# Targeted Cancer Therapeutics

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## Abstract

Targeted therapies can be defined as drugs developed against a specific target based on its important biological function in cancer. In contrast, nontargeted therapies are drugs identified by phenotypic screening of natural products or chemical libraries against established cancer cell lines or preclinical animal models without *a priori* knowledge of the target. Targeted therapies are designed to selectively inhibit a target that is abnormal in malignant compared with normal tissues; these drugs often affect proximal events in signaling pathways that drive abnormal growth and have relatively low toxicity. In contrast, nontargeted therapies affect proteins or nucleic acids that may or may not be abnormal in malignant compared with normal tissues; these drugs often target the downstream consequences of activated signaling pathways, e.g., DNA synthesis and microtubule assembly, and are toxic. Whereas targeted therapies are highly effective in selected hematopoietic malignancies, most have shown limited efficacy against complex solid tumors. In contrast, nontargeted therapies include some of the most effective yet most toxic drugs in the oncology pharmacopoeia. In the future, advances in genomics, proteomics, biology, biomarkers, chemistry, and protein engineering will coalesce to accelerate the development of increasingly selective and effective targeted therapies. Understanding the target in context will help identify biomarkers predictive of response. Finally, a detailed understanding of the target's structure and function will help anticipate and identify mechanism of drug resistance and help design drugs and combinations of drugs that retain activity. [Cancer Res 2009;69(4):1263–7]

“In FDA’s view, new science is not being used to guide the medical product development process in the same way that it is accelerating the discovery process. The path that a medical product takes from development to mass production and availability to the public—what we call the Critical Path—has become increasingly challenging, inefficient, and costly.”

Janet Woodcock

“The more we know, the more our ignorance unfolds”.

John Fitzgerald Kennedy

## Introduction

All drugs have targets. Therefore, the term “targeted therapy” is artificial unless it is carefully defined. For purposes of this discussion, I will define targeted therapies as those where a target was chosen first, and then drugs were developed to selectively inhibit its activity. Trastuzumab (Herceptin) is an excellent example of a drug that meets the definition of a targeted therapy. The target, Her-2/Neu, was identified by Weinberg and colleagues (1) as a transforming factor in a malignant glial cell line. Salmon (2) recognized the importance of this oncogenic receptor tyrosine kinase in certain forms of breast cancer ultimately leading to the development of trastuzumab (3).

In contrast, nontargeted therapies can be defined as drugs discovered empirically by screening chemical libraries, natural products, or monoclonal antibodies without first knowing the target, which may or may not be ultimately identified. A prime example of this nontargeted approach is the discovery of the anthracyclines, whose target(s) remained a subject of debate for many years. This discussion will focus on whether the targeted approach will be superior to the nontargeted method.

## Background

It is incorrect to assume that only in the last 20 years have we developed cancer therapeutics based on our knowledge of cancer biology. For example, the work of Elion and Hitchings (4, 5) led to targeting the enzymes of DNA synthesis to develop drugs such as 6-mercaptopurine and 6-thioguanine. Work done in collaboration with investigators at Memorial Sloan Kettering Cancer Institute resulted in Burchenal's testing of 6-MP in childhood leukemia (6, 7). It is useful to note that the early demonstration that these antimetabolites could produce complete remissions in childhood leukemias led to the approval of 6-MP by the Food and Drug Administration (FDA) in 1953, approximately 2 years after it was first synthesized in the Wellcome Research Laboratories.

Similarly, in the 1950s, Heidelberg and colleagues (8) began work on the biosynthesis of nucleic acids and recognized the abnormal uptake of uracil by cancer cells, which began a search for pyrimidine antimetabolites. With collaborators at the University of Wisconsin and Hoffman LaRoche, they ultimately identified the fluoropyrimidines to be highly effective agents (9).

