
2007	Temsirolimus	Torisel®	mTOR	Renal cell carcinoma	122
2007	Lapatinib	Tykerb®	ERBB2/EGFR	HER2-positive breast cancer	123, 124
2009	Everolimus	Afinitor®	mTOR	Giant cell astrocytoma; renal cell carcinoma; PNET	59, 125
2011	Crizotinib	Xalkori®	ALK	ALK-rearranged non-small-cell lung cancer	43
2011	Vemurafenib	Zelboraf™	BRAF	V600E *BRAF*-mutated melanoma	29, 126
2011	Abiraterone	Zytiga™	CYP17	Castration-resistant prostate cancer	127

Abbreviations: ALK, anaplastic lymphoma kinase; CYP17, cytochrome P450 17A1; EGFR, epidermal growth factor receptor; mTOR, mammalian target of rapamycin; PNET, pancreatic neuroendocrine tumor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

unacceptably high levels of late-phase drug attrition, and antitumor agents that are generally ineffective for the majority of individual patients with relatively modest overall survival benefits (11). This is evidenced by the low success rates of drugs progressing from first-in-human trials to drug registration in oncology and spiralling drug development costs. A better approach is clearly required.

The change from a one-size-fits-all approach to the paradigm of individualized drug development requires the incorporation of a range of informative molecular biomarkers. Such biomarkers will, for example, enable the focusing of clinical trials on genomically stratified patient subgroups, thereby increasing the likelihood of drug responses. This will, in turn, decrease the time and

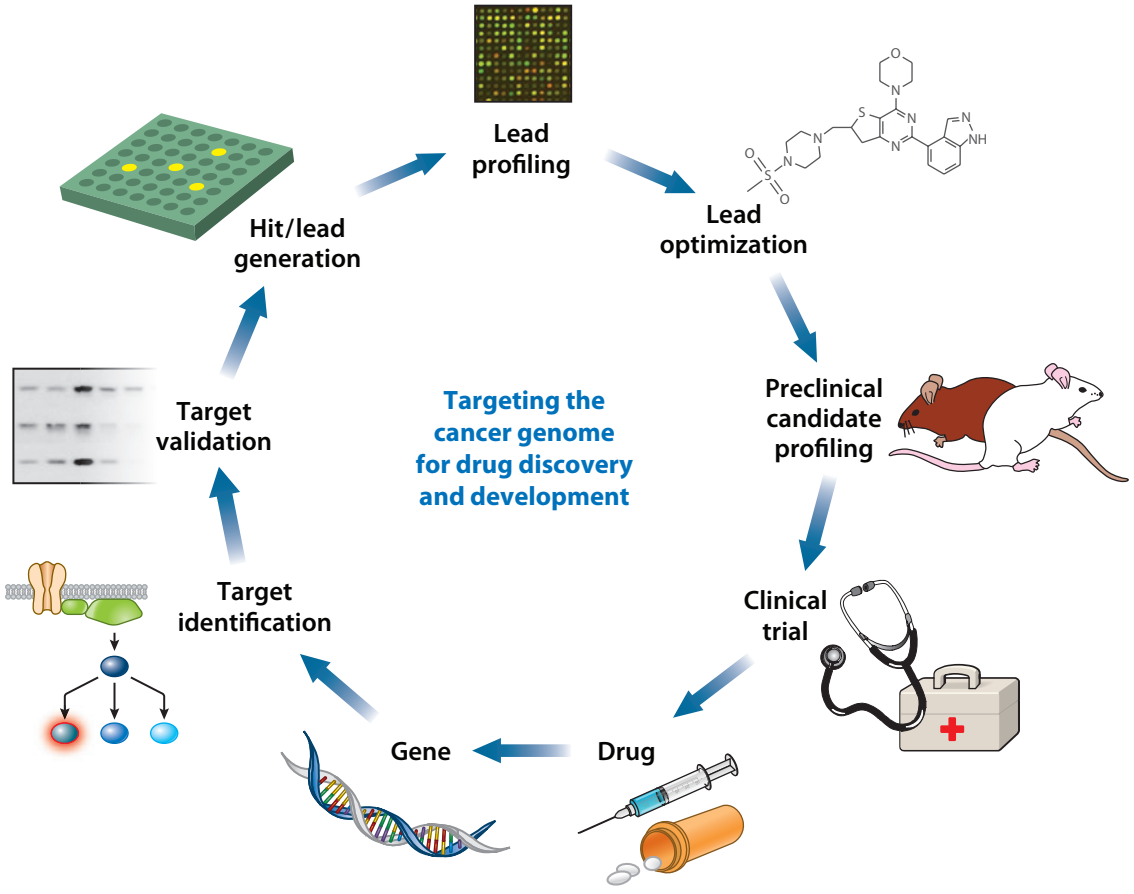

Figure 1

Targeting the genome for drug discovery: schema showing the different phases of modern drug discovery and development. Modified and redrawn from Reference 8a.

cost of the molecular cancer therapeutic pipeline. The clinical development and implementation of the essential biomarkers need to begin as early as the first-in-human studies so that they can inform the Phase I and II studies and be ready for clinical qualification in Phase III trials (8).

Indeed, biomarkers are also essential for all stages of preclinical discovery as well as clinical development in order to inform and drive these studies in a rational fashion and achieve maximal therapeutic impact. Furthermore, we need to rethink our overall clinical trial designs and use biology-driven studies to progress our new molecularly targeted drugs as quickly as possible to regulatory approval and patient benefit.

Nevertheless, although there have many recent examples of success with the molecularly targeted approach, a number of challenges remain, including the seemingly inevitable development of clinical drug resistance to targeted therapeutics, the consequent need for combinatorial therapies, and the paucity of validated and clinically qualified predictive biomarkers for the enrichment of likely responders in selected patient populations.

In this review, we begin by discussing the roles of different biomarkers—particularly predictive, pharmacokinetic (PK), PD, pharmacogenomic, and intermediate endpoint or surrogate biomarkers (12)—and show how they can be exploited in contemporary drug development strategies to target the cancer genome. We discuss the importance of novel trial designs for the development of molecularly targeted therapeutics. In addition, we detail and exemplify the exciting new approaches offered by molecular targeting strategies for drugging the cancer genome, including oncogene and nononcogene addiction, drugging the oncogenic lipid kinome, synthetic lethality, and overcoming apoptotic resistance.

BIOMARKER DEVELOPMENT

As defined by the Biomarkers Definitions Working Group in 2001, a biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (13). This group of biomarkers includes predictive, PK, PD, pharmacogenomic, and intermediate endpoint or surrogate biomarkers (12). We are already starting to see a significant increase in the use of biomarkers in clinical trials of new cancer drugs. For example, we are clearly moving away from toxicity-driven Phase I trials to biomarker-driven studies, with a greater role for PD biomarkers to provide evidence of proof of mechanism for target and pathway modulation. We are also moving toward the incorporation of predictive, intermediate endpoint, or surrogate biomarkers and other molecular markers such as pharmacogenomic assays to optimize patient benefit, provide early evidence of clinical response, and minimize drug-related toxicities. It is key that such biomarkers be analytically validated and eventually clinically qualified and that the right biomarker be used for the right drug in the right patient. Use of an inappropriate tumor marker may have more far-reaching adverse consequences than those caused by an unsuitable drug because it could adversely impact multiple drug development programs.

It is thus crucial for biomarkers to go through stringent series of validation and qualification stages that span both preclinical and clinical studies. An important issue that needs to be resolved in the coming years is the standardization of the definitions used to describe the stages of biomarker development (14, 15). It is also important to appreciate that the biomarker validation and clinical qualification process progresses from bench to bedside and back again in an iterative process (9).

At the preclinical stage, following new target identification, validation, and selection, the drug and companion biomarker discovery programs should ideally be carried out in a closely integrated fashion (16). In addition to analytically validated predictive biomarkers that can be employed for patient selection and hypothesis testing, more exploratory endpoints can also be used for hypothesis generation in first-in-human Phase I trials. If proved robust and potentially useful in early clinical trials, such predictive biomarkers can then be subject to further clinical qualification, prospectively or retrospectively, in large randomized controlled trials before potential regulatory approval. The success of this approach is illustrated by the increasing numbers of molecularly targeted agents that are approved with a label requiring the use of a companion biomarker for patient selection. For PD biomarkers involved in go/no-go decisions, researchers should adhere to Clinical Laboratory Improvement Amendments laboratory standards to ensure technical standardization.

In summary, biomarkers should ideally be incorporated at all stages of drug discovery and development so that their potential to facilitate a rational approach is maximized. We need to rethink our trial strategies and employ appropriate biology-driven studies in order to take promising molecular agents as quickly as possible to Phase III and beyond, so as to enhance the potential for patient benefit.

UP-FRONT SELECTION OF PATIENTS WITH PREDICTIVE BIOMARKERS

Currently, when patients are referred for consideration of a targeted therapy, investigators typically use their preexisting knowledge and experience to allocate the drugs in the most rational way possible, with the aim of offering the patients the highest chance of benefit. With the molecular characterization now available, rather than using such a best-guess approach, researchers are able to analyze fresh or archived tumor with appropriate assays for validated or putative predictive biomarkers, using techniques such as gene sequencing, gene expression microarrays, fluorescence in situ hybridization (FISH), or immunohistochemistry. Such techniques ensure that patients are matched with the appropriate drug on the basis of the molecular characteristics of their tumors (12).

An interesting small pilot study involved 86 patients with a range of advanced solid tumors from multiple centers (17). A central Clinical Laboratory Improvement Amendments lab was used to analyze all tumor biopsies obtained with immunohistochemistry, FISH, and gene expression microarray studies in real time prior to the allocation of patients to an appropriate therapy on the basis of the molecular profiles of their cancers. Patients in this study showed preliminary signs of patient benefit with this strategy, indicating that the up-front selection of patients for allocation to molecular therapies is a feasible and practical approach.

Another example of a study that used up-front patient selection for the allocation of different molecular therapies is the randomized Phase II BATTLE (Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination) clinical trial (18). In BATTLE, approximately 40% of patients were randomly assigned to receive one of four treatments in the first phase of the trial: erlotinib [epidermal growth factor receptor (EGFR) inhibitor], vandetanib [vascular endothelial growth factor (VEGF) inhibitor], sorafenib (multikinase inhibitor), or erlotinib-bexarotene [retinoid X receptor (RXR) activator]. During the second phase of the study—the adaptive phase—the allocation of treatments was based on the results of biomarker testing in the previous phase; that is, the remaining trial patients were allocated to drugs that had proven effective in first-phase patients with specific molecular aberrations, such as *EGFR* and *KRAS* mutations. These are, of course, still hypothesis-testing approaches with the aim of interrogating the underlying tumor biology to improve patient benefit in the future, but they indicate the direction of travel in personalized medicine.

In addition to the choice of biomarker, the choice of the best assay platform for the up-front selection of patients will also be important. A platform now in use by major drug development centers is Sequenom's MassARRAY® OncoCarta Panel, which can molecularly profile patients for key genetic alterations so that each patient can then be matched with an appropriate trial treatment (4). This platform interrogates 238 mutations in 19 common oncogenes and, because of its multiplexing capacity, is able to analyze multiple genomic events in a single sample with high sensitivity. The OncoMap mutation profiling platform analyzes 400 mutations in 33 known oncogenes and tumor suppressors known to predict response or resistance to targeted therapies.

POSTTREATMENT BIOMARKERS

For early-phase trials, especially first-in-human studies, patients should also have detailed PK profiling to ensure active exposures and PD biomarkers assessed to confirm target and pathway modulation and to establish PK-PD efficacy and toxicity relationships. It is important that these relationships be established preclinically through the quantitative correlation of the duration and extent of drug exposure and target modulation with the antitumor efficacy and toxicities observed. These

preclinical PK-PD-outcome data can then be utilized to model the likely human situation and to direct Phase I studies by providing target PK-PD thresholds to aim for. For example, we have recently shown in preclinical studies of the pan-Class I phosphatidylinositol 3-kinase (PI3K) inhibitor GDC-0941 that AKT phosphorylation needs to be inhibited by more than 90% over several hours to achieve a 50% decrease in proliferation cells in vitro, with a corresponding level of growth arrest in tumor xenograft models (19, 20). This information is being used to inform the ongoing Phase I dose-escalation study of GDC-0941 (21, 22). Ideally, during dose escalation, PD studies should be conducted serially in normal tissues such as platelet-rich plasma, peripheral blood mononuclear cells, hair follicles, and skin. Use of appropriate normal tissue can be relatively less invasive than tumor biopsies and allows serial sampling. However, it remains important to monitor effects within the malignant tissue. Thus, especially when the maximum tolerated dose is reached, paired tumor biopsies should also be obtained for the PD analysis of target and pathway modulation.

When receiving treatment with molecularly targeted agents, patients should continue to be monitored with well-established imaging tools, such as computed tomography (CT) and magnetic resonance imaging (MRI) scans. Although these imaging modalities are well established in the clinic, their readouts are valuable but incomplete indicators of treatment response for many targeted agents because they are structural imaging methods to assess tumor growth and the efficacy of therapeutics by measuring tumor volume (23). These readouts, although useful, have limited utility and in general do not address specific molecular processes (24). We are now seeing the development of novel imaging probes, including functional imaging techniques capable of tracking specific molecular pathways. Molecular imaging methods can be employed in the assessment and monitoring of the hallmarks of cancer, such as angiogenesis, metabolism, cell proliferation, and apoptosis (24–26). Noninvasive functional imaging, with either single- or multiple-modality approaches, potentially allows the accurate assessment and monitoring of the progression of precancerous lesions to malignancy and the assessment of tumor progression following malignant transformation, through the visualization of cancer-specific molecules, signaling pathways, and functional parameters. Imaging methods that are already being widely used include dynamic contrast-enhanced MRI, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), magnetic resonance spectroscopy of tumor metabolism, and diffusion-weighted imaging.

Efforts should be made to incorporate intermediate endpoint biomarkers, which may assess patient responses to therapy earlier than would be required to attain the primary objective of the study. Promising examples of such biomarkers include circulating tumor cells (CTCs) and circulating free DNA. Changes in CTC counts during treatment are now recognized as a prognostic marker in patients with metastatic breast, prostate, and colorectal cancers (8). CTCs are being assessed as an intermediate endpoint for overall survival in ongoing clinical trials, such as a randomized Phase III trial of the CYP17 inhibitor abiraterone in patients with castration-resistant prostate cancer (**http://www.clinicaltrials.gov**). Apart from the enumeration of CTCs, these cells may also be molecularly characterized to evaluate genetic aberrations that may play key roles in tumor pathogenesis. If serially sampled, CTCs can be used to provide a longitudinal analysis of the underlying and evolving biology of the tumor, potentially sparing the need for repeated invasive biopsies. CTCs, which may be thought of as "liquid biopsies," also have the potential to allow patient stratification according to the molecular profiles of risk, prognosis, and likely antitumor response. Once patients develop disease progression, their tumor should, if feasible, be reanalyzed for mechanisms of resistance, so that the patient can be started on an appropriate alternative targeted agent and in order to identify new resistance mechanisms.

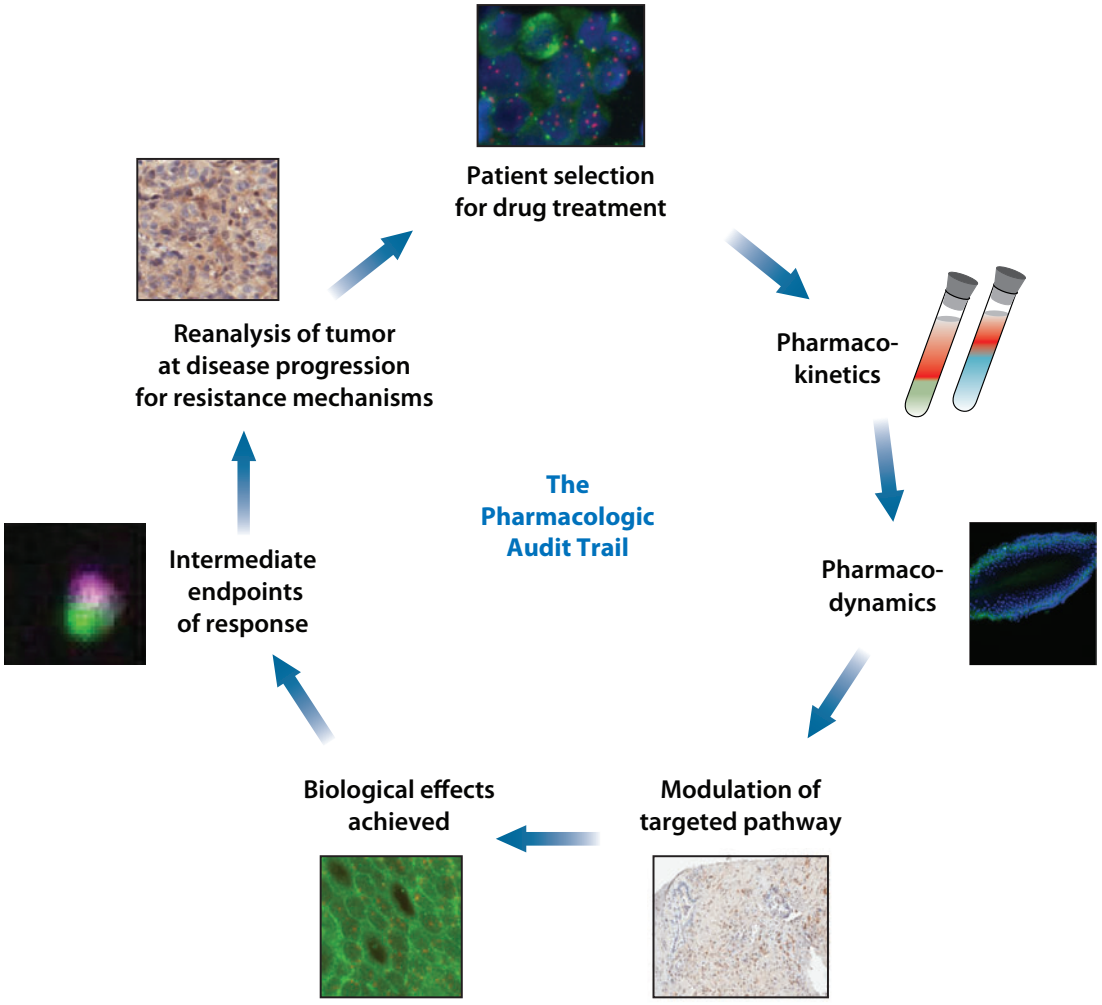

Figure 2

The Pharmacologic Audit Trail provides a rational framework for decision making during the development of a molecularly targeted agent. The likelihood of drug attrition decreases as sequential questions are successfully answered. Modified and redrawn from Reference 8a.

PHARMACOLOGIC AUDIT TRAIL

A conceptual and practical framework that can be used to link biomarkers for decision making in drug development and for the integration of biomarkers at all stages of the patient journey is the Pharmacologic Audit Trail (**Figure 2**) (27, 28). The framework includes the following sequential steps: (*a*) up-front patient identification with a predictive biomarker assay, if available; (*b*) incorporation of PK profiling of the drug to determine if active exposures are achieved; (*c*) measurement of target and pathway modulation with PD biomarkers to test for sufficient biochemical effects; (*d*) determination of intermediate endpoint biomarkers, such as CTCs and functional imaging modalities, to assess clinical response; and (*e*) reassessment of various endpoints including biomarkers of resistance when patients develop disease progression, so that they can then

be considered for suitable alternative antitumor agents. Iterative use of the Pharmacologic Audit Trail is important.

PROS AND CONS OF A BIOMARKER APPROACH

An individualized molecular approach is not necessarily appropriate for all drugs, e.g., cytotoxic agents. Also, not all molecular agents have robust, single predictive biomarkers already fully developed, as is currently the case with inhibitors of the PI3K/AKT pathway. Furthermore, upfront patient selection may exclude those without the proposed essential molecular aberration who may still potentially benefit from the drug, e.g., as is the case with multikinase inhibitors such as sorafenib (Nexavar®; Bayer). Finally, biomarker costs and implications for the speed and ease of trial accrual for selected populations of patients may be significant.

Nonetheless, a rationally based biomarker-driven approach should always be considered. Predictive biomarkers should be used when there is strong preclinical rationale for the utility of predictive assays. The predictive biomarker-led approach allows investigators quickly to identify the selected population of patients who may benefit most and to minimize the number of patients who receive ineffective treatments. Where assays can be developed to assess PD and downstream effects, this can provide reassurance or otherwise that target and pathway modulation has been sufficient. Both types of assays proved valuable in the recent development of mutant BRAF inhibitors (29, 30). Such biomarkers allow key biological questions to be answered about the underlying molecular basis of the drug's action and the signaling networks that it acts upon. Moreover, their use can reduce late-phase attrition in drug development, which can, in turn, offset biomarker costs. Prospective use of predictive biomarkers may also minimize the need for retrospective data dredging in late-phase clinical trials involving an unselected population.

HYPOTHESIS-TESTING BIOMARKER-DRIVEN CLINICAL TRIALS

On the whole, clinical trial designs have not changed substantially despite the move toward biomarker-based drug development with molecular therapeutics. Thus, we recommend that efforts should focus on tailoring clinical trials for such selective targeted therapies, rather than using traditional trial designs. Phase I trials should move from being predominantly toxicity-driven studies to being biology-driven ones that involve hypothesis-testing questions (**Figure 3**).

Although PK-PD biomarkers potentially allow selection of an optimal effect dose, it is important to continue to dose to the maximum tolerated level and to confirm adequate or optimal drug exposure as well as target and pathway inhibition through PK and PD studies using both tumor and normal tissue, such as blood, hair, and skin biopsies. The reason for this is to avoid underdosing, which may lead to the potential activity of the drug being missed. Once the maximum tolerated dose is reached, treatment of expansion cohorts should be carried out to assess the initial efficacy of the molecular therapeutic in one or more selected populations of patients and to explore the correlation between the biomarker and antitumor responses (8). The advantages of carrying out Phase I expansion cohorts in selected populations over multiple Phase II trials are that they involve a seamless transition, they allow the continued assessment of multiple tumor types, and they facilitate efficacy and toxicity assessments at different dose levels.

If a strong efficacy signal is observed in a selected population, one may potentially move on to randomized Phase II to III trials that incorporate early stopping rules. For example, such a randomized Phase II to III trial could mandate an interim data analysis. If the efficacy seen following an early data analysis indicates that the trial does not meet preset requirements, a no-go decision might be made on the basis of these randomized data, resulting in early trial cessation (8). However, if the data are promising and meet preset criteria, a decision could be made to proceed

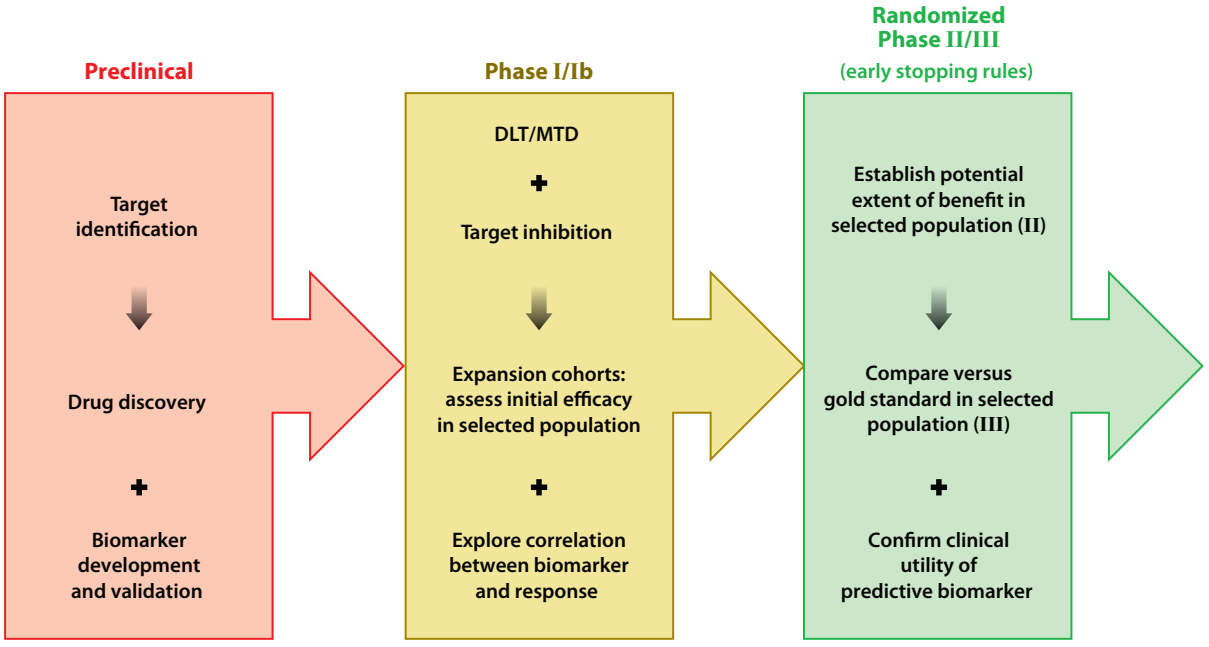

Figure 3

Future clinical trial paradigm. With a solid platform of robust and innovative technological developments and a switch in the focus of drug development to molecularly targeted therapies, smart, hypothesis-testing and hypothesis-generating preclinical and clinical studies will be possible with the use of validated biomarkers. Abbreviations: DLT, dose-limiting toxicity; MTD, maximum tolerated dose.

seamlessly to Phase III evaluation of the novel agent using a larger population of patients in order to confirm the clinical utility of the predictive biomarker and demonstrate therapeutic value.

PHASE III CLINICAL TRIALS: IS THE CURRENT SYSTEM STILL VIABLE?

The need for large randomized Phase III trials when patient subgroups with responsive tumors have already been identified in early Phase I/II trials has been questioned recently (8, 31, 32). This is especially true for cancers lacking approved effective therapies, when access to potentially important new treatments could otherwise be delayed for months to years.

Following demonstration of the early promise of vemurafenib (PLX4032, Zelboraf™; Plexxikon/Roche) and crizotinib (Xalkori®; Pfizer) in V600E BRAF-mutated cancers and ALK-rearranged non-small-cell lung cancer (NSCLC), respectively, in Phase I escalation and expansion study cohorts, randomized Phase III trials were started immediately, without the traditional Phase II study to confirm their efficacy. Patients in the Phase III study control arm who developed disease progression were subsequently permitted to receive the active drug in a Phase II trial of the same agent, although such trials were limited in number and availability.

It should be noted that in the current age of the social electronic network, patients are more likely to be made aware of any novel experimental trial drugs with high response rates and may be less keen to enter a large Phase III trial in which they may be randomized to receive an alternative and potentially inferior control drug or placebo.

It may be time to consider a change in the rules that govern regulatory approval of promising molecularly targeted drugs, especially in cases when the selected population is rare and accrual

to a large Phase III trial is likely to be prolonged. The near future may see the adoption of a new accelerated-approval regulatory pathway to register drugs with high response rates (e.g., >50%) and minimal toxicities, e.g., seen in approximately 100 patients from Phase I escalation and expansion study cohorts, especially if there is an urgent unmet need.

Such accelerated approvals of molecular therapies should, of course, be dealt with on a case-by-case basis and will not be appropriate for agents with borderline response rates or those with known late toxicities. Further studies should continue to be conducted with all agents, even after drug approval, to establish the long-term benefits and potential toxicities and also to determine the optimal dose and schedules, understand resistance mechanisms, and construct rational drug combinations.

STRATEGIES FOR DRUGGING THE CANCER GENOME

A range of therapeutic approaches are being adopted to exploit information on the cancer genome and related biology. We now discuss various strategies for drugging the cancer genome, focusing on blocking oncogene addiction, drugging the oncogenic lipid kinome, addressing nononcogene addiction, exploiting synthetic lethality, and overcoming apoptotic resistance with small molecules (the last of which is addressed in the **Supplemental Material** accompanying this review; access this section by following the **Supplemental Materials link** from the Annual Reviews home page at **http://www.annualreviews.org**).

Supplemental Material

Oncogene Addiction

The concept of oncogene addition is based on the observation that cancers can be dependent on a certain pathogenic oncogene, which drives malignant progression (33). Consequently, such cancers are exquisitely sensitive to the genetic removal or pharmacologic inhibition of the specific oncoprotein, unlike cells that lack the molecular aberration (33–35).

The oncogene addiction principle has been exploited with great success in recent years, with the discovery and development of targeted therapies that have been matched with specific molecular drivers of different malignancies. This approach was exemplified by the success of the monoclonal antibody trastuzumab in HER2-positive metastatic breast cancer (5) and with imatinib targeting BCR-ABL in CML and mutant KIT in gastrointestinal stromal tumors (6, 7). Other approvals that exploit oncogene addiction include gefitinib (Iressa™; AstraZeneca) (36) and erlotinib (Tarceva®; OSI Pharmaceuticals/Genentech) for the treatment of patients with EGFR-mutated NSCLC (37).

Exploiting pathogenic oncogene addiction at the molecular level has transformed the lives of CML patients by significantly improving survival with minimal drug-related toxicities (38). These findings thus validated the strategy of targeting single kinase addiction.

