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Is Anticancer Drug Development Heading in the Right Direction?

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Abstract

The success of molecularly targeted agents, such as imatinib, has led to expectations of a new era in anticancer drug development, and to a greatly increased focus on targeting as a strategy. However, the number of successes to date is small, and recent results suggest that the success of imatinib, for instance, in treating chronic myelogenous leukemia and gastrointestinal stromal tumor may be the exception rather than the rule. Here, we argue that the search for new anticancer agents needs to continue on as many fronts as possible, and not be focused on one strategy alone. [Cancer Res 2009;69(4):1259–62]

Background

The rate of approval of new agents for the treatment of cancer has decreased steadily over the past decade (Fig. 1), and to date, only one new compound has been approved in 2008.[1] In addition, many of the agents approved over the past few years are either antibodies or do not represent entirely new directions in drug development (1), suggesting a slowing in the development of new classes of compounds for treating cancer. In these circumstances, it is important to ask whether the optimal mix of strategies is being pursued in the development of new anticancer agents. Up until the 1990s, anticancer drug development was largely based on the testing of compounds derived from a variety of sources including, substrate analogues, natural products, combinatorial syntheses, and large libraries, typically using *in vitro* cytotoxicity assays followed by *in vivo* assessment of toxicity and efficacy. Since then, and particularly following the determination of the human genome and the emergence of increasing insights into the genetic changes associated with cancer, drug development has moved into the "molecular target" era (1, 2). There have been some successes as a result of this strategy, but they are small in number and are not without significant limitations. Gleevec (Glivec, imatinib mesylate), in particular, has rapidly become the treatment of choice for chronic myelogenous leukemia and gastrointestinal stromal tumors, and has greatly improved the prospects of patients with these cancers (3), leading to the expectation of a new "golden era" for cancer drug development (2). However, recent results showing, yet again, the genetic complexity of cancers have led to the suggestion that imatinib may be the exception and not the rule (4), and therefore, it might represent a "false dawn" or be pointing us in the wrong direction. In this article, I address the issues surrounding molecular targeting that may be contributing to the slow output of new anticancer agents and suggest strategies for the future.

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Molecular Targeting

Molecular targeting in the treatment of cancer is based on the premise that the molecular basis of cancer is associated with one or more genetic abnormalities that give rise to increased production or activation of some molecules and/or decreased production or activation of others (2). Determination of the structure of the target enzyme allows for the design of often exquisitely selective and effective inhibitors, enabling the selective inhibition of the up-regulated group of enzymes or activation of the down-regulated. This is expected to lead to inhibition of the pathways that typify cancer and to the death of the cancer cells, with low effect on normal cells and, therefore, low toxicity. However, there are a number of problems with this strategy.

Progression of a normal cell to cancer cell has recently been shown to involve dozens of genetic mutations, and therefore, targeting even a few gene products may be ineffective (5–7). Inhibition of pathways that are the hallmark of cancer may be an effective strategy, but these recent results show that up to 12 different pathways can be involved in a single cancer type. In addition, most biological processes have alternate pathways, developed as a result of evolutionary pressures, which can be up-regulated should one pathway be blocked, giving rise to a redundancy that is unlikely to be bypassed by a single, highly targeted agent or, perhaps, even by groups of targeted agents.

Selective inhibition of an enzymic target can have unexpected consequences, as the experience with the cyclooxygenase-2 inhibitors has revealed, when the protein or its subtypes being inhibited have multiple roles—and it now seems that this is the case for many enzymes. The range of problems that can result from high selectivity has been well covered in a recent review by Fairlie and colleagues (8). These include the rapid development of resistance, which is more likely if a single molecular target is being inhibited with high selectivity. As mentioned, imatinib has been one of the outstanding successes of the molecular targeting approach, but in many cases it becomes ineffective after prolonged use. Genetic analysis at this point reveals that the targeted tyrosine kinase has often mutated and is no longer sensitive to imatinib (9). Whereas this confirms the ability of imatinib to target a specific molecule, it reflects an important weakness in therapy based on the inhibition of a single enzyme. It may be possible to develop a bank of kinase inhibitors, some of which are not cross-resistant with molecularly targeted compounds, and a range of second and third generation kinase inhibitors are already in use for treating cancers that have developed imatinib resistance (9). However, this is a highly costly strategy, and it may not always be effective.