Yet it was the era of molecular biology that dramatically accelerated our understanding of cancer biology, created great expectations, and placed enormous pressure on our ability to translate these discoveries into effective treatments for patients. Modern cancer biology also helped explain why the early chemotherapeutic drugs were effective. The identification of oncogenes led to an appreciation that cancer cells usurped normal signal transduction pathways used by growth factors to stimulate proliferation and sustain viability. The interaction of growth factors with their cognate receptors activate pathways that culminate in DNA synthesis through transcriptional activation of cell proliferation genes, removal of cell cycle check points, inhibition of apoptotic fail safes, ultimately leading to cell division through...
the assembly and disassembly of the mitotic apparatus. The discovery of tumor suppressor genes further solidified our fundamental knowledge of malignant transformation and helped further explain the activity of empirically derived anticancer drugs. For example, the retinoblastoma protein is inactivated during oncogenesis through mutation, phosphorylation by cyclin-dependent kinases, sequestration by viral oncoproteins, or degradation by caspases (10). This unleashes the cell from cell cycle checkpoints and releases a family of bound transcription factors (E2F) that activate genes critical for the malignant phenotype, including thymidylate synthase and dihydrofolate reductase. Therefore, it is not surprising that some of our most effective chemotherapeutic agents work downstream of these early signal transduction events to inhibit the enzymes of DNA synthesis (fluoropyrimidines, methotrexate), DNA function (alkylating agents, topoisomerase poisons), transcription (actinomycin-D), and microtubule dynamics (Vinca alkaloids and taxanes) and have the broadest spectrum of activity and the greatest toxicity. By combining drugs that target DNA, e.g., the platining agents (carboplatin and cisplatin), with drugs that target microtubules, e.g., taxanes and Vinca alkaloids, we understandably created the most effective forms of combination therapy. Today, lung (both small cell and non–small cell), bladder, ovarian, breast, and several other solid tumors are treated with some variation of this fundamental combination.

Steroid hormone growth factors work differently. These molecules interact with nuclear receptors directly to activate the transcription of genes whose products stimulate the growth and viability of hormone-dependent malignancies such as breast and prostate cancer. Selective estrogen receptor (ER) modulators and aromatase inhibitors interfere with this process, and are highly effective targeted therapies and well-tolerated anticancer therapeutics (11).

Most of the recently developed targeted therapies work on proximal events in signal transduction cascades rather than affecting the downstream output of these pathways (Fig. 1). Bcr:abl, CD20, Her-2/NEU, and epidermal growth factor receptor (EGFR) represent important targets of “targeted therapies” of the modern era. If these are our best examples, what characteristics do the targets have in common? Most striking is their subcellular location, i.e., the plasma membrane. For all but CD20, the downstream signaling pathways are well defined, using ras, Jak/stat, mitogen-activated protein (MAP) kinase, or PI3-kinase signaling that ultimately results in the downstream activation of genes that replicate DNA and polymerize microtubules. Thus, the upstream location of these targets makes the drugs that inhibit

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Subcellular localization of the targets of targeted and nontargeted therapies. Malignant transformation activates signal transduction pathways that culminate in DNA synthesis, assembly of the mitotic apparatus, and ultimately, increased cell division and viability. Targeted therapies inhibit upstream components of signal transduction systems creating susceptibilities to downstream abrogators of response. Drug A targets an activated oncoprotein tyrosine kinase pathway and is susceptible to resistance in the presence of an activated pathway b or c. Drug B targets a nuclear receptor (selective ER modulators) that directly interacts with DNA and is less susceptible to downstream abrogators. Drug C targets DNA directly (e.g., alkylating agents, anthracyclines), and drug D targets microtubules (Vinca alkaloids, taxanes). The latter are less affected by upstream events. The double helix is from the National Library of Medicine collection. The microtubules are from Jordan MA, Wilson L. Microtubules as a target for anticancer drugs. Nat Rev Cancer 2004;4:253–265 with permission.
them susceptible to downstream mechanisms of resistance (Fig. 1). The EGFR receptor, which is activated by growth factors, overexpression, or mutation, turns on downstream signal transduction cascades and was one of the earliest targets for both small molecule and protein therapeutics. However, as shown in Fig. 1, these upstream events are susceptible to pathway redundancies that create resistance to the effects of a targeted therapy. In fact, recent evidence indicates that Kras mutations are responsible for at least one way a cancer cell defeats a targeted agent (12).

