Forty Years of Translational Cancer Research

William N. Hait

Summary: Forty years after the signing of the National Cancer Act, we have produced a stunning repository of scientific information that is being translated into better therapies for patients. Although challenges remain, many solutions have been adopted, leading to early signs of progress against some of humankind’s most dreadful diseases. This Prospective attempts to highlight some of the approaches that have been successful and analyze some that have not, and peers into a future in which renewal of the investment in cancer research will produce further benefits for patients. Cancer Discovery. 1(5), 383–90. ©2011 AACR.

INTRODUCTION

The signing of the National Cancer Act 40 years ago unleashed the creativity of a generation of scientists. Consequently, today we are witnessing an exciting surge in translational research. Yet, despite substantial progress, challenges remain. Even the definition of translational research has been controversial. The American Association of Cancer Research has stressed both the bench-to-bedside and bedside-to-bench nature of the enterprise with a stated goal of “…understanding the heterogeneity of human disease.” National Institutes of Health Director Francis Collins used the phrase “…turning discovery into health” in his announcement of the formation of the National Center for Advancing Translational Science. Duke Ellington could have perhaps summed up translational research best: “If it sounds good, it is good.”

So after 40 years, how does one assess progress in translational cancer research? One measure is rates of mortality, which despite downward trends in the United States, continue to increase in other parts of the world; it is now estimated that by 2030 there will be approximately 30 million new patients diagnosed with cancer annually. However, cancer is a hypernym for approximately 200 types of malignancies cataloged by site of origin and/or histology linked by shared “hallmarks” (described and recently updated by Hanahan and Weinberg) (1). Therefore, when we evaluate progress, it is important to consider advances in specific tumor types, some of which have been breathtaking (e.g., childhood acute lymphoblastic leukemia, Hodgkin’s disease, testicular cancer) and others disappointing (e.g., pancreatic cancer, non–small cell lung cancer [NSCLC] in smokers).

Harold Varmus, Director of the National Cancer Institute (NCI), put this into perspective, stating, “It is gratifying to see the continued steady decline in overall cancer incidence and death rates in the United States—the result of improved methods for preventing, detecting, and treating several types of cancer. But the full repertoire of numbers reported today also reflects the enormous complexity of cancer, with different trends for different kinds of cancers, important differences among our diverse people, and different capabilities to prevent, detect, and treat various cancers. Moreover, as our population continues to age, we have an obligation to discover and deliver better ways to control all types of cancers” (2).

Translational research is not new. Sir Edward Jenner’s work offers an early example. Jenner observed that dairymaids who contacted cowpox appeared to be protected from smallpox. He hypothesized, then demonstrated, that vaccination with sera from recovered dairymaids would protect against smallpox. These results, published in 1798, ultimately led to widespread vaccination. Imagine the challenges that Dr. Jenner would face today. The Jenner example points out that successful translational research begins with an observation, be it clinical, epidemiological, or laboratory-based (Fig. 1). This observation, once linked to a medical problem and a stated hypothesis, can produce a discovery that can ultimately impact patients. As in the laboratory, the first experiment in the clinic should be designed to gain insights into the problem through further observation and further testing. Thus, translational research, like most research, is an iterative process.

ADDRESSING THE PROBLEM OF DRUG DEVELOPMENT

We are unable to consistently deliver highly effective therapies to patients despite a deepening understanding of cancer biology. The drug-development process is slow, inefficient, and expensive. It can take more than 10 years of preclinical investigation before a target has a drug ready to enter the clinic, and it then takes an average of 8 years for drugs to reach patients who are literally dying to receive them. Once in the clinic, the probability of an oncology drug achieving approval is ~12%. Finally, at an estimated cost of at least one billion dollars per drug, this model is unsustainable. (The calculation is determined by approved drugs per overall research and development investment and therefore is high in part because of numerous failures.)
During the last 15 years, the number of filings of New Molecular Entities to the Food and Drug Administration (FDA) has decreased, and the success rate for drug approvals has failed to improve despite a massive increase in our understanding of malignant disease (3). Explanations for this apparent decrease in productivity have included that “all the low-hanging fruit” have been picked (i.e., monogenic diseases have been adequately addressed), the “regulations have gotten much tougher,” or the competition is more intense. True, as more effective drugs reach the market, the hurdle for developing even better “follow-ons” becomes higher.

Although these problems are likely contributing factors, they are not uniquely recent ones and therefore cannot explain the apparent stall in cancer drug discovery. Another possibility is that our inability to improve upon previous successes has been an unanticipated consequence of technological advances that facilitated deconstruction of the drug-development process: the sequencing of the human genome, the ability to clone genes and express and crystallize their protein products, and improved structural approaches to rational drug design. These major technological advances led to remarkably potent and selective inhibitors, yet it is not clear that this increase in potency has led to a proportional increase in drug activity.

Unfortunately, the understanding of how a target is wired into a specific tumor type is usually not obvious, rendering even optimal target engagement insufficient to produce striking clinical benefits. Modern approaches to target validation can be self-fulfilling, such as when transgenic models are created in which the target is essential for viability and knockdown or drug targeting gives the desired result. This ability to override complexity with forced overexpression could lead to misleading results.

An alternative to target-based discovery is phenotypic screening, which is not based on targets but instead relies on a readout that may be a better predictor of efficacy in the clinic. For example, injection of a drug into a dog that results in a decrease in blood pressure might be a good predictor of an active antihypertensive agent, despite our not knowing the drug’s mechanism of action. Following the isolation of paclitaxel from the pacific yew by Wani and Wall (4) and the demonstration of activity in the clinic, it took several years before the mechanism of action of paclitaxel was identified by Horwitz and colleagues (5). Phenotypic screens, however, are not trivial; they require libraries optimized for cell penetration, assays that are reliable downstream readouts, and a robust capability to ultimately deconvolute the precise target to optimize lead compounds.

For both the target-based and the phenotypic approaches, the rate-limiting step in cancer drug discovery remains predictive preclinical models. The relative advantages and disadvantages of the targeted versus phenotypic approaches to drug development have been recently debated (6, 7). Combining the two approaches should yield better outcomes for patients.

My analysis of the problem suggests another approach. Many of our most effective targeted therapies were identified by understanding the biology of a specific malignancy to identify the critical pathways in need of disruption (Table 1). In other cases, the effectiveness of a new drug was later explained by the biology of the disease, such as bortezomib’s disruption of proteasomal protein degradation in myeloma and gefitinib and erlotinib’s increased activity in certain lung cancers harboring an activating mutation in the catalytic domain of the epidermal growth factor receptor (EGFR). The reason that some drugs are active in one disease but not in others (e.g., bevacizumab, cetuximab, sunitinib, sorafenib, everolimus) remains unclear. Yet, few pharmaceutical companies are organized around tumor types, and most lack the disease-specific expertise most often found in academic institutions. Herein lies an exceptional opportunity for collaboration; companies would gain a more robust understanding of disease complexity, and academicians would become more deeply involved in drug development.

**BARRIERS TO TRANSLATIONAL CANCER RESEARCH**

**Target Selection and Validation**

Successful target-based drug discovery requires valid targets. Target selection evolves from an understanding of cancer biology and/or through genome sequencing. The former is nicely demonstrated by the work on BCR-ABL in chronic myeloid leukemia and the latter by the uncovering of a common BRAF mutation in melanoma (V600E). Knockin, transgenic, and knockout mouse technologies are powerful approaches to understanding many aspects of disease pathophysiology. However, they are imperfect models of most acquired human malignancies because most cancers are not the consequence of germline mutations but rather result from somatic alterations acquired over the course of many years. Consequently, the knockout of a gene or knockdown of a gene product in these models may or may not represent a validation of a target. Target overexpression is also an overrated predictor of efficacy, for example, overexpression of EGFR is an unreliable predictor of response to EGFR inhibitors. Many gene products are overexpressed, and although some may be supporting cell growth and viability, others may represent a cellular attempt to limit unbridled growth. Inhibition of the
### Table 1. Drugs developed on the basis of tumor biology

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease</th>
<th>Biology</th>
<th>Target</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen (Nolvadex)</td>
<td>Breast</td>
<td>Estrogen dependence</td>
<td>Estrogen receptor</td>
<td>Selective estrogen receptor modulator</td>
</tr>
<tr>
<td>Fulvestrant (Faslodex)</td>
<td>Breast</td>
<td>Estrogen dependence</td>
<td>Estrogen receptor</td>
<td>Degradation of estrogen receptor</td>
</tr>
<tr>
<td>Anastrozole (Arimidex), letrozole (Femara), exemestane (Aromasin)</td>
<td>Breast</td>
<td>Estrogen dependence</td>
<td>Aromatase</td>
<td>Aromatase inhibitor</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>Breast</td>
<td>HER2/neu expression drives cell growth and viability</td>
<td>HER2/neu extracellular domain</td>
<td>Binds HER2/neu, inhibits extracellular domain, induces antibody-dependent cellular cytotoxicity</td>
</tr>
<tr>
<td>Abiraterone acetate (Zytiga)</td>
<td>Prostate</td>
<td>Androgen dependence</td>
<td>CYP17A1</td>
<td>Inhibits activity of CYP17, decreasing androgens to subcastration concentrations</td>
</tr>
<tr>
<td>Bicalutamide (Casodex), flutamide (Eulexin), nilutamide (Nilandron)</td>
<td>Prostate</td>
<td>Androgen dependence</td>
<td>Androgen receptor</td>
<td>Competitive inhibition of testosterone binding to androgen receptor</td>
</tr>
<tr>
<td>Leuprolide (Lupron)</td>
<td>Prostate</td>
<td>Androgen dependence</td>
<td>Gonadotropin-releasing hormone receptor agonist</td>
<td>Decreases circulating androgens</td>
</tr>
<tr>
<td>Imatinib (Gleevec)</td>
<td>Chronic myelogenous leukemia</td>
<td>Philadelphia chromosome</td>
<td>BCR-ABL tyrosine kinase abnormality produces oncogenic fusion protein BCR-ABL</td>
<td>TKI</td>
</tr>
<tr>
<td>Imatinib (Gleevec)</td>
<td>Gastrointestinal stromal tumors</td>
<td>cKIT drives proliferation and viability</td>
<td>cKIT tyrosine kinase</td>
<td>TKI</td>
</tr>
<tr>
<td>Dasatinib (Spryce), nilotinib (Tasigna)</td>
<td>Chronic myelogenous leukemia</td>
<td>Mutations in BCR-ABL produce resistance to imatinib</td>
<td>BCR-ABL tyrosine kinase</td>
<td>TKI</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>Lymphoma</td>
<td>CD20 is a commonly expressed surface antigen</td>
<td>CD20</td>
<td>Binds CD20 and activates antibody-dependent cellular cytotoxicity</td>
</tr>
<tr>
<td>Ipilimumab (Yervoy)</td>
<td>Melanoma</td>
<td>Immunogenicity of melanoma</td>
<td>CTLA4</td>
<td>Binds CTLA4, releasing inhibitory checkpoint</td>
</tr>
</tbody>
</table>

**Drugs whose activity was revealed by later understanding of tumor biology**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease</th>
<th>Biology</th>
<th>Target</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib (Iressa), erlotinib (Tarceva)</td>
<td>NSCLC</td>
<td>Activating mutations in EGFR increased dependence on target</td>
<td>EGFR</td>
<td>TKI</td>
</tr>
<tr>
<td>Bortezomib (Velcade)</td>
<td>Myeloma</td>
<td>Proteasomal inhibition in face of massive intracellular protein excess</td>
<td>Chymotrypsin-like $\beta$5 subunit of the catalytic chamber of the 20S proteasome</td>
<td>Proteasome inhibitor</td>
</tr>
</tbody>
</table>

former might provide a therapeutic effect, whereas inhibition of the latter could be a disaster.

**Understanding Targets in Context**

Albert Einstein reportedly once said, “Make things as simple as possible, no simpler.” Signal transduction pathways originally appeared to follow this principle and were thought to be linear and lack substantial redundancy. By depicting the interaction of a growth factor with its cognate receptor as a singular event that sets off a biochemical cascade culminating in transcriptional activation of genes involved in DNA replication, microtubule...
reorganization, and cell division, we neatly categorized drugs by their mechanism of action. We now understand that signaling pathways are complex, redundant networks and that targeting a single protein within a complicated grid is unlikely to be highly effective. Imagine that our goal was to block traffic from moving from the West Side to the East Side of Manhattan and our target for inhibition was 42nd Street. Effective inhibition would slow traffic down—perhaps increase “time to progression”—but ultimately the traffic would find alternative, redundant pathways to get to the East Side—so at steady state there might be no demonstrable effect at all (“overall survival”).

How might this redundancy be addressed? Historically, biologic complexity and drug resistance were approached with drug combinations, the basis for successfulantineoplastic and antimicrobial therapies. However, efficient codevelopment of drugs requires meeting regulatory standards designed for single agents or fixed-drug combinations. The traditional approach of adding a new agent to the current standard of care may not be useful, or in fact may be antithetical to the underlying biology. Rational combinations of targeted agents may also require studying two or more unapproved agents. Suggested requirements for this “Two New Molecular Entities” approach include the existence of a strong biological rationale, predictive biomarkers, evidence of therapeutic synergy without synergistic toxicity, and characterization of potential drug–drug interactions (8). An alternative to drug combinations is combination drugs: a single drug that inhibits multiple targets, such as sorafenib, sunitinib, lapatinib, and dasatinib. These multitarget kinase inhibitors simultaneously block components of several signaling pathways and have shown activity across a spectrum of tumor types.

However, understanding the intricate wiring of a cancer cell in isolation is still not sufficient to fully appreciate the complexity of cancer biology. As stated by Dr. Robert Weinberg, “There has also been an explosion of information indicating unambiguously that the tumor microenvironment has strong effects on the behavior of tumors” and that “cancer is actually a disease of tissues” (9). If there were any doubt, I call your attention to the photomicrograph in Figure 2, which shows a biopsy taken from a patient with lymphocyte-predominant Hodgkin’s disease. The only malignant cell in this field is the Reed–Sternberg cell (arrow). Understanding the commensal relationships between the multiple components of malignant tissues will be an important step toward new approaches to treatment and prevention.

**Preclinical Models Do Not Reliably Predict Drug Activity in the Clinic**

Xenografts originating from cells propagated on plastic have been the workhorse of preclinical *in vivo* testing. Yet, activity in these models does not reliably predict activity in patients. The underlying problem is illustrated by the histology of tumor biopsies from patients, which differ dramatically from the histology of xenografts originating from cells propagated on plastic. For example, human carcinomas contain a supporting stroma and a complex microenvironment, whereas xenografts derived from propagated cell lines lack an architecture and stroma resembling the corresponding human tumor. These cell line-derived xenografts may therefore be insensitive to the microenvironmental signals of the host and act far more autonomously than patient-derived primary tumor cells. However, when biopsies are taken directly from patients and engrafted in mice, there is a greater resemblance to the original tumor. Furthermore, 3-dimensional cultures, in which stromal components are added to an artificial matrix, have different sensitivities to drugs than those obtained when the cells are grown on plastic. Whether these approaches or the use of genetically engineered mouse models will more reliably predict clinical activity remains to be determined.

**The Clinical Trials Process Is Slow and Inefficient**

The authors of a recent Institute of Medicine report focused on NCI-sponsored cooperative groups concluded that “…the system for conducting cancer clinical trials in the United States is approaching a state of crisis. If the clinical trials system does not improve…the introduction of new treatments for cancer will be delayed and patient lives will be lost unnecessarily” (10). Today, approximately 20% of patients in the United States are eligible for clinical trials, but only 3% participate. Yet, as Clifton Leaf recently pointed out, when incentives are aligned between patients, physicians, and sponsors (e.g., when there is a very active new drug), the process can move at a rapid pace (11). For example, the imatinib registration study enrolled 1,106 patients with chronic myeloid leukemia in only 18 months. Furthermore, we might approach the design of clinical trials more like we approach a problem in the laboratory, i.e. conducting small preliminary experiments from which we learn what experiment (if any) should be done next.
Biomarkers Are a Mainstay of Modern Drug Development

The targeted approach is amenable to a clinical development paradigm that uses methods such as the “pharmacological audit trail” popularized by Paul Workman (12). Biomarkers include pharmacodynamic markers, which help obtain an early estimate of desired drug activity and predictive markers, which may help select patients for clinical trials and identify those patients most likely to benefit. Surrogate end points help monitor drug response and, if validated, could shorten the time to regulatory approval and contribute to prevention and early intervention strategies.

However, simultaneously developing biomarkers that predict response to treatment and delivering companion diagnostic tests to the clinic is difficult. In addition, the validation of predictive biomarkers, especially those derived from complex datasets, is fraught with pitfalls. For example, a retrospective analysis of a dataset of only 10 biomarkers against a clinical result has a 40% probability of having at least one significant ($P < 0.05$) random association (13). Currently approved predictive biomarkers measure the status of a target or pathway, but no molecular profiles are currently approved by the FDA. This area has been the topic of several white papers, including a recent comprehensive report put together by the American Association for Cancer Research, FDA, and NCI (14) and a recent FDA draft guidance (8).

At present, biomarker discovery and development has been hindered by a requirement for serial tissue sampling. Repeat biopsies place a substantial burden on patients, physicians, and departments of radiology and pathology. A possible alternative is circulating tumor cells (CTC), which offer a noninvasive method to repeatedly capture, enumerate, and study cancer cells. Recently, Daniel Haber, Mehmet Toner, and their colleagues at Harvard and MIT have developed new platforms for more efficient CTC capture, enumeration, and evaluation (see the section “Drug Resistance”).

Drug Resistance

From the earliest days of cancer therapeutics, it was observed that most patients who appeared to enter a complete remission relapsed and that these patients no longer responded well to retreatment. In fact, a principle of medical oncology described in *Holland-Frei Cancer Medicine* states that “...the first treatment is the best treatment...” (15) and that in most cases, the second-line treatment provides half the benefit of the first in terms of response rate and duration, and the third-line treatment half the benefit of the second.

Resistance can be categorized as native or acquired. An example of native drug resistance is a germline polymorphism in the FCγ receptor, which affects the response to rituximab. Cartron and colleagues (16) compared the response to rituximab in patients with the 158V high-affinity allotype to that of the 158F lower-affinity form. Those with the high-affinity FCγ receptor had a greater response rate and longer overall survival. Interest in acquired drug resistance accelerated in the early 1980s when Biedler and Riehm (17) reported that exposure to a single drug produced cross-resistance to several structurally unrelated drugs, a phenomenon known as pleiotropic or multidrug resistance.

Knowing the mechanism of action of a drug may facilitate understanding of acquired drug resistance. For example, the duration of response of patients with NSCLC harboring activating *EGFR* mutations to gefitinib is often brief, and biopsies obtained at the time of relapse frequently reveal secondary *EGFR* mutations at T790M. Replacement of a threonine with a bulky methionine residue at the gatekeeper site increases the affinity of the enzyme for ATP (18). Maheswaran and colleagues (19) found that CTCs harboring T790M resistance mutations existed in low abundance before treatment and increased markedly at the time of relapse. Furthermore, the presence of even a small number of T790M cells at diagnosis portended a markedly shortened prognosis (19). Although second-generation tyrosine kinase inhibitors (TKI) that overcome or prevent resistance should improve the treatment of patients with NSCLC, attempts at restoring drug sensitivity in other settings have generally failed, suggesting that better results might be achieved by anticipating resistance and by using drug combinations, combination drugs, or irreversible inhibitors (drugs that destroy enzyme activity regardless of acquired mutations) to prevent resistance.

Regulators Are a Key Partner in Translational Research

The rapid pace of scientific discovery has placed challenges on the workforce of regulatory agencies. The deluge of biomarkers, companion diagnostic tests, and active drugs create a variety of methodologic and even ethical challenges for all stakeholders. For example, there is uncertainty around the magnitude of an approvable therapeutic index. A safe and highly effective drug will almost always be approved, and a drug with minimal efficacy and serious untoward effects will rarely be accepted. However, many drugs fall in the gray zone, requiring exquisite judgment by regulators and volunteers serving as regulatory advisors.

However, regulatory approval no longer guarantees access to a new drug because payors will increasingly determine whether the cost of the drug is worth the expense. Oncology drugs are expensive. Many have relatively low activity; few patients are cured, with a brief, if any, increase in survival. Furthermore, we often have little way of identifying patients who will benefit and those who will not. As health technology assessors gain more influence, it is possible that future clinical trials will not only compare the experimental agent to the most effective standard of care but also to a cost comparator. How these factors impact access to oncology care when cost-effectiveness is the metric by which new drugs are measured is an area requiring more public debate. One solution to the access problem may be similar to the one Johnson & Johnson reached with the National Institute for Health and Clinical Excellence (NICE) for access to bortezomib, a drug development partnership between Johnson & Johnson and Millennium/Takeda, in which “the National Health Service will fully fund continued treatment of patients who show a full or partial response, but treatment of patients who do not will be discontinued and the costs refunded by the manufacturer.”

Other regulatory areas needing clarification, change, or improvement include (1) the variety of acceptable end points (progression-free survival, radiographic progression-free...
survival, overall survival, time-to-progression); (2) the lack of
global harmonization; (3) the regulatory path for combina-
tions based on rational design or synthetic lethality; (4) the
lack of surrogate end points; and (5) the practice of first ap-
proving drugs in relapsed, refractory patients in whom there
is often the least benefit and the greatest toxicity. In addition,
highly active new agents threaten equipoise with standard-of-
care regimens (often required as control arms of registration
studies) and poststudy access to new agents may obscure an
effect of an active new agent on overall survival.

A Vanishing Workforce

Clinical research requires clinicians who are trained to con-
duct increasingly complex translational studies. It is time,
in my opinion, to reassess how these individuals are trained
and rewarded in a system increasingly concerned with driving
down costs.

ASSESSING OUR PROGRESS

Despite these challenges, the progress in translational
research has been substantial. The benefits from imatinib,
trastuzumab, and rituximab are emblematic of early suc-
cesses. Several newer examples are reviewed below.

Non–Small Cell Lung Cancer

The observation that NSCLCs overexpressed EGFR led to
the development of monoclonal antibodies against the extrac-
cellular domain of the protein and inhibitors of its in-
tracellular receptor tyrosine kinase domain. Initial results
with gefitinib and erlotinib were disappointing. However,
investigators in Boston identified a subset of patients who
responded dramatically. These patients were more likely to
be non- or light smokers, women of Asian descent, and have
adenocarcinoma with bronchoalveolar features. Lynch and
colleagues (20) and Paez and colleagues (21) both reported
alterations in the catalytic domain of EGFR in these patients’
tumors that produced constitutive enzyme activation and
were predictive of response to gefitinib in the
EGFR

assessments. Gefitinib pro-
duced a 50% improvement in progression-free survival over
derived a spectacular cascade of events in NSCLC research.

Melanoma

Melanoma is one of the most vicious of human malignan-
cies, with a median survival for patients with metastatic dis-
 ease of less than 1 year. The observation that melanoma can
be immunogenic, as manifested by spontaneous regression
and vitiligo, focused attention on immunotherapies. Steve
Rosenberg and colleagues demonstrated that activation of
cytotoxic T lymphocytes could produce dramatic responses.
Jim Allison hypothesized that inhibiting the function of cyto-
toxic T-lymphocyte-associated antigen-4 (CTLA4) with ipil-
imumab, a monoclonal antibody that enhances T-cell activation,
would be an effective treatment. Hodi and colleagues (25)
randomized 676 patients who were progressing on therapy to
ipilimumab plus the gp100 protein vaccine, ipilimumab plus
placebo, or gp100 plus placebo. Unlike other drugs studied
against melanoma, ipilimumab significantly improved overall
survival, leading to a recent FDA approval. There were, how-
ever, serious side effects, including drug-related deaths (7/540
patients) associated with autoimmune reactivity in the skin,
gastrointestinal tract, and endocrine system. In previously un-
treated melanoma patients, ipilimumab plus dacarbazine also
improved overall survival compared with dacarbazine alone
with no reported treatment-related deaths (26).

Meanwhile, the sequencing of the melanoma genome
uncovered a mutation (V600E) in the BRAF gene in ~60%

of patients (27). This change replaces a valine for a nega-
tively charged glutamic acid, leading to constitutive activa-
tion of the enzyme. Flaherty and colleagues (28) enrolled
55 patients in a dose-escalation phase I trial of PLX4032,
a selective inhibitor of this mutant form of the kinase, and
32 additional patients in an extension cohort. Strikingly,
among the 32 patients with the V600E mutation in the
extension cohort, 24 had partial responses, and 2 had com-
plete responses for an 81% overall response rate. A notable
adverse event was the appearance of low-grade cutaneous
squamous carcinomas.