Although such an oncogene addiction approach should also be applicable to other molecular drivers in a range of tumor types, the observed efficacy and duration of antitumor responses have not been as impressive as those observed with imatinib in CML. There are several potential reasons for this. Oncogene addiction may be context-dependent and possibly even organ-specific (33). This may arise from the complex network of signaling cascades present, particularly in advanced solid tumors with multiple oncogenic abnormalities. There are likely to be signaling cross talk and feedback mechanisms that can limit or overcome inhibition of the driver oncogene. Resistance may arise through mutation of the primary molecular target or the induction of alternative pathways. Furthermore, a major challenge in all cancer therapies is the presence of multiple cancer cell clones that may have alternative molecular drivers that are selected for by the drug therapy. All of these factors can lead to eventual drug resistance. Nevertheless, imatinib and trastuzumab have certainly led the way in targeting oncogene addiction, and the past few years have seen several further successes.

Targeting anaplastic lymphoma kinase–rearranged non-small-cell lung cancer. One of these successes has been the development of the dual ALK/MET (mesenchymal-epithelial transition factor) kinase inhibitor crizotinib for the treatment of patients with ALK-rearranged NSCLC. Activating mutations or translocations in ALK were detected in anaplastic large cell lymphoma, neuroblastoma and NSCLC, and other cancers (39–42). Following the demonstration of the exquisite sensitivity of tumor cells with *ALK* abnormalities to crizotinib, a Phase I clinical trial demonstrated the safety and stunning activity of crizotinib in patients with NSCLC that harbored ALK rearrangements (43). All the responding patients had ALK rearrangements detected by FISH, but not MET amplification or EGFR mutations.

Crizotinib was well tolerated, with main toxicities of mild gastrointestinal symptoms, including nausea and diarrhea, as well as mild visual disturbances (43). A total of 57% (46/82) of *ALK*-rearranged patients selected from a total of 1,500 screened for the Phase I clinical study had a Response Evaluation Criteria In Solid Tumors (RECIST) response to crizotinib (43). The estimated median progression-free survival (PFS) at 6 months was estimated as 72%.

Phase III studies confirmed the activity of crizotinib in the stratified patient population, leading to drug approval in 2011 (**http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm270058.htm**). Thus ALK inhibition used in patients with *ALK*-rearranged NSCLC tumors has now joined EGFR inhibitors in the growing list of genotype-stratified therapies available for NSCLC. Crizotinib has the potential to be effective in tumor types other than NSCLC, especially anaplastic large cell lymphoma and neuroblastoma, where activating mutations or translocations in ALK have been found. However, as with other oncogene addiction strategies, there are likely to be context-dependent modifier genes at play.

Targeting V600E BRAF melanoma. Another exciting recent development has been the pharmacologic inhibition of the kinase activity of the activated BRAF oncogene product by potent and selective inhibitors (29, 30). *BRAF* was the first oncogene to be identified through large-scale cancer genome sequencing in tumors, particularly melanoma, thyroid, and colorectal cancers (44).

The majority of *BRAF* mutations, including the V600E variant, cause hyperactivation of the kinase activity of BRAF and thus of the downstream MAP kinase (MAPK) cascade (45, 46). Efforts in the development of potent and selective inhibitors against this target did not prove successful initially; for example, sorafenib was originally developed as CRAF inhibitor but was later confirmed to be a multikinase inhibitor, with primary pharmacologic effects on the angiogenic VEGF receptor kinase (47). The potent and selective BRAF inhibitor vemurafenib was recently discovered using structure-based design. It inhibits the RAS/RAF/MEK/MAPK pathway in mutated *BRAF* cancer cells and leads to regression of human tumor xenografts driven by mutant *BRAF* (48).

Vemurafenib was well tolerated in patients with advanced solid tumors, and, crucially, antitumor responses were observed in the Phase I dose-escalation clinical trial in patients with V600E *BRAF*-mutated melanoma (29). Following the strong preclinical rationale and preliminary signals of efficacy, a seamless transition to a dose expansion cohort in patients with V600E *BRAF*-mutated melanoma was undertaken; this expansion cohort demonstrated that vemurafenib doses that caused >80% inhibition of extracellular signal-regulated kinase (ERK) phosphorylation resulted in an impressive 81% RECIST response rate, including two complete responses (29, 30). The median PFS in this Phase I trial was estimated to be at least 7 months compared with only 2 months for historical controls. Significantly, as a proof of concept for this oncogene addiction approach, tumor regressions and disease control were observed in patients with mutant but not wild-type *BRAF* status.

The adverse effects of vemurafenib observed in clinical testing include fatigue, skin rash, and arthralgia. Importantly, 31% of patients developed keratoacanthoma, an early form of squamous

cell carcinoma (29). Mechanistic studies suggest that the process responsible for keratoacanthoma formation is the paradoxical activation of wild-type RAF kinase activity through dimerization following inhibition of the mutant BRAF protomer in skin cells already harboring activating *KRAS* mutations or other alternative priming events (49–51).

Although the response rates with vemurafenib in patients with V600E *BRAF*-mutated melanoma have been impressive and durable, lasting up to 18 months, acquired drug resistance is still inevitable, and not all patients with *BRAF* mutations responded, suggesting underlying mechanisms of intrinsic and acquired resistance. Crucially, the observed drug resistance has not resulted from the gatekeeper mutations that block drug binding (as is seen with many other kinase inhibitors such as imatinib, gefitinib, and erlotinib); this observation has led to the design and development of second-generation BCR-ABL and EGFR inhibitors to overcome the gatekeeper mutations (29). Instead, in the case of vemurafenib, the preclinical studies and reverse translation studies with clinical tumor material have suggested that the increased expression of COT, an alternative activator of MEK, is able to circumvent RAF to provide a bypass pathway to ERK activation (52). Thus, potential strategies for circumventing resistance mechanisms may be through RAF/COT inhibitor combinations. Furthermore, other reverse translation studies of tumor material from treated patients show that resistance can arise through either of two additional, mutually exclusive mechanisms: (*a*) the upregulation of platelet-derived growth factor-β (PDGFβ) expression, or (*b*) *NRAS* mutations (53). This points to the potential utility of adding or combining BRAF inhibitors with PDGFβ or MEK inhibitors, respectively. The use of MEK inhibitors may also, in theory, prevent the development of keratoacanthomas caused by mutant *BRAF* inhibition, as long as the skin toxicities, seen with each individual agent, are tolerable.

Targeting the Hedgehog pathway. Yet another recent example of a successful drug discovery and development project that has exploited pathogenic oncogene addiction, this time by inhibiting a nonkinase target, has been the use of smoothened homolog (SMO) inhibitors in basal cell carcinoma of the skin and medulloblastoma (54, 55).

Hedgehog is a key regulator of cell growth and differentiation during embryogenesis and development, but it is inactive in adult tissues. The extracellular Hedgehog protein binds to the 12-transmembrane receptor PTCH1 and prevents PTCH1-mediated inhibition of signaling by the protein SMO. SMO then leads to the activation of transcription factors encoded by GLI family zinc finger (*GLI*) and to the resultant induction of Hedgehog target genes, including *GLI1* and patched homolog 1 (*PTCH1*). Mutations in the Hedgehog pathway genes, mainly the loss-of-function *PTCH1* genes and, less commonly, the gain-of-function *SMO* mutations, result in constitutive Hedgehog pathway signaling. In basal cell carcinomas, this process may mediate unrestrained proliferation of basal cells of the skin and may drive malignant progression.