In contrast, because DNA synthesis and microtubule assembly are the end results of these processes, targeting these downstream consequences of malignant transformation bypasses redundant signaling pathways and results in a greater probability of efficacy but at a high price of toxicity. The single agent activity and toxicity of the recently approved targeted therapies in solid tumors (trastuzumab, lapatinib, cetuximab, gefitinib, erlotinib, sunitinib, sorafenib, etc.) or chronic myelogenous leukemia (CML) in blast crisis (imatinib, dasatinib) is low. If this lower efficacy is due to the accumulation of mutations or other means of activating signaling pathways that evolve during the long process of malignant transformation, one might anticipate that the treatment of premalignant conditions would be less susceptible to resistance due to molecular complexity. In fact, the activity of the cyclooxygenase 2 (cox-2) inhibitor, celecoxib, is high against adenomatous polyps of the colon (13), but cox-2 inhibitors are ineffective and potentially toxic against adenocarcinoma of the colon. This difference in activity is probably due to the accumulation of mutations that create pathway redundancies so that inhibition of one pathway is insufficient to block proliferation and survival signals (Fig. 1). It is in this context that we might better understand the remarkable activity of imatinib in chronic phase CML, and the decreased activity in accelerated and blast phases of the disease.

Why Will the Targeted Therapy Approach Ultimately Deliver Safer and More Effective Cancer Therapeutics?

Based on the above discussion, one could make a legitimate argument for both the targeted and nontargeted approaches to developing new anticancer drugs. It is my thesis, however, that the targeted approach will ultimately deliver safer and more effective medications. This opinion is based on several premises: (a) increased knowledge of cancer biology will identify critical targets and their inhibitors at a more rapid pace; (b) new techniques will allow more rapid progression from target identification to clinical candidates; (c) detailed knowledge of the target in the context of specific malignancies will produce predictive biomarkers and companion diagnostic tests that will enable more precise prescribing of drugs; (d) understanding the target in detail will uncover the mechanisms of drug resistance and point to how they can be overcome.

Increased Knowledge of Cancer Biology Will Identify Targets and Their Inhibitors at a More Rapid Pace

A valid criticism of the targeted approach is the time it can take from identifying and validating a target to the launch of a new medication. For example, it took over 40 years from the identification of the Philadelphia chromosome to the launch of imatinib. The observation by Nowell and Hungerford (14) in 1960 that the presence of the Philadelphia chromosome, was due to a reciprocal translocation t(9;22)(q34;q11) in which a piece of the long arm of chromosome 9 (q34) is exchanged for a fragment of the long arm of chromosome 22 (q11). It was eight years later when the c-abl sequences were shown to be translocated from chromosome 9 to chromosome 22q— (16, 17). Owen Witte and colleagues (18) reported in 1990 that bcr-abl is transforming for myeloid precursors and, therefore, represents the underlying pathologic event in the formation of CML. The demonstration of the tyrosine kinase activity of bcr-abl (19) led to the realization that this might be a target for a new way to treat cancer. In the early 1990s, Brian Druker (20) began studies of small molecule inhibitors of abl kinase with essential collaborators at Ciba Geigy. They identified STI571 as a clinical candidate. Druker’s and Sawyers’groups then carried out clinical studies that showed the remarkable activity of imatinib in chronic phase of CML, with real but lesser activity in accelerated phase and blast crisis (21, 22). FDA approved Gleevec on May 10, 2001, for the treatment of patients with CML in blast crisis, accelerated phase, and chronic phase after failure of IFN; accelerated approval took about three months from time of submission (23).

Today, the targeted approach can move rapidly. It is now possible to simultaneously identify and validate a target using RNA interference. RNAi libraries can be used to screen for targets that selectively kill cancer cells, and these RNAs can be deconvoluted with “molecular zip codes” or other techniques to identify the target (24). The effect of RNAi screening can be confirmed by overexpressing a nondegradable mRNA to show on target effects. The target can then be cloned and expressed, and chemical libraries containing hundreds of thousands or even millions of compounds are screened against the activity of the purified enzyme in high-throughput assays to generate “hits,” chemical structures that show a defined level of activity. These structures can be optimized against the purified target and then in cancer cell lines often engineered to be “dependent” on the target of interest. Ultimately, this process delivers candidates for further testing. The power of structural biology coupled with fragment-based chemistry is leading to the rapid production of lead compounds with improved drug-like properties, increasing the probability of better lead optimization and ultimately more effective compounds (25). Similarly, phage displays can be used to identify antibodies against targets of interest, thereby accelerating the process of hybridoma creation and screening of thousand of clones (26).

In contrast, in the nontargeted approach, natural products or chemical libraries are screened against cellular processes that are part of the malignant phenotype such as proliferation, migration, invasion, etc. These empirical screens are agnostic to the target, and only later is the target identified. This nontargeted approach has the drawback that lead compounds cannot be readily optimized because the target is not immediately known. Although new methods are being developed to rapidly identify these targets (27), there is no guarantee that the target will be identified and, therefore, difficulties in optimizing leads remain. In addition, we are in the midst of uncovering new genetic abnormalities in human tumor specimens and in compilations of hundreds of cancer cell lines. The study of human tissue specimens to uncover the molecular underpinnings of oncogenesis was pioneered by Vogelstein and colleagues (28) at Johns Hopkins who used human tissues to define the accumulated genetic defects that occurred as normal colonic epithelium transformed through
adenomatous polyps to adenocarcinoma. More recently, the human genome atlas project sponsored by National Cancer Institute has uncovered new genetic alterations in 206 human glioblastoma specimens, confirming the importance of ERBB2, NF1, and p53, as well as PI3KIR1 and MGMT promoter methylation (29).

**Detailed Knowledge of the Target in the Context of Specific Malignancies Will Produce Predictive Biomarkers and Companion Diagnostic Tests That Will Enable More Precise Prescribing of Drugs**

Developing drugs that inhibit important targets with both potency and selectivity is no guarantee of clinical efficacy. In fact, quite the opposite is true, as over 90% of compounds entering clinical trials in oncology fail to gain approval despite excellent preclinical profiles against the target. Rather, major advances will require a more sophisticated understanding of how the target is wired into the specific malignancy of the patient undergoing treatment. Without knowing the target of a drug, it will be more difficult than it already is to identify predictive biomarkers for response. To date, the best predictive biomarkers are based on an understanding of the target, such as hormone receptors and HER-2/Neu in breast cancer, and the Philadelphia Chromosome in CML. ERs represent one of the earliest and most useful predictive biomarker but also highlight some of the problems that lie ahead. Hormone receptors (ER, PgR) are expressed in approximately 50% of breast cancers and predict response to antiestrogen therapy. However, only 50% of hormone receptor-positive patients respond to antiestrogen treatment. Similarly, the expression of HER-2/neu predicts response to trastuzumab. However, whereas 25% of patients’ breast cancers express HER-2/neu, <25% of these individuals respond to trastuzumab (30). It will be the ability to understand why some patients who express the target respond to treatment and others do not that will revolutionize the future application of targeted therapies and the personalization of medicine.

In both examples, it is useful to evaluate why these biomarkers are predictive. First, both the ER and HER-2/neu are key to the biology of breast cancer and in fact represent distinct subsets of the disease (31). In addition, in both cases, the biomarker is also the target of the therapeutic agent. In the case of HER-2/neu, the biomarker is also indicative of a poor outcome; not the case with ER or EGFR.

**Knowing the Target Will Help Uncover the Mechanisms of Drug Resistance and How They Can Be Overcome**

The targeted approach provides better insights into drug resistance. Solving the structure of imatinib bound to bcr:abl led to an understanding of its mechanism of action, why it is relatively selective, and how drug resistance can occur (32). Like other tyrosine kinase inhibitors, imatinib binds to the ATP binding fold of the kinase domain. However, rather than competitively blocking access of ATP to the active site, imatinib locks the catalytic domain in an inactive conformation. Patients who become resistant to imatinib can do so through mutations in the catalytic domain of bcr:abl that prevent the binding of imatinib. By knowing the target, it was possible to identify inhibitors that remained active in the presence of at least some of these resistance-producing mutations, leading to the development of dasatinib by Talpaz and colleagues (33), and investigators at Bristol Meyers Squibb.

The observation that certain patients with bronchoalveolar lung cancer, who were often nonsmokers and of Japanese descent, had significantly better results when treated with gefitinib than others with non–small cell lung cancer led to the discovery that those patients’ malignancies harbored activating mutations in the EGFR TK catalytic domain that caused a form of oncogene addiction that increased drug sensitivity (34, 35). Furthermore, we have begun to appreciate that Kras mutations can abrogate the response to EGFR antagonists in a variety of malignancies, and that cMet overexpression may further define resistance to EGFR inhibitors (36). Rosen’s group (37) has shown that mutations in Kras decreased the sensitivity of melanoma cell lines to Braf inhibitors, but increased the sensitivity to inhibition of MAP/ERK kinase. Thus, knowing the molecular status of the target and its abrogators can predict the responsiveness to targeted therapeutics. Having this information directs us to develop combination therapies that target EGFR, Kras, and/or cMet, and should lead to an improvement in therapeutic outcomes.

**Conclusions**

The promise of targeted therapies will be realized as our understanding of cancer biology continues to improve. The targeted approach, when correctly applied, will produce further improvements in drug safety and efficacy. Furthermore, an understanding of the target in context and the identification of biomarkers predictive of response will allow more precise prescribing of these new drugs. Knowledge of the target can give rapid insights into drug resistance, help identify new drugs that retain activity, and design more rational combination therapies. It would be unwise to abandon our accumulated knowledge to select targets for targeted drug development and return to the days of “unsupervised” phenotypic screening of natural products and chemical libraries, only to later identify the targets. On the other hand, it would be equally foolish to abandon phenotypic screening and disregard the possibility that excellent drugs will be discovered using the less supervised approach.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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**References**

The success of targeted agents such as imatinib is due to the inhibition of a single enzyme being sufficient to halt the development of the cancer in question. The central thesis in Dr. Hait’s article is that “the targeted approach will ultimately deliver safer and more effective medications” for the treatment of cancer, including nonhematopoietic cancers. Fundamental to this being achieved is the need to identify what he refers to as “critical targets” for the cancers that have proven resistant to molecularly targeted agents thus far. However, it is not yet clear whether critical targets exist for all cancer types. Cancer is a multifactorial disease, and its development typically involves a sequence of many mutations and changes. Therefore, targeting one modified enzyme or pathway may not be sufficient to effectively treat many cancers. If some cancers are the result of a large number of subtle changes, then targeting even a subset of them may not be possible or successful. The limited success of targeted agents in treating solid tumors, in particular, may be due to the same factors that limit the effectiveness of other classes of anticancer agents, such as limited uptake, and natural and acquired resistance. However, it may be related to the complex nature of the genetic changes that led to the development of the cancer and the consequent lack of a single critical difference that can be exploited to make that cancer vulnerable.

Dr. Hait makes the good point that compounds developed using the nontargeted approach cannot necessarily be optimized in a rational way because the target is not immediately known. This is supported by the development of some cytotoxic drugs, which has typically involved blanket testing of thousands of compounds, rather than guided selection of a few. However, we argue that the existing arsenal of cytotoxicity is likely to be sufficient for most tasks, and what we need now is to learn how to use them more effectively and make them more selective for the tumor by exploiting the physiologic differences between the tumor and healthy tissues. Thus, optimization can occur at the pharmacologic level, often by preparation of less toxic prodrug forms of existing agents and by finding means of selectively delivering these to tumors.

As Dr. Hait points out, most nontargeted cytotoxic drugs work by interfering with downstream targets, whereas most targeted agents work by inhibiting upstream targets. The former leads to toxicity, whereas the latter is susceptible to multiple modes of resistance. This suggests that targeting enzymes associated with the cellular response to cytotoxins (e.g., those involved in the apoptotic cascade) could result in increased consequences from cytotoxin action. If tumor-specific downstream targets could be identified, lower doses of cytotoxins might be coupled with inhibitors or activators of these targets, leading to increased efficacy at these lower and, hopefully, less toxic doses. Particularly notable in this regard is the association between dysfunctional p53 and the resistance of the tumor to cytotoxic assault.

It is indisputable that molecularly targeted agents can provide more insights into the biochemistry of tumors and healthy tissues, and that it will lead to a better understanding of cancer and how it should be addressed. However, the results, to date, suggest that for the foreseeable future, both targeted and nontargeted agents will need to be used in conjunction, and that this reality needs to be taken into consideration in the future development of both classes of agent.
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