Oncology Drug Discovery: Planning a Turnaround

Carlo Toniatti, Philip Jones, Hilary Graham, Bruno Pagliara, and Giulio Draetta

Summary: We have made remarkable progress in our understanding of the pathophysiology of cancer. This improved understanding has resulted in increasingly effective targeted therapies that are better tolerated than conventional cytotoxic agents and even curative in some patients. Unfortunately, the success rate of drug approval has been limited, and therapeutic improvements have been marginal, with too few exceptions. In this article, we review the current approach to oncology drug discovery and development, identify areas in need of improvement, and propose strategies to improve patient outcomes. We also suggest future directions that may improve the quality of preclinical and early clinical drug evaluation, which could lead to higher approval rates of anticancer drugs.

LIMITED SUCCESS IN CANCER DRUG DISCOVERY

Given the recognized medical need for new oncology drugs and the consequent commercial opportunity, many large pharmaceutical and biotechnology firms have invested heavily in oncology therapeutics in the past 25 years. Despite intense efforts, however, only a few effective therapies have emerged, and oncology drug development remains challenging. We examined the fate of new oncology drugs, both chemical and biologic entities, that were in clinical development during 2004 and 2005, and followed their progress until May 7, 2013. Forty-five of the 529 compounds were approved in at least one major geographic area (United States, Europe, or Japan), 95 compounds are still in active clinical development, and 389 have been discontinued or abandoned (Metrics from Onkos database, unpublished data; ref. 1). This evaluation revealed that 7.5% of the oncology drugs that entered phase I clinical development and 33.2% of drugs that entered phase III trials were eventually approved by the U.S. Food and Drug Administration, European Medicines Agency, or Japanese Ministry of Health and Welfare (Table 1). Of these drugs, targeted therapies (e.g., monoclonal antibodies, signal transduction machinery inhibitors) had the highest approval rate (14%; Table 2); in contrast, classic chemotherapy agents and other approaches (e.g., cancer vaccines, hormone therapy, radiosensitizers or chemosensitizers, cancer supportive care therapies) had approval rates of 4% and 2.2%, respectively. However, matching targeted agents to the patients who would benefit most from them has proved extremely difficult. This difficulty in successfully matching patients and drugs is likely the cause of such drugs’ tempered clinical benefit, as measured by extension of life (2).

UNDERSTANDING CANCER

Since the discovery of the first oncogenes in the 1980s, researchers have made extraordinary progress in identifying the genetic mutations, genomic aberrations, and pathway modifications that are responsible for tumor development (3). High-throughput “omics” technologies, such as genomics, epigenomics, transcriptomics, proteomics, and metabolomics, are rapidly developing alongside the bioinformatics infrastructure and analytic tools required to manage and interpret the vast amounts of data generated by omics technologies (4). The omics approach will increase our understanding of cancer biology by enabling us to ask and answer complex questions with previously unattainable depth. Identifying the aberrations critical to tumor growth and survival will provide the knowledge necessary to develop efficacious targeted therapies (5).

With recent transformative advances generated by initiatives such as The Cancer Genome Atlas and the International Cancer Genome Consortium, we are now able to comprehensively compile the genetic alterations in several human cancers at diagnosis and throughout treatment (6). Such data will undoubtedly change the way we envision and deliver cancer therapy with the next generation of targeted agents, and in some instances this has been already accomplished. For example, the cancer hallmarks initially proposed by Hanahan and Weinberg (7, 8) are now unequivocally recognized as alterations associated with cancer. In addition, we now know that similar tumors can have alterations in distinct pathways, as well as in different elements within the same pathway (4). The complexity and interpatient variation of such alterations demonstrate the critical need to identify the genetic makeup of individual tumors and develop personalized treatment strategies to successfully treat patients with cancer.
The biology of treatment-naïve primary tumors is complex. An increasing number of studies posit that anticancer treatment often fails because of intratumor heterogeneity, i.e., the genomic alterations detected in one part of the primary tumor are distinct from those detected in other regions of the same tumor and/or its metastases (9). By this understanding, multiple biopsies at different regions of the tumor are needed to identify the best treatment options. In addition, as treatment progresses, tumors rapidly adapt to survive through the upregulation of bypass pathways and/or antiapoptotic responses. These two factors, coupled with tumors’ propensity to evolve and acquire new adaptive mutations, demonstrate the futility of prescribing a single monolithic strategy with very successful treatments, such as BRAF inhibitors in melanoma, suggest that single-agent therapy is unlikely to provide a sustained benefit. Even experiences with very successful treatments, such as BRAF inhibitors in melanoma, suggest that single-agent therapy is unlikely to cure a patient because of the rapid emergence of compound-specific resistance (10). Combination therapy is the future for oncology patients, as is the requirement that tumors be comprehensively characterized before, during, and after treatment (11, 12).

Researchers have taken a reductionist approach in order to focus on asking and answering specific questions. The use of methods and models to assess only a single aspect of a complex disease leads to an insufficient understanding of the relevance of putative cancer targets in different contexts that account for the ultimate success of a therapy. For example, most of the approximately 14,000 preclinical studies of phosphoinositide 3-kinases (PI3K) and their related pathways have primarily demonstrated that the same signaling characteristics in established cell lines have similar genetic dependencies. Similarly, one could ask to what extent the current emphasis on the development of companion diagnostics for a specific targeted agent reflects a well-reasoned strategy for the field at large (13). We know each tumor contains numerous mutations, and we know that “omics” technologies are being used to make tremendous progress that will reveal insights that are not directly “under the lamppost.” To meet the coming wealth of knowledge, we should strive to develop flexible diagnostic tests that support patient-centered care instead of specific diagnostic tests that support only one specific drug. In pragmatic terms, licensing all single tests separately would be cost-prohibitive and squander precious patient samples (14).

We now have an enormous arsenal of reagents, tools, and technologies that we can use to interrogate the biology of tumors and develop better therapies. Now is the time to start leveraging these technologies to maximize treatment benefit. If we cannot start eradicating cancer, then we must at the very least stop treating patients with ineffective—or worse, dangerous—drugs.

**DISEASE MODELING**

Animal models are some of the most effective tools in the cancer research arsenal, but they have significant limitations. Until recently, oncology drugs were tested solely in established cancer cell lines propagated in tissue culture for in vitro studies and in immunodeficient mice implanted with human cancer cell lines for in vivo experiments. Unfortunately, such models have been of little use in predicting clinical outcomes because they have limited intratumoral heterogeneity, lack human stroma and a competent host immune system, and have proliferation rates that are higher than those of human tumors; in addition, single models have a limited variety of subtypes (15). Despite their limitations, in vivo studies in xenograft models remain the fundamental methodology guiding preclinical drug discovery and development; specifically, they can be used to rapidly assess the relationship between pharmacokinetic and pharmacodynamic measures of target modulation within the tumor or in a surrogate tissue and to determine the efficacy and toxicity of drugs. This approach has proved valuable in evaluating the efficacy of targeted therapy in tumors that depend on critical pathways or driver mutations, such as ligand-independent Hedgehog signaling or EGF receptor (EGFR) mutants, as well as in optimizing the dosing schedule to minimize toxicity, as in the case of Notch inhibitors (16-18). Notably, syngeneic mouse models in which immunocompetent mice are transplanted

**Table 1. New oncology drugs’ approval probability by development phase**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Approval probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>7.5%</td>
</tr>
<tr>
<td>II</td>
<td>11.5%</td>
</tr>
<tr>
<td>III</td>
<td>33.2%</td>
</tr>
<tr>
<td>Preregistration</td>
<td>79%</td>
</tr>
</tbody>
</table>

NOTE: Probability estimated from 529 oncology drugs that were in clinical development in 2004 and 2005 and were followed until May 7, 2013 (metrics from Onkos database, unpublished data; ref. 1).

**Table 2. New oncology drugs’ approval probability by mechanism of action cluster**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Other therapy (n = 160)</th>
<th>Chemotherapy (n = 133)</th>
<th>Targeted therapy (n = 236)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2.2%</td>
<td>4%</td>
<td>14%</td>
</tr>
<tr>
<td>II</td>
<td>4%</td>
<td>7%</td>
<td>20%</td>
</tr>
<tr>
<td>III</td>
<td>13%</td>
<td>31%</td>
<td>48%</td>
</tr>
<tr>
<td>Preregistration</td>
<td>50%</td>
<td>82%</td>
<td>89%</td>
</tr>
</tbody>
</table>

NOTE: Probability estimated from 529 oncology drugs that were in clinical development in 2004 and 2005 and were followed until May 7, 2013 (metrics from Onkos database, unpublished data; ref. 1). Other therapy included immunotherapy, hormone therapy, radiosensitizers/chemosensitizers, and cancer support therapies; chemotherapy included classic cytotoxic chemotherapy; and targeted therapy included monoclonal antibodies, signal transduction inhibitors, and other novel therapies.
with tumors derived from the same genetic background share several of the limitations with xenograft models but, nonetheless, represent a useful model system to study the impact of the immune system on response (19).

Patient-derived tumor xenograft (PDX) models developed by academic or commercial entities are becoming increasingly popular (20). PDX models are implanted in immuno-suppressed animals, but they may mimic the heterogeneity, histology, drug responsiveness, and overall gene expression profiling of the original tumor more closely than traditional xenograft models do (15). Nonetheless, whether PDX models can be used to predict clinical results remains to be determined.

In the coming years, the development of rigorous, standardized methodologies will be critical to the characterization of PDX models in terms of “omics,” histology, and genetic drift from the primary tumor. In addition, preclinical criteria and endpoint measurements must be developed to rigorously compare response in PDX models to response in humans.

More sophisticated spontaneous tumor models that lack many of the weaknesses associated with xenograft and PDX models and recapitulate the natural evolution of human disease with greater accuracy are now available. Genetically engineered mouse (GEM) models provide a system in which a tumor’s drug response and resistance are determined in a microenvironment that more accurately reflects the natural locale of the disease. GEM models are being used more and more often to elucidate mechanisms of resistance to targeted agents, chemotherapeutic agents, and combinations thereof and to identify novel response biomarkers (21, 22).

In the past, GEM models were not extensively used for drug discovery and development because of the “oncous patients” enrolled by Philip Leder and Timothy Stewart at Harvard Medical School, which were assigned to DuPont. These patents, enacted in the early 1980s, profoundly affected the ability of pharmaceutical companies to generate spontaneous tumor models, because they broadly covered “a transgenic non-human eukaryotic animal whose germ cells and somatic cells contain an activated oncogene sequence introduced into the animal, or an ancestor of the animal, at an embryonic stage.” Because they had to acquire a commercial use license to use the GEM models, many pharmaceutical companies decided against pursuing studies that used GEM models until after the patents expired in 2005 (23).

If we want to bring to the clinic novel compounds that truly benefit patients, we must fully leverage all available tools, including GEM models, in preclinical and coclinical research settings (24). In this context, the recent development of chimeric, nongermline GEM models has the potential to bypass the logistical hurdles associated with the generation of novel oncogenic alleles. Because they are generated by injecting embryonic stem cells that harbor oncogenic alterations into wild-type blastocysts, chimeric models combine the benefits of genetic engineering with the speed of xenografts (25).

More importantly, we must recognize that no preclinical model is perfect and that all preclinical models are useful if interrogated properly. For example, many researchers question whether xenograft models that rely on cancer cell lines with high proliferation rates and short doubling times should be used to evaluate the efficacy and determine the dosing schedule of mitotic and checkpoint inhibitors that are currently being developed for use against solid tumors. In fact, the doubling times of human tumors are much longer than those of xenografts, and only a small fraction of tumor cells undergo mitosis or are at the appropriate cell-cycle phase at a given time. Consequently, data generated from the xenograft models given should be interpreted with caution before they are used to inform on the use of these drugs in humans (26). The biology of these model systems might also explain why this class of drugs has elicited better results in hematologic tumors, which have rapid proliferation rates.

In the past, the bar for advancing novel agents into the clinic has been set too low. In many cases, the demonstration of a modest growth delay in a xenograft model has been considered sufficient for investigators to begin testing a new agent in patients with cancer. This is an approach that fails patients too often. To increase the probability of clinical success, we must robustly characterize existing models and use each model appropriately. We must also thoroughly vet compounds and advance only those whose mechanisms of action have been validated and whose efficacy in vivo has been shown to be the consequence of target engagement as measured using robust pharmacodynamic markers.

TARGET IDENTIFICATION

Since its discovery, RNA interference (RNAi) has been widely used in in vitro and in vivo studies to identify and validate key drivers of tumorigenesis and potential “drug-gable” targets for cancer therapy. With some notable exceptions, the results acquired using RNAi have failed to match initial expectations because of the technology’s intrinsic limitations, such as off-target activities and variable degree of silencing, and challenges in data reproducibility. In addition, when targeting enzymes, the silencing of a gene does not necessarily provide information about the role and relevance of the catalytic activity in the corresponding protein (27, 28). As a consequence, published data on putative cancer targets identified using RNAi are not always reproducible or informative. For example, targets that have been reported to be essential in tumors with mutant KRAS using RNAi have not been confirmed using RNAi in different experimental settings and laboratories or using chemical inhibitors of the enzymatic activity (29–34). Moving forward, scientists seeking to identify novel targets should couple RNAi knockdown studies with rescue experiments to advance the research into the drug discovery space. In addition, to demonstrate the role of the protein’s functional domain, researchers should conduct studies in which the gene is reintroduced and the lost phenotype restored with proteins mutated at the active site.

The gold standard of novel target validation should rely on the drug itself; therefore, the identification and use of the appropriate chemical probes for proof-of-concept studies is very important (35). Chemical probes do not need to
have all the characteristics of an approved drug, but to be informative, they must be sufficiently potent (e.g., IC_{50} < 100 nmol/L for the target protein in vitro), selective (ideally 50- to 100-fold selective vs. related targets), and cell permeable and provide sufficient exposure when administered in vivo. Unfortunately, the quality of the compounds used in proof-of-concept studies is often extremely poor, or agents with promiscuous activity are used to interrogate specific questions. For example, the indiscriminate use of UCN-01 (nonspecific checkpoint kinase 1 inhibitor) or LY294002 (nonspecific PI3K inhibitor) to link a specific phenotype with a mechanism of action in a given model often led to unjustified conclusions (36, 37). In addition, the use of specific small-molecule inhibitors at very high concentrations is not best practice and makes discriminating between specific and unspecific effects difficult (35).

**DRUG DISCOVERY AND DEVELOPMENT**

The poor quality and incomplete characterization of preclinical candidates have limited the probability of identifying drugs that have significant clinical impact. Too often, researchers rapidly advance drugs into the clinic with the best intentions of accelerating patients’ access to potential cures, but this approach has resulted in millions of patients being subjected to unnecessary treatments that have led to only marginal improvements and undesirable side effects. In addition, the cumulative costs of such efforts, which are astronomical, have limited private investors’ financing of new oncology start-ups and shuttered many of the pharmaceutical industry’s oncology research and development programs.

The need to fill a product pipeline is the wrong motivation for rushing a compound into the clinic, and doing so can disappoint drug companies and patients alike. For example, imiparib, a putative PARP-1/2 inhibitor, and tivantinib, a putative MET inhibitor, were moved into phase III clinical trials based on the results of phase I and II trials and ultimately failed. Further studies revealed that imiparib and tivantinib are not PARP1/2 and MET inhibitors, respectively, but are active on cancer cells by unrelated mechanisms (38–41). In both cases, a more rigorous understanding of the drug’s “true” mechanism of action would have allowed the design of more appropriate trials and the recruitment of patients most likely to benefit from these drugs.

Patient need, not corporate interest, should drive accelerated drug development. Empiricism could be justified only in the early days of oncology clinical trials, when agents such as anthracyclines, platinum, and taxanes were first identified, because these trials occurred in the absence of any knowledge of the genetic underpinnings of the disease. Moving forward, the mechanisms of action of new targeted agents must be unequivocally identified and validated both in vitro and in vivo, and the plasma exposure required in appropriate preclinical models to ensure efficacious target engagement in the tumor must be clearly understood before these agents enter the clinic. Advancing compounds that lack robust and reproducible preclinical data linking efficacy with target engagement in vivo is no longer acceptable.

The standards for developing oncology drugs have been lower than those for developing drugs targeting other diseases, and this is also unacceptable. Several oncology compounds currently in clinical development lack an identified mechanism of action, which makes generating a solid responder hypothesis that could be tested in selected patient cohorts in phase Ib and phase II trials impossible. This lack of early clinical foresight has forced companies to perform large, lengthy, expensive phase II and III trials in unscreened patients with the hope that they would be able to retrospectively identify a responder population. The majority of clinical compounds used for non-oncology indications are held to a different standard than those used for oncology indications. In advancing agents for oncology applications, investigators have accepted higher thresholds for unwanted activities, such as inhibition of the potassium channel hERG, or a compound’s potential to affect the metabolism of other drugs concomitantly administered. Such liabilities can manifest as cardiovascular complications in patients or as an inability to combine novel agents with other agents in development or with standard treatment. Although our end goal is to eradicate cancer, we should also work to render it a chronic disease by developing safe drugs that can be administered over the long term without compromising patients’ quality of life or damaging their health.

**CLINICAL DEVELOPMENT**

The dramatic change in the drug discovery environment has resulted in major changes in oncology clinical trials. Before the early 1990s, only a limited number of oncology drug candidates were available for testing in the clinic. Starting in the late 1990s, however, expanded efforts in biotechnology and large pharmaceutical companies fueled the discovery and development of significantly more antibody- and small molecule–based oncology drugs that subsequently entered clinical testing. As a result of the clinical success of imatinib in chronic myeloid leukemia, rapid platforms for drug discovery were developed, as were great expectations for targeted agents. The relatively low success rate in the clinic and the companies’ limited returns on their investments, combined with the recent financial challenges facing most companies as a result of patent expirations, have significantly changed attitudes toward oncology drug development across the pharmaceutical industry (42).

Although clinicians are asking for a better rationale for testing novel compounds in patients (a position we think is good news for patients), some trials with weak underlying rationales continue unabated. In contrast, pharmaceutical and biotechnology companies, as well as the majority of venture capitalists, are less interested in oncology programs and are no longer willing to invest in programs that are not substantially advanced (43). This environment has produced a “herd mentality” that has resulted in nearly every company pursuing drugs targeting molecules in a handful of “validated” pathways—in some cases, the same enzyme within a pathway. For instance, 20 compounds targeting...
Compounds and are waiting to “reposition” them based on...
Table 3. Proposed steps needed to move the field forward in the development and delivery of effective novel cancer drugs

1. Generate a complete compendium of cancer-relevant targets in specific disease contexts and in different tumor types, including longitudinal characterizations of disease progression.

2. Use network modeling to determine the connectivity and redundancy of target candidates and use functional genomics to assess a target’s relevance in different cancers.

3. Model the disease at the preclinical level in appropriate genetic and pathophysiologic contexts and consider tumors as “neo-organs.”

4. Focus on understanding the biologic and genotypic context in which the targets selected for drug discovery are rate-limiting and/or cooperative.

5. Design preclinical and clinical, biomarker-driven trials of single-agent and combination therapies that leverage the concept of mechanistic coextinction in appropriately selected patients. The insight gained from preclinical models will inform biomarker-driven trials of single-agent and combination therapies, which will later be leveraged in clinical studies conducted in suitably selected patient subpopulations.

6. Develop a full spectrum of biomarker data to inform the design of clinical trials, facilitate optimal patient selection, and improve scientists’ ability to learn from clinical trials.

7. Identify high-quality drug candidates, both small molecules and biologics. Candidates with adequate potency, specificity, and selectivity that have the appropriate pharmacokinetic and pharmacodynamic properties should be advanced. Compounds that are not predicted to be compatible with the desired pharmacokinetic target, lack evidence of adequate tumor tissue exposure, or elicit safety concerns should be removed from development early.

8. Act now—patients with cancer deserve nothing less.

FUTURE PERSPECTIVES

We have summarized in Table 3 the proposed next steps toward the realization of optimally driven discovery of effective therapies. Recently, we have made great strides in our understanding of cancer biology, thus paving the way for the realization of personalized medicine. For example, in one recent study from MD Anderson (53), the median survival duration of a heavily pretreated highly heterogeneous population of patients with cancer who received targeted therapy chosen on the basis of their disease mutations (13.4 months) versus those who didn’t (9.0 months) was shown; in addition, the response rate of the patients who received targeted therapy was 5 times higher than that of the control population. Moving forward, researchers should design trials that include mandatory biopsies before, during, and after treatment, as well as the rigorous use of biomarkers throughout all stages of clinical development (54–56).

The extensive use of molecular profiling technologies should enhance our insight into cancer biology and increase the success rate of personalized cancer therapy. Although some may express concern that personalized genetic profiling is cost-prohibitive, we should remember that, in the early 1990s, many people thought that we would have never be able to sequence the entire human genome. Sequencing the first human genome cost about $1 billion and took more than 10 years; today, we can sequence the entire genome for less than $5,000 and in 1 to 2 days. We can reasonably expect whole-genome sequencing to be part of the routine diagnostic panel within 6 to 10 years. We can anticipate similar technological leaps and cost reductions in other “omics” areas as well as in the analytic infrastructure (e.g., informatics), which will become increasingly critical in managing the extensive patient data collected with “omics” technologies (57).

Developing personalized cancer therapy is a formidable challenge, and collaboration between industry and academia is crucial to modify the current trends in oncology drug development. We must work to foster strong partnerships that fully leverage the strengths of academia and the biotechnology and pharmaceutical industries. Only in this integrated, innovative, and collaborative fashion can we succeed in our collective mission.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

This work was supported by funds from the Sheikh Ahmed Center for Pancreatic Cancer Research at The University of Texas MD Anderson Cancer Center.

Published online April 4, 2014.
REFERENCES