This strong preclinical rationale led to a Phase I trial (55) of the first-in-class SMO inhibitor vismodegib (GDC-0449; Genentech), which inhibits activation of downstream Hedgehog target genes, in patients with advanced basal cell carcinoma. Impressively, of the 33 patients assessed, 18 had an objective response to vismodegib, according to radiological assessment ($n = 7$), physical examination ($n = 10$), or both ($n = 1$). The median duration of the study treatment was 9.8 months. Furthermore, a patient with metastatic medulloblastoma that was refractory to multiple therapies had a rapid although transient regression of the tumor and reduction of symptoms. These preliminary findings provided proof of concept for targeting the Hedgehog pathway. Vismodegib was generally well tolerated; significant grade-3 adverse events that were possibly related to vismodegib included fatigue ($n = 4$), hyponatremia ($n = 2$), muscle spasm ($n = 1$), and atrial fibrillation ($n = 1$).

Drugging the Oncogenic Lipid Kinome

The Class I PI3K family of lipid kinases phosphorylate the 3 position hydroxyl group of the inositol ring of phosphatidylinositol (PtdIns), producing second messengers that activate downstram kinases such as AKT. The identification through cancer genome sequencing of *PIK3CA* mutations provided the first example of a mutated lipid kinase oncogene (56). *PIK3CA*, which encodes the p110α catalytic subunit of PI3K, is the most commonly mutated kinase in the human genome identified to date (**http://www.sanger.ac.uk/genetics/CGP/Census/**). In addition to *PIK3CA* mutations, there is clear evidence for *PIK3CA* amplification and overexpression, as well as mutation and loss of expression of the negative regulator *PTEN*, which is the second most common tumor suppressor gene after *p53* (**http://www.sanger.ac.uk/genetics/CGP/Census/**). Thus, the pharmacologic targeting of the PI3K/AKT pathway is a key priority.

Targeting the PI3K/AKT pathway. Drug development efforts have involved molecular inhibitors of key components of the PI3K pathway (57), primarily PI3K, AKT, and mammalian target of rapamycin (mTOR) (58). Although PI3K and AKT inhibitors are only in early-phase clinical testing, mTOR inhibitors, such as the rapamycin analogs temsirolimus (Torisel®; Wyeth) and everolimus (Afinitor®; Novartis), have already obtained regulatory approval for the treatment of advanced renal cell cancer. Everolimus has also been recently approved for the treatment of pancreatic neuroendocrine tumors as a result of a positive Phase III study (59; see also **http://www.cancer.gov/cancertopics/druginfo/fda-everolimus**). These rapamycin analogs or rapalogs act indirectly on mTOR by binding to an abundant intracellular binding protein, FKBP-12, to form a complex that binds at the rapamycin binding domain. The primary differences between the rapalogs are their PK and pharmacologic properties (60). The intravenously administered temsirolimus and the oral everolimus, unlike rapamycin, do not commonly induce immunosuppression. Following the successful development of these first-generation rapalogs, novel catalytic inhibitors of TORC1/TORC2 are now in preclinical and early clinical development (58).

Multiple PI3K inhibitors with a range of specificities and potencies have entered Phase I/II clinical trials. These include the pan-Class I PI3K agents, such as GDC-0941 (Genentech), which potently inhibits all four oncogenic Class I PI3K isoforms (α, β, δ, and γ), and the dual-Class I PI3K/mTOR inhibitors, such as NVP-BEZ235 (Novartis) and GDC-0980 (Genentech) (19, 61, 62).

PI3K isoform selectivity. It is likely that for these PI3K agents to be successful, several key issues need to be addressed. The ideal profile(s) of target blockade required across the PI3 kinome for optimal antitumor effects is unclear. It is also not known if these profiles will be context driven, i.e., determined through different factors such as tumor, genotype, or other variables. The design and discovery of PI3K inhibitors with varying isoform selectivity patterns have been aided by pioneering chemical and structural biology techniques that build on early chemical tools (63, 64). Apart from the pan-Class I PI3K agents and dual-Class I PI3K/mTOR inhibitors, potential PI3K profiles of interest may include p110α-selective drugs for *PIK3CA* mutant cancers, p110β-selective agents with potential in PTEN-deficient tumors (65, 66), and p110δ-selective agents such as CAL-101, which is showing promise in chronic lymphocytic leukemia and other cancers (67).

Predictive biomarkers. Despite several years of ongoing research, it is still unknown which biomarkers are likely to be useful for robustly enriching the target population with antitumor responses. It is also unclear how dependent this will be on the PI3K isoform profile in question

(62). The predictive biomarkers thought to have the greatest potential to enrich for antitumor responses to PI3K inhibitors include *PIK3CA* mutations, loss of PTEN expression, and *HER2* amplification, whereas certain *KRAS* mutations may confer resistance (19, 68). However, no single biomarker may be sufficiently robust or specific to result in a strong efficacy signal. This is likely to be because of the abundance of cross talk and feedback loops in this network of signaling cascades. Although exceptions may apply, it is likely that a predictive gene expression signature or a collection of markers will prove to be more helpful than a single biomarker in predicting responses to a specific PI3K pathway inhibitor.

Combinatorial regimens. Unless a specific population of tumors is identified to respond with a robust predictive biomarker, the optimal use of specific PI3K inhibitors will be in rational combination regimens with drugs acting on the same pathway, on parallel pathways, or in other pairings. Such combinations are especially relevant in view of the negative feedback mechanisms activated upon drug target engagement, including mTORC1 inhibitor-mediated activation of upstream PI3K/AKT pathway signaling (69). Furthermore, AKT inhibition induces expression and phosphorylation of multiple receptors, including HER3, insulin-like growth factor 1, and insulin receptors, in part owing to mTORC1 inhibition and FOXO-dependent activation of receptor expression (69). In addition, a potential pitfall of inhibiting AKT alone in some *PIK3CA* mutant cancers is the preclinical observation of AKT-independent signaling downstream of oncogenic *PIK3CA* mutations; this signaling involves phosphoinositide-dependent kinase-1 and serine/threonine-protein kinase 3 (70).

Rational combinations of PI3K pathway drugs with other molecularly targeted agents, including MEK inhibitors that act on parallel pathways, are thus likely to be crucial in revealing the full potential of targeting addiction to *PIK3CA* and additional oncogenic PI3K pathway abnormalities. For example, in cancers in which AKT suppresses HER3 expression, the combined inhibition of AKT and HER kinase activity was more effective than single-agent therapy (69). When considering rational combination regimens, one should also not ignore the potential for PI3K inhibitors to affect tumor angiogenesis and tumor-host cell interactions (71).

Nononcogene Addiction

Nononcogene addiction refers to the dependency of tumor cells on the diverse gene products and networks that are not directly oncogenic but are nonetheless essential for cancers to survive and proliferate (72). The systematic search for such genes has been facilitated by genome-wide, high-throughput RNAi screens (73). Novel agents that exemplify nononcogene addiction (72) include inhibitors of heat shock protein 90 (HSP90) (74, 75), which exploits the cellular dependency on molecular chaperones, and histone deacetylase (HDAC) inhibitors (76), which are also examples of epigenetic therapy.

Targeting heat shock protein 90. An important feature in the initial description of nononcogene dependency was the stressed state of cancer cells, which can arise from the abundance of genetic abnormalities and pressures of the tumor microenvironment, supporting the addition of stress management to the established hallmarks of cancer (72, 77). Heat shock factor-1 (HSF1) is necessary for the initiation and regulation of the malignant state in cancer cells by various oncogenes, and its genetic ablation results in apoptosis or selective cell cycle arrest in cancer cells (78). Although as a nonligand transcription factor, HSF1 is difficult to target directly, the downstream molecular chaperone HSP90 is a druggable nononcogene addiction target.

Targeting HSP90 as an antitumor strategy offers several key advantages. First, inhibiting the ATP binding and ATPase activity of HSP90 (79) affects the stress pathway that is key to the survival and proliferation of malignant cells to a greater extent than is true for normal cells. Second, HSP90 inhibitors result in the combinatorial pharmacologic and therapeutic targeting of multiple mutated and overexpressed oncoproteins, which require the HSP90 chaperone for their activation and stability (74, 75). There has thus been great interest in this target, and multiple HSP90 inhibitors have entered Phase I/II clinical testing (74, 75).

The first HSP90 inhibitors to enter clinical trials were analogs of the natural product geldanamycin. One of these, tanespimycin (17-AAG; Bristol-Myers Squibb), has shown promise in trastuzumab-refractory HER2-positive metastatic breast cancer, probably in view of the extreme dependency of HER2 on HSP90 (80). High HSP90 expression is an adverse prognostic factor in breast cancer, consistent with addiction to this nononcogene (81).

Early clinical activity with tanespimycin and its geldanamycin analog alvespimycin (17-DMAG; Kosan) has been observed in patients with breast cancer, prostate cancer, melanoma, and other tumors for which key oncogenic drivers are HSP90 clients, particularly transcription factors such as the estrogen and androgen receptors and many oncogenic kinases (82). The observation of objective responses by RECIST criteria in trastuzumab-refractory HER2-positive breast cancer has validated HSP90 as a clinical target. The studies with the these early inhibitors also validated the Pharmacologic Audit Trail PD biomarkers of depleted client proteins and increased HSP expression.

Following the initial proof-of-concept studies with the geldanamycin analogs, numerous synthetic small-molecule HSP90 inhibitors have entered clinical development, including purine- (83) and resorcinol-based agents, the latter exemplified by NVP-AUY922 (Novartis) (84, 85). These agents overcome the formulation and hepatotoxicity and resistance issues seen with geldanamycin analogs.

By hitting key oncogenic networks at multiple points, HSP90 inhibitors have the potential to minimize the development of drug resistance, e.g., through kinase mutation or pathway switching (86). However, a key issue with inhibiting HSP90 is the resulting induction of the HSF1 pathway, which induces expression of cytoprotective HSPs. This may, however, potentially be overcome by inhibiting other related heat shock proteins and molecular chaperones, such as HSP70 (87).

Targeting histone deacetylase. HDAC enzymes are zinc-dependent proteins that catalyze the removal of acetyl groups from lysine residues of histone proteins, compact chromatin, and consequently repress the transcription of associated genes (88). Preclinical studies with chemical inhibitors have revealed a greater dependency on HDACs in tumor cells than in healthy cells (89). Furthermore, evidence from genome-wide screens of clinical tumors has revealed epigenetic deregulation of gene expression, changes in epigenetic histone marks, and mutations of chromatin-modifying genes, supporting the development of HDAC inhibitors (90). In addition, preclinical studies have shown that HDAC inhibitors can be utilized in combinatorial therapy to inhibit the development of a chromatin-mediated drug-tolerant state with stem cell–like features, for which the underlying mechanism involves the JARID1A histone lysine demethylase (91).

Small-molecule HDAC inhibitors generally follow the cap-linker-pharmacophore model, and although many inhibitors have demonstrated broad evidence of activity across HDAC families, different selectivity patterns are emerging (92). A range of HDAC inhibitors have been developed and can be classified on the basis of their chemical structures as hydroxamates, short-chain fatty acids, cyclic tetrapeptides, and benzamides. The hydroxamate vorinostat (Zolinza®; suberoylanilide hydroxamic acid; Merck) and cyclic tetrapeptide romidepsin (depsipeptide, Istodax®; Gloucester Pharmaceuticals) have recently been approved for the treatment of cutaneous T cell lymphoma,

whereas multiple other HDAC inhibitors are in early-phase trials, including belinostat (PXD101; Topotarget), panobinostat (LBH589; Novartis), etinostat (MS-275, SNDX-275; Syndax Pharmaceuticals), mocetinostat (MGCD0103; MethylGene Inc.), givinostat (ITF2357; Italfarmaco), CHR-3996 (Chroma Therapeutics), and PCI-24781 (CRA-02781; Pharmacyclics) (93). These and other HDAC inhibitors appear to have wider activity in preclinical models, and their full clinical potential is still being explored in early-phase clinical trials. In the future, the optimal application of these inhibitors is likely to involve the use of rational combination strategies and the use of predictive biomarkers that are yet to be identified.

Synthetic Lethality

Synthetic lethality is a phenomenon in which two nonlethal genetic mutations are innocuous when they occur individually but result in lethality to a cell when they occur in combination (94). This concept may involve genes in related pathways or genes acting along a single pathway, in which loss of both genes, rather than just one, significantly affects pathway signaling or function. The targeting of malignant cells, which bear particular genetic aberrations, through the use of specific molecular therapeutics that inhibit the synthetic lethal gene partner of that abnormality should, in theory, result in selective tumor cell death, with a large therapeutic window (95). Large-scale screens for synthetic lethality are being carried out in human cancer cells, with the aim of identifying potential synthetic lethal targets for the development of anticancer therapeutics (96).

Targeting poly(ADP-ribose) polymerase in tumors with germline *BRCA1* and *BRCA2* mutations. Cancer cells that have inactivating *BRCA1/2* gene mutations, and therefore that are deficient in DNA double-strand break repair by homologous recombination (HR), are exquisitely more sensitive to cell kill by poly(ADP-ribose) polymerase (PARP) inhibitors (97, 98). PARP plays a key role in the repair of DNA single-strand breaks through the base excision repair pathway. PARP inhibition in such HR-deficient cells should therefore lead to the accumulation of DNA single-strand breaks and subsequently to DNA double-strand breaks at replication forks. This results in genomic instability and eventual cellular apoptosis. The first pharmacologic exploitation to validate the synthetic lethal approach in the clinic was the use of the potent, oral PARP inhibitor olaparib (AZD2281; AstraZeneca) to *BRCA1* and *BRCA2* (*BRCA1/2*) mutation carriers with advanced solid tumors (99–102).

The first-in-human Phase I study of olaparib followed the Pharmacologic Audit Trail framework. It used a PK profiling step to confirm active drug exposures and utilized detailed PD biomarker studies to demonstrate target inhibition, including the suppression of poly(ADP-ribose) in peripheral blood mononuclear cells and tumor tissue and the induction of γH2AX foci as a measure of DNA double-strand breaks in plucked eyebrow-hair follicles (99). This early-phase study that enrolled patients with a range of solid tumors incorporated provisions in the protocol to enrich each dose-escalation cohort with germline *BRCA1/2* mutation carriers, as well as an expansion cohort that mandated carriers of *BRCA1/2* mutations (99).

As predicted from preclinical studies, objective evidence of antitumor activity by RECIST and tumor marker criteria was observed only in *BRCA1/2* mutation carriers with ovarian, breast, or prostate cancer. Of the patients with advanced *BRCA1/2*-mutated ovarian cancer treated with olaparib in this Phase I trial, there was a 40% response rate by RECIST criteria with a median response duration of 28 weeks (99). The antitumor activity observed in patients with *BRCA1/2*-mutated ovarian cancer appeared to correlate with platinum sensitivity, implying common resistance mechanisms, although responses were seen in patients with platinum-resistant and even platinum-refractory disease (100). This has important implications for the treatment of patients

with *BRCA1/2*-mutated ovarian cancer because platinum-based chemotherapeutic regimens are the current gold standard for such patients.