Two of the most widely pursued molecular targeting strategies relate to the inhibition of matrix metalloproteinases and angiogenesis-promoting enzymes, such as vascular endothelial growth, factor and epidermal growth factor receptor. The logic behind these strategies is sound—matrix metalloproteinases are highly

[1] http://www.centerwatch.com/drug-information/fda-approvals

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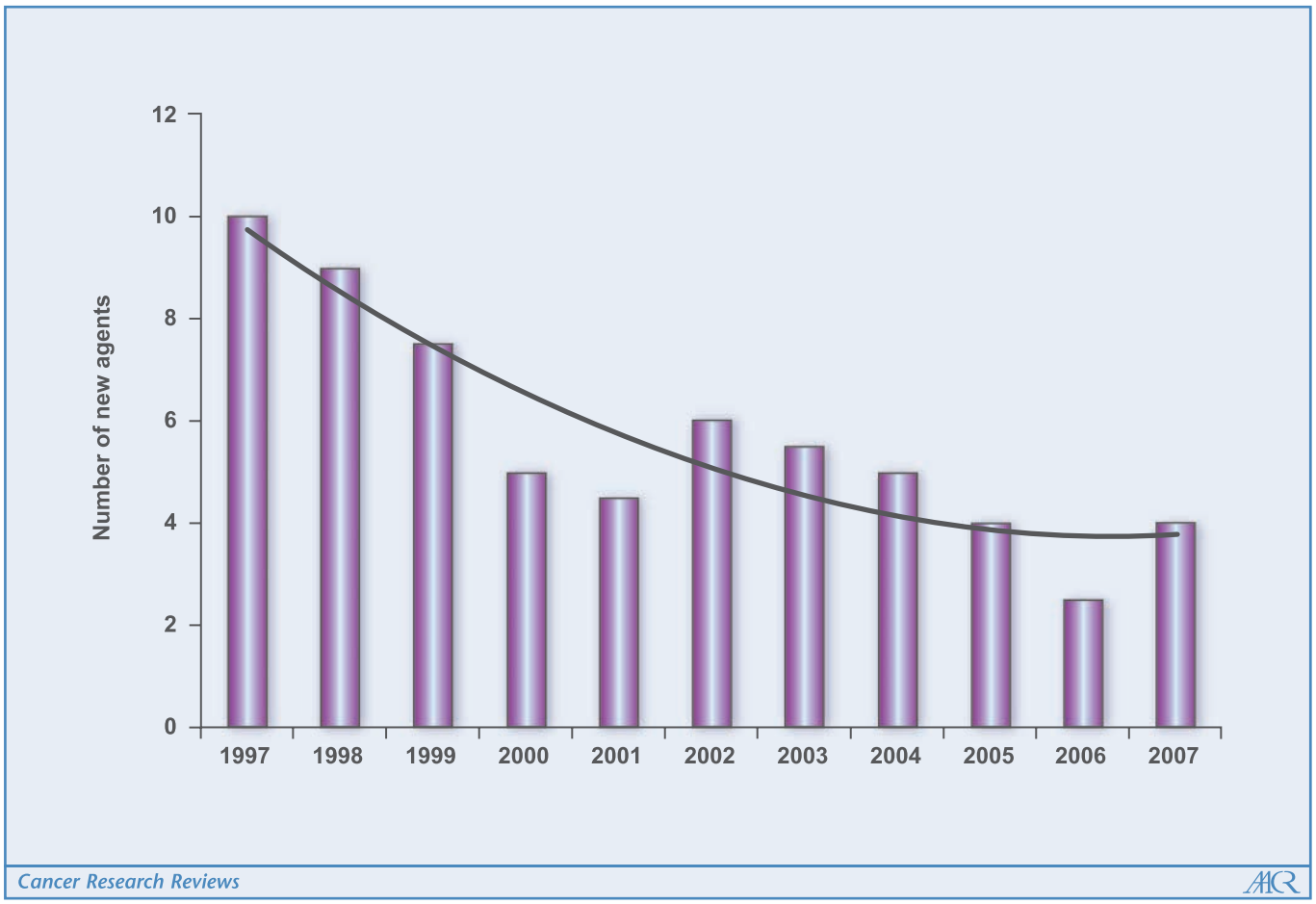