Prostate Cancer

Prostate cancer is the most commonly diagnosed malign-
ancy in American men and the third most common cause of
death. Translational research in prostate cancer was long
hampered by the conventional wisdom that cancers that re-
ocurred after medical or surgical castration were no lon-
ger sensitive to hormonal manipulation because the tumors
were “androgen independent.” However, several groups reported that androgen receptor (AR) signaling remained robust in these patients and that tumor tissue synthesizes androgens in the microenvironment (29). This finding led to a rekindling of interest in whether more effective targeting of androgen-mediated signaling might provide further therapeutic benefit and spare older men the toxicities of chemotherapy.

To test this possibility, Scher and colleagues (30) at UCLA and Medivation, Inc., designed a high-affinity AR antagonist, MDV3100. Scher led a clinical trial that recruited 140 patients with progressive, metastatic, castration-resistant prostate cancer to a phase I/II study. The majority of patients, either before or after chemotherapy, had decreases in prostate-specific antigen, demonstrating that AR signaling was intact and that it could be effectively inhibited by the drug. Objective responses were seen in 22% of patients and stable disease in 49% (30).

In the early 1990s, Jarman, Goddard, Barrie, and colleagues (31) at the Imperial Cancer Research Fund synthesized abiraterone acetate, a potent and selective inhibitor of CYP17, an enzyme that mediates the synthesis of both androgens and estrogens. Work on this compound was recently rejuvenated by Johann de Bono and colleagues at the Royal Marsden Hospital following the observations that intratumoral androgen concentrations were greater than serum concentrations and that CYP17 was active within the tumor and its microenvironment. This led to the hypothesis that a potent and selective CYP17 inhibitor would ablate sources of extragonadal androgens and lead to additional clinical benefit. In early clinical studies, abiraterone reduced circulating androgens to subcastration concentrations and increased upstream steroids consistent with robust target engagement (32). A phase III trial reported by de Bono, Scher, Molina, and colleagues (33) randomly assigned 1,195 heavily pretreated patients with both hormonal and docetaxel chemotherapy 2:1 to either abiraterone plus prednisone or placebo plus prednisone. In this study, abiraterone increased median overall survival by ~4 months with a hazard ratio of 0.65. Furthermore, all secondary end points favored abiraterone, including objective response, prostate-specific antigen response, and measurements of disease progression (33). Overall, adverse events were no greater than prednisone plus placebo, with the exception of greater mineralocorticoid side effects such as fluid retention, hypokalemia, and hypertension, and reversible elevations of liver function tests.

CONCLUSIONS

Forty years after the signing of the National Cancer Act, we have emerged from a lag period between the introduction of second-generation cytotoxic and hormonal agents to enter an era empowered by a more thorough, but still incomplete, understanding of cancer biology. A focus on drugs that targeted enzymes in signaling pathways upstream of DNA synthesis and microtubule assembly, which led to early successes beginning with imatinib, rituximab, and trastuzumab, is now being followed by an avalanche of new drugs. The investment in basic cancer research has produced information that is now being effectively translated into new and better treatments for patients with cancer.

The opportunities for translation and further investment have never been this great. Today there are more than 700 new drugs in the clinic, 300 to 500 drugs in preclinical development, more than 10,000 clinical trials with novel and approved agents alone or in combination, with 1,200 drugs entering phase III studies. We are truly reaching the Golden Age of translational cancer medicine, a time that cries out for greater, not lesser investment in this life-saving enterprise.

Disclosure of Potential Conflicts of Interest

W. N. Hait is an employee of Johnson & Johnson (abiraterone acetate [Zytiga] and bortezomib [Velcade] commercial interests).

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Correction: Forty Years of Translational Cancer Research

In this article (Cancer Discovery 2011;1:383–90), which was published in the October 2011 issue of Cancer Discovery (1), Institute of Cancer Research (ICR) was incorrectly referred to as Imperial Cancer Research Fund. The online version of the article has been corrected and therefore no longer matches the print version. The author regrets the error.

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Correction: Drugs, Diagnostic Tests Approved Quickly

In this article (Cancer Discovery 2011;1:371), which was published in the October 2011 issue of Cancer Discovery (1), the agent later named crizotinib was incorrectly referred to as PLX4032 rather than PF-02341066. The online version of the article has been corrected and therefore no longer matches the print version. The author regrets the error.

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