Poly(ADP-ribose) polymerase inhibitor resistance. Mechanisms of resistance to PARP inhibitors are beginning to be unraveled. Recent studies in cancer cell lines have shown that resistance to PARP inhibitors and cisplatin may be acquired through the intragenic deletion of a mutation in *BRCA2*, leading to restoration of the open reading frame and of BRCA2 repair function to maintain genomic integrity (103, 104). Other resistance mechanisms are likely to be involved, including (*a*) the compensatory upregulation of other proteins mediating DNA repair; (*b*) induction of other mediators of cancer progression, such as PI3K/AKT or RAS/RAF pathway abnormalities; or (*c*) mutations in PARP, leading to altered drug-target interactions (94).

Wider application of poly(ADP-ribose) polymerase inhibitors. The importance of the use of PARP inhibitors with such a synthetic lethal approach lies in the potential that it may be applicable to tumors with a range of sporadic oncogenic abnormalities (96). For example, PARP inhibitors have antitumor activity in non-*BRCA1/2*-mutated metastatic high-grade serous ovarian cancer, which bears somatic mutations that result in nonfunctioning HR (105). Other somatic cancers with HR DNA repair defects, such as tumors that lack expression of the tumor suppressor gene *PTEN*, may also prove to be sensitive to PARP inhibitors (106, 107). These are clearly exciting times for the use of PARP inhibitors as single agents or combined with chemotherapy in defined populations.

The concept of synthetic lethality is especially attractive in drug discovery, in scenarios where pharmacologically modulating the primary molecular target directly is not possible, for example, if the target involves loss of functionality or has challenging druggability. An example is the loss of function of the *MLH1* or *MSH2* genes that encode DNA mismatch repair proteins, which have a potentially synthetic lethal relationship with the DNA polymerases POLG and POLB, respectively (108).

FUTURE CONSIDERATIONS

Exciting progress has been made in the discovery and development of molecularly targeted therapies, but many challenges remain. The use of PK-PD biomarkers in the Pharmacologic Audit Trail is now commonplace. We are also now seeing the combined use of a molecular therapeutic alongside a predictive biomarker for patient selection. We strongly advocate the rule of "no biomarker, no drug project" wherever possible. The extent to which this is possible will ultimately depend on the characteristics of both the drug and the target tumor and whether a biomarker is biologically applicable to and technically feasible for the particular program.

The selection of new molecular targets for drug discovery should be made on the basis of a strong biological hypothesis and developed through the use of cutting-edge medicinal chemistry and/or molecular techniques, particularly structure-based design. Expanding the envelope of druggability to embrace more technically challenging targets is a key priority. Following a successful drug discovery phase, innovative, smart clinical trials must be carried out using analytically validated PK and PD assays to confirm adequate drug exposures and proof of adequate target engagement. If appropriate and feasible, these studies should also incorporate predictive biomarkers for up-front patient selection.

It is already common in several cancer research institutions to carry out tests for the status of one or many oncogenes and to use the resulting information as a guide to treatment. The decrease in sequencing costs will mean that routine sequencing of whole cancer genomes in patients may soon

become a reality (1). The incorporation of advanced molecular imaging tools, proteomics, and metabonomics into clinical trials is likely to increase as well. The utility of validated intermediate endpoint biomarkers, such as CTCs, will also become commonplace in the near future.

We also need to increase the use of novel adaptive clinical trial designs (109, 110). Adaptive trial strategies allow the statistical model used to learn from experience as the study progresses. For example, interim assessments could be done to adapt the sample size or to stop the trial early because of success, futility, or harm. In addition, such adaptive studies may allow the switching from a hypothesis of noninferiority to one of superiority or vice versa, and it may also allow arms or doses to be dropped. These studies may also allow adaptive patient allocation to modify the randomization rate during a trial, in order to increase the probability that a patient is allocated to the best treatment. Such a strategy thus facilitates the potential for real-time assessment of the drug-biomarker combination to help direct therapy. Early examples of trials using this approach are the BATTLE study in NSCLC (18) and the I-SPY2 trial in locally advanced breast cancer.

Another future consideration is to rethink the approach of combination strategies with specific targeted therapies. This is important because unless a specific population of patients is identified to respond strongly and durably when selected with a robust predictive biomarker, the greatest likelihood for selective targeted therapies to provide benefit for patients is in rational combination regimens. This view is reinforced by the common emergence of resistance to most targeted therapies, as is also the case with traditional cytotoxic drugs. We need to think about how best to do this quickly and safely for our patients. Can we design combinations to overcome or prevent resistance? Can we design trials that allow a second or even third drug to be added seamlessly to a selective drug in the same study for a synergistic or additive response? This could perhaps be done following the development of drug resistance with the first agent, when potential resistance mechanisms can be investigated with a tumor biopsy and such resistance can be overcome through the introduction of a subsequent appropriate drug. Such an approach would, of course, not be appropriate if both drugs are associated with overlapping toxicities. There is also no guarantee that such an approach would inhibit the responsible drivers of cancer. Thus, improvements in the development and use of predictive mouse models would be valuable. The challenges of intratumor heterogeneity and the emergence of resistant clones may potentially be tackled by targeting tumor stem cells.

Although there are now several examples in which individualized or stratified drug therapy is already a reality, the current approach to cancer treatment is still driven by organ- and tumor-based treatment strategies. However, as we move into the future—and especially in view of the molecular complexities involved in malignancies and the presence of common molecular mechanisms across tumor types—it is likely that gene- and mechanism-based approaches will provide a better way to tackle the development and application of individualized treatments for our cancer patients.

CONCLUDING REMARKS

These are exciting times in oncologic drug discovery development. We are finally entering an era of genuine personalized medicine. As discussed here, there are now many strategies for drugging the cancer genome. The principles that have emerged from basic cancer research—and have been accelerated by large-scale cancer genome sequencing, molecular profiling, and functional screening efforts—are clearly finding successful applications in the cancer clinic. This success is exemplified by several key trailblazing agents, which have now been approved for use in a range of malignant diseases, including tumor types such as melanoma and certain lung cancers that have long been considered difficult to treat.

In order to maximize progress, we need to continue to foster and enhance close collaborations among academic, industry, and regulatory bodies, so as to synergize efforts that accelerate novel drug discovery and development, accelerate speed to approval, and reduce late-stage attrition. Although the instances of blockbuster successes for individualized drug-companion biomarker combinations are so far relatively few, this number is expected to grow in the coming years. With a solid platform of robust and innovative technological developments, and a switch in the focus of drug development toward smart, hypothesis-testing and hypothesis-generating preclinical and clinical studies using validated biomarkers, we are cautiously optimistic that progress will continue to be made in generating effective and safe drugs to improve the lives of our cancer patients. In this way, our understanding of the genomes of healthy and malignant cells will be maximized for patient benefit.

DISCLOSURE STATEMENT

The authors are employees of The Institute of Cancer Research (United Kingdom), which has a commercial interest in the development of several classes of the drugs described here. P.W. is scientific founder of Piramed Pharma (acquired by Roche) and of Chroma Therapeutics. Intellectual property on PI3 kinase inhibitors was licensed to Piramed and Genentech (both acquired by Roche). Intellectual property on HSP90 inhibitors was licensed to Vernalis and Novartis. Intellectual property on PKB was licensed to Astex Pharmaceuticals and AstraZeneca. P.W. is a consultant to Novartis, Wilex, and Nextech Ventures.

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Errata

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