Figure 1. The number of new agents for the treatment for cancer approved by the Food and Drug Administration between 1996 and 2007, plotted as 2-year averages [i.e., 1997 = (1996 + 1997)/2]. Taken from http://www.centerwatch.com/patient/drugs/druglist.html.

overexpressed in many tumors and are almost certainly involved in metastasis, and angiogenesis is required for tumors to continue to grow—and the preclinical data for many compounds targeting these enzymes has been promising. However, the clinical outcomes have been less promising, particularly when such agents are used alone, and there may be flaws with both examples. Preventing the remodeling of the extracellular matrix is likely to result in tumors becoming more dense, which can be expected to result in increased hypoxia, decreased responsiveness to anticancer treatments, and increased development of aggressive phenotypes, including metastasis (10). Inhibition of angiogenesis could have similar effects and will also result in reduced delivery of anticancer agents to all regions of the tumor.

It is notable that the most significant successes of molecularly targeted agents have been against leukemias and lymphomas with relatively little effect being made against most adult epithelial cancers. Solid tumors are highly heterogeneous, typically being made up of multiple cell types and having multiple environments. These environments range from almost normal—for those cells in the vicinity of the vasculature—to nonviable, resulting in necrosis in the regions most distant from the vasculature. In between are environments that are highly stressed as a result of hypoxia, acidity, and high interstitial pressure. As a consequence, cells can exist in a variety of states, which may make them more or less responsive to most drugs including molecularly targeted agents. It is unlikely that all will be equally responsive to any one class of highly targeted anticancer agents, and some may be completely resistant on a time scale that corresponds to the pharmacologic half-life of the agent.

Alternative Strategies

If molecularly targeted agents alone are unlikely to be effective in treating all classes of cancer, what other directions should be considered? It is arguable that the development of new cytotoxics has plateaued, and the chances of major advances in this area are diminishing. Combinatorial approaches have not yielded the successes expected and, although variations on current drugs continue to have an impact at least similar in magnitude to that of molecularly targeted agents, as the emergence of oxaliplatin shows (11), developments in this area alone cannot be relied on to lead to the type of advances needed for the treatment of currently unresponsive cancers. There exists an arsenal of highly effective cytotoxic agents, but their toxicity limits their use and, ultimately, their effectiveness. Finding means to target cytotoxic agents to tumors has only been addressed to a relatively small extent and is almost certainly amenable to further development and exploitation. The physiologic differences between tumors and normal tissues, such as lower pH, hypoxia, and a leaky vasculature can

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almost certainly be exploited to achieve increased tumor selectivity (12) as can their increased needs for nutrients, such as iron and glucose. There have been some advances on this front with hypoxia selective agents undergoing clinical trials (13). The toxicities that have emerged during the use of molecularly targeted agents suggest that they too could benefit from physiologic targeting.

Another issue that has received remarkably little attention until relatively recently is the extent of uptake of anticancer agents in solid tumors (i.e., macroscopic uptake versus cellular uptake; ref. 14). Recent imaging studies have shown that agents such as doxorubicin, which is a key component of many treatment regimens, is not able to migrate more than 40 to 50 μm (3–5 cells in diameter) from the vasculature (15, 16), leaving many cells exposed to negligible doses and, perhaps worse still, a population of cells to sublethal doses that can be expected to contribute to the development of resistance. Macroscopic uptake will be an issue for molecularly targeted agents as much as cytotoxics and other classes of anticancer drugs. An overemphasis on cellular studies and on achieving good cellular uptake in the earlier stages of drug development may be resulting in the exclusion of compounds that would be more effective in treating the whole tumor. It is likely that to effectively attack cells in all parts of the tumor, it will be necessary to treat with a combination of compounds, some of which are able to diffuse throughout the tumor and others which target the rapidly dