Impact of Genomics on Personalized Cancer Medicine
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Abstract
Recent advances in tumor genetics and drug development have led to the generation of a wealth of anticancer targeted therapies. A few recent examples indicate that these drugs are mainly, if not exclusively, active against tumors of a particular genotype that can be identified by a diagnostic test, usually by detecting a somatic alteration in the tumor DNA. However, for the majority of targeted therapies in development, there are still no clinical tools to determine which patients are most likely to benefit or, alternatively, be resistant de novo to these novel agents or drug combinations. Clin Cancer Res; 18(3): 612–8. ©2012 AACR.

Introduction
Over the past 2 years, a series of clinical trials have continued to underscore the importance of appropriate patient selection for accelerating drug development. For example, vemurafenib, a small molecule that blocks a mutant form (V600E) of the serine–threonine kinase B-RAF, which is present in up to 50% of melanomas, has shown remarkable clinical efficacy against melanomas harboring this mutation (1). Crizotinib, an inhibitor of anaplastic lymphoma kinase (ALK), was also shown to be markedly effective in a subgroup of patients with non–small cell lung cancer (NSCLC) who had been selected for the presence of an oncogenic EML4-ALK translocation in their tumor (2). In this landmark trial (ClinicalTrials.gov Identifier: NCT00585195), 1,500 patients with advanced NSCLC were prescreened to identify 82 patients (5.4%) with the translocation. These patients exhibited an almost unprecedented clinical benefit rate of 90% upon treatment with crizotinib. Of note, only 4 years separated the discovery of the EML4-ALK translocation (3) from the approval (in August 2011) by the U.S. Food and Drug Administration (FDA) of crizotinib for the treatment of NSCLC harboring this molecular alteration. A Janus-activated kinase 2 (JAK2) small-molecule inhibitor was shown to be clinically active against a form of myelodysplastic syndrome or preleukemia that harbors an activating mutation in the JAK2 gene (4). In a trial of olaparib (ClinicalTrials.gov Identifier: NCT00516373), an inhibitor of PARP, an enzyme that is required for the repair of DNA single-strand breaks through excision repair, was shown to be very active against cancers arising in carriers of a BRCA1 or BRCA2 mutation (5). Two points of interest about this trial are that (i) the remarkable clinical activity of olaparib was seen during the phase I dose escalation study, and (ii) the trial was the result of an open-ended RNA interference (RNAi) screen in the laboratory. This screen identified a synthetic lethal interaction between BRCA and PARP in breast and ovarian cancer cells with BRCA mutations, and thus a deficiency in DNA excision repair (6). These examples support the concept that a dominant gain-of-function oncogene or loss of a tumor suppressor leads to a wiring of signaling pathways on which tumor cells depend, or, alternatively, point to a phenotypic lesion that is not shared by normal cells (i.e., DNA repair deficiency) and can be exploited therapeutically with specific drugs.

Significant progress continues to be made in the molecular profiling of human tumors, such as DNA copy number, patterns of gene expression, and sequencing of specific cancer-associated genes that are not detectable by DNA microarray analysis [reviewed in Macconaill and Garraway (7)]. However, this depth of molecular characterization of individual human cancers has yet to be fully exploited in the conduct of clinical trials and drug development. This disconnect exists in part because of the not-infrequent difficulty of obtaining appropriate tumor tissues by invasive biopsies. Thus, it is important to also be able to assess tumors by using noninvasive approaches that will enable molecular analyses without subjecting the patients to multiple invasive interventions. Fortunately, complementary approaches based on profiling of circulating tumor cells, circulating proteins or tumor DNA, and molecular imaging are ready for clinical exploitation. It is anticipated that these approaches will strengthen an overall strategy aimed at identifying patients with molecularly defined cancers that can be in turn treated with drugs specifically targeted to those molecular lesions. A positive outcome of this strategy would be the
approval of a diagnostic test paired with an anticancer
drug. This perhaps is best illustrated by the standardized
immunohistochemical assay for the HER2 (ERBB2) pro-
tein (HercepTest; DAKO) and approval of the HER2 anti-
body trastuzumab for patients with HER2-overexpressing
breast cancer.

Application

Preclinical approaches

Whole-scale sequencing of cancer genomes, first by the
Sanger Center and later by U.S. and international con-
sortia, provided a comprehensive analysis of somatic
mutations in cancer that can be targeted therapeutically.
Important advances in genome-scale sequencing includ-
ed the discovery of highly recurrent and specific muta-
tions in B-RAF and PIK3CA, the gene encoding the cata-
lytic subunit p110α of phosphatidylinositol-3 kinase
[PI3K (8, 9)]. However, most mutations identified by
these analyses appear to be rare and are not necessarily
shared across multiple tumors (10). In addition to their
low frequency, it appears that not all of these alterations
are pathogenic or causally associated with tumor progres-
sion and, as such, appropriate drug targets. Evidence
that a molecular lesion is indeed a driver mutation, and
therefore a therapeutic target, will ultimately have to be
based on the clinical response of a cancer harboring
this alteration to a targeted inhibitor. For example, the
marked clinical response to EGFR tyrosine kinase inhibi-
tors (TKI) in patients with NSCLC bearing an activat-
ing EGFR mutation shows that these lesions are not
simply passengers of mutational load but drivers of
cancer progression (11–13). On the other hand, whereas
V600E B-RAF mutant melanomas respond dramatically
to vemurafenib, a recent clinical trial that examined this
small molecule in patients with colon cancer harboring
the same mutation showed few mixed responses (14).
This last example suggests the need to couple mutational
analyses to the wiring of signaling pathways in different
tumor types in order to identify the most promising drug
targets. To ask this question in tumors with this
mutation, clinical trials that will include multiple cancer
types from different anatomical sites, all harboring V600E
B-RAF, will be initiated.

The use of large panels of cancer-derived human cell
clines is emerging as an effective approach for validating
both the molecular target and the inhibitor. With few
exceptions, individual cancer cell lines have limited pre-
dictive value. However, when they are investigated in
large aggregates, they are better at capturing the molecular
heterogeneity of the tumor type of origin and their
sensitivity to inhibitors of EGFR, ALK, MET, fibroblast
growth factor receptor (FGFR), and B-RAF (15), to cite a
few examples. Recent preclinical studies identified cancer
cell lines with PIK3CA mutations and HER2 gene ampli-
fication as being particularly sensitive to PI3K inhibitors
(16, 17), suggesting tumor genotypes that can be enriched
in early trials with these drugs.

Other preclinical efforts to identify and validate targets
have relied on suppression of gene expression using RNAi
screens focused on the entire kinome against a selected
cell type. Applications of this approach include searching
for new targets that upon RNAi-mediated knockdown
reverse their acquired resistance to targeted inhibitors.
One example is the identification of loss of the PTEN
tumor suppressor as a mechanism of resistance to tras-
tuzumab in HER2-dependent breast cancer cells (18). A
second application is the screening for synthetic lethality,
in which a drug target becomes essential within a specific
genetic context. A relevant example is the discovery of
PARP as a critical viability factor in DNA repair-deficient
tumor cells with BRCA gene mutations (6). A third
application, which is not yet widely exploited, is the
testing of novel inhibitors together with an RNAi screen
aimed at identifying combinations required to block
interdependent or compensatory pathways implicated in
de novo or secondary drug resistance.

Oncogene-dependent human cancer cell lines have
also been helpful in the search for mechanisms of
acquired drug resistance. In some cases, this resistance
involves the acquisition of secondary mutations within
the drug-binding site, such as the gatekeeper T790M
mutation in NSCLC with a primary drug-sensitive EGFR
mutation (19, 20). Other cases involve activation of an
alternative, drug target–independent signaling pathway,
such as K-RAS mutation or MET gene amplification in
EGFR-mutant NSCLC lines with acquired resistance to
EGFR TKIs (21–23). Genetically engineered mouse mod-
els have also provided information about novel combi-
nations that abrogate drug resistance. For example, trans-
genomic mice bearing mutant K-RAS lung cancers respond to
a combination of a mitogen-activated protein–extracellu-
lar signal-regulated kinase (MEK) inhibitor and a PI3K
inhibitor, but not to each inhibitor alone (24). Further,
transgenic lung tumors that acquire a T790M mutation in
the EGFR gene overexpress EGFR-activating ligands and
respond to retreatment with the irreversible EGFR TKI
afatinib and the EGFR antibody cetuximab (25). This
combination is already showing remarkable activity in
patients with NSCLC harboring a T790M drug-resistant
mutation (26).

Clinical approaches

Biomarkers. The impact of tumor genomics on per-
sonalized cancer medicine will depend to a large degree on
the development and application of surrogate biomarkers
that can predict response to therapy, as well as novel
clinical trial designs. As it applies to cancer biomarkers,
it is helpful to make a distinction among predictive,
prognostic, and pharmacodynamic biomarkers, and the
role they play in the process of approval of targeted
therapies. Prognostic biomarkers generally require tumor
tissue obtained at diagnosis. They can be used to predict
the natural course of an individual cancer, distinguish
between good and poor patient outcomes, and help define
who should be treated and how aggressive the treatment
should be. Recent examples include the breast cancer gene expression signatures marketed as Oncotype DX (Genomic Health) and MammaPrint [Agendia (27, 28)]. These signatures can be used to estimate the probability that the primary breast cancer will recur after it has been surgically removed. As such, they can help physicians decide who should receive adjuvant systemic chemotherapy to eliminate clinically silent micrometastases and reduce the risk of cancer relapse.

Predictive biomarkers (of response) differ in that they are used to assess the probability that a patient will benefit from a particular treatment. For example, breast cancers with amplification of the HER2 (ERBB2) oncogene or overexpression of the HER2 protein benefit from oncogene-targeted therapy with the HER2 antibody trastuzumab and the HER2 TKI lapatinib (29, 30). Patients with breast cancers expressing detectable levels of estrogen receptors (ER) are considered hormone dependent, and benefit from antiestrogen therapy with tamoxifen, aromatase inhibitors, or ovarian ablation. Of note, the absence of these biomarkers is very highly predictive of lack of response to these drugs. Therefore, patients with HER2-negative or ER-negative tumors are not (and should not be) offered anti-HER2 or antiestrogen therapy, respectively. Similarly, patients with leukemia carrying the PML-RAR translocation respond to all-trans retinoic acid, and those with the BCR-ABL fusion gene resulting from a Philadelphia chromosome 19:22 translocation respond to imatinib, dasatinib, and nilotinib (31, 32). Other examples of generally accepted biomarkers that predict tumor response to a targeted therapy, and others that await confirmation or prospective investigation in the clinic, are listed in Table 1. Conversely, certain biomarkers predict a lack of response. For example, K-RAS mutations in NSCLC are markers of patients who do not benefit from EGFR TKIs (23). Similarly, patients with K-RAS mutant colon cancers do not respond to therapy with EGFR monoclonal antibodies (33, 34). Finally, patients with glioblastoma multiforme harboring a truncated active EGFR mutant respond to EGFR TKIs. However, patients with EGFR mutant glioblastoma multiforme in which the tumor also lacks the tumor suppressor phosphatase PTEN do not respond to these inhibitors (35).

Pharmacodynamic biomarkers measure the early effects of a drug on the tumor or the host, and as such can be used to guide the selection of an optimal biologic dose during phase I development of a molecularly targeted drug. Drug target inhibition as assessed by a relevant pharmacodynamic biomarker is critical for drug development. Indeed, an increasing number of drugs do not proceed in their clinical development if drug development. Indeed, an increasing number of drugs do not proceed in their clinical development if they do not show target modulation in vivo. Pharmacodynamic biomarkers with a wide dynamic range are particularly helpful because they allow investigators to study the impact of a drug on its molecular target across a range of doses. In turn, this approach of target engagement allows the selection of a dose for phase II efficacy studies on the basis of the magnitude of target modulation and not necessarily maximally tolerated toxicity. Cancer biomarkers can also play combined prognostic, predictive, and pharmacodynamic roles. For example, predictive biomarkers can also be prognostic. In the absence of therapy, patients with NSCLC harboring EGFR-activating mutations exhibit a better long-term outcome than do patients with NSCLC with wild-type EGFR (36). The same can be said of ER-positive

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Molecular target</th>
<th>Cancer type</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen receptor (IHC)</td>
<td>ER</td>
<td>Breast cancer</td>
<td>tamoxifen, aromatase inhibitors</td>
</tr>
<tr>
<td>HER2 gene amplification (IHC, FISH)</td>
<td>HER2 receptor</td>
<td>Breast and upper GI cancers</td>
<td>trastuzumab, lapatinib, neratinib, pertuzumab, trastuzumab-DM1</td>
</tr>
<tr>
<td>BCR-ABL translocation</td>
<td>ABL kinase</td>
<td>CML</td>
<td>imatinib, dasatinib, nilotinib</td>
</tr>
<tr>
<td>EGFR kinase domain</td>
<td>EGFR kinase</td>
<td>NSCLC</td>
<td>erlotinib, gefitinib</td>
</tr>
<tr>
<td>PML-RAR translocation (not T790M)</td>
<td>PML-RAR</td>
<td>APL</td>
<td>all-trans retinoic acid</td>
</tr>
<tr>
<td>B-Raf V600E mutation</td>
<td>B-Raf kinase</td>
<td>Melanoma</td>
<td>vemurafenib</td>
</tr>
<tr>
<td>Mutant KIT</td>
<td>KIT kinase</td>
<td>GIST</td>
<td>imatinib</td>
</tr>
<tr>
<td>Mutant PDGFRα</td>
<td>PDGFR kinase</td>
<td>CMML</td>
<td>imatinib</td>
</tr>
<tr>
<td>EML4/ALK translocation</td>
<td>ALK kinase</td>
<td>NSCLC</td>
<td>crizotinib</td>
</tr>
<tr>
<td>EGFR-T790M</td>
<td>EGFR (drug resistant)</td>
<td>NSCLC</td>
<td>afatinib - cetuximab</td>
</tr>
<tr>
<td>TSC1 mutations</td>
<td>TORC1/2</td>
<td>Pancreas NET</td>
<td>everolimus</td>
</tr>
<tr>
<td>PIK3CA hot spot mutations</td>
<td>p110α</td>
<td>Breast, endometrial, colon cancer</td>
<td>PI3K inhibitors</td>
</tr>
</tbody>
</table>

Abbreviations: APL, acute promyelocytic leukemia; CML, chronic myelogenous leukemia; CMML, chronic myelomonocytic leukemia; GI, gastrointestinal; GIST, gastrointestinal stromal tumor; PDGFR, platelet-derived growth factor receptor.
compared with ER-negative breast cancers. Recent retrospective series suggest that patients with breast cancers with PIK3CA mutations, a likely biomarker of PI3K dependence and thus sensitivity to PI3K inhibitors (37, 38), also have a better outcome compared with patients harboring cancers with wild-type PIK3CA. This potential better prognosis should not influence the indication of treatment of these types of cancers, particularly considering the availability of well-tolerated therapies that are specifically targeted in such cases to the ER and mutant oncoproteins (EGFR and PIK3CA). On the other hand, some pharmacodynamic biomarkers have provided therapeutically predictive, longer-term information. One example is the proportion of proliferating cancer cells as measured by Ki-67 immunohistochemistry (IHC) in the treated tumor. In the IMPACT trial, patients with ER-positive breast cancer were given neoadjuvant therapy with aromatase inhibitors or tamoxifen for 3 months prior to surgical resection. The Ki-67 index in a research biopsy at 2 weeks and in the surgical specimen, but not in the diagnostic, pretreatment biopsy, correlated statistically with overall survival following surgery and adjuvant endocrine therapy (39).

**Clinical trial strategies.** There is a growing awareness that traditional clinical trial designs are not well suited for addressing the current need to develop a large portfolio of anticancer targeted therapies. Traditionally, in a phase I study, investigators test an agent for safety and tolerability, and usually determine the appropriate dose based on maximal patient tolerability but not inhibition of the molecular target. This dose is then tested in phase II efficacy studies, usually limited to a tumor type (e.g., breast or colon) and not tumors of a particular molecular genotype (e.g., PTEN loss or K-RAS mutation). If clinical activity is observed in phase II, a large randomized phase III trial is conducted in which the new drug (or combination) is compared with a standard that does not always have high efficacy and is generally more toxic. If success is achieved, this process may lead to FDA registration of the new drug or combination.

This approach to drug development has been associated with a high and expensive failure rate. Even in studies with a statistically positive outcome, the magnitude of clinical benefit is sometimes only modestly incremental in nonselected patient populations. Conventional multi-institutional clinical trials have relied on enrolling large numbers of unselected patients with advanced disease, followed by retrospective analysis of tumors in archival material in only a fraction of cases. This approach is ill suited for conducting pretreatment tumor genotyping of even modest depth, and is underpowered for discovering rare tumor subsets within the overall trial population in which the new drug (or combination) is highly effective. For these reasons, a new model of phase I investigation is emerging in which patients with tumors of a molecular genotype of interest (e.g., PIK3CA mutation, EML4-ALK translocation, and luminal B or basal-like breast cancers) are enrolled. Such trials include an extended, biopsy-intense phase during which predictive and pharmacodynamic biomarkers (e.g., the degree of drug target inhibition, functional imaging, and circulating tumor cells) are vigorously investigated. In addition to trials of crizotinib, olaparib, and vemurafenib, results obtained with new targeted therapies suggest that this new approach will dramatically increase the historically low clinical response rate in phase I trials (40).

Phase II-III trials are no longer exclusively focused on patients with advanced disease. For example, early randomized testing of post-phase I, well-tolerated combinations is being integrated into the initial care of patients, with the goal of matching the drug or combination under study with specific tumor subsets. A recent example is the randomized study of letrozole ± the TOR inhibitor everolimus in newly diagnosed patients with ER-positive breast cancer (41). The NeoSphere trial tested the combination of trastuzumab and pertuzumab ± chemotherapy in the neoadjuvant setting in patients with newly diagnosed HER2-positive breast cancer (42). Likewise, the concept of dual HER2 blockade with trastuzumab and the TKI lapatinib was also successfully explored in a neoadjuvant randomized phase III study (43). These study designs are suited for obtaining on-study tumor biopsies. Further, the availability of post-treatment tumor tissue from surgically resected cancers enables investigators to discover biomarkers and mechanisms of drug resistance using state-of-the-art molecular methods.

Although dramatic clinical responses to targeted therapies have been achieved [e.g., in advanced chronic myelogenous leukemia, NSCLC, and melanoma], acquired drug resistance generally occurs. The rebiopsy of tumor recurrences led to the identification of mechanisms of resistance involving second-site mutations in the drug target that are targetable with mutant-selective kinase inhibitors (31, 44) or the acquisition of amplified compensatory signaling networks (21, 45, 46). Such findings are reducing the overall threshold in the medical community for rebiopsing and studying tumor recurrences in some depth. These examples also suggest that any unanticipated dramatic tumor response to a new targeted drug should signal the need for an in-depth analysis of the tumor or its recurrence. This approach may identify subsets of patients who would not be predicted to be sensitive to the new drug, and lead to new diagnostic tests and indications. In other cases, the rebiopsy of tumors after treatment has unmasked mechanisms of compensation that explain the limited activity of a targeted drug as a single agent. For example, patients who were treated with TOR inhibitors showed upregulation of insulin-like growth factor I-receptor (IGF-IR) activation in situ when TOR was blocked (47). This led to a phase I study in which both TOR and the IGF-IR were inhibited simultaneously. This combination showed interesting clinical activity in patients with metastatic breast cancer (48).
Challenges and Recommendations

Targeted drugs stand to benefit from the integration of their development with experimental systems in the appropriate genetic and biologic context. Preclinical screens should test drug efficacy in panels of human tumor cell lines where the drug target is causally associated with cancer viability. These preclinical platforms (i.e., cell lines and animal models) can be used to generate gene expression signatures that predict drug efficacy. In turn, these signatures can be validated in the clinic, potentially reducing the number of patients required in a clinical trial for it to be informative (49). We should note, however, that this approach involves serious challenges (50).

Many hurdles must be overcome to maximize the impact of genomics on personalized cancer medicine. The fact that targeted drugs will be effective against small subtypes of cancers implies higher costs of drug development up front but also the promise of a shorter time to registration, as illustrated by the fast approval of crizotinib and vemurafenib. However, as these small subgroups of patients throughout the world take these drugs during their now-extended, productive life, this situation can generate important financial returns to the drug makers, who in turn can reinvest in further therapeutic research.

Another hurdle is the overall reluctance of the clinical trials community to design studies that require access to additional tumor tissues for appropriate correlative studies. This is particularly true for phase II studies in patients with metastatic disease, where documentation of drug target inhibition is generally not assessed even when metastatic disease is readily accessible. In general, these phase II trials with targeted therapies are still called “positive” or “negative” even though there is no evidence of drug target engagement. Reasons for this complacency include concerns about slower patient enrollment, added costs, and an inadequate research infrastructure for molecular analyses. We anticipate, however, that with increasing examples of the actionable knowledge generated by molecular information from tumor rebiopsies in patients receiving novel therapies (in addition to the examples highlighted above), these concerns will lessen and a collective effort to address them will be implemented.

In summary, the recent approvals of targeted therapies and other discoveries highlighted above clearly suggest some action items we can pursue to facilitate the impact of genomics on personalized cancer medicine. These are summarized in Box 1. As noted above, these approaches should collectively shorten the time required to progress from molecular target discovery to drug development to drug registration and approval.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References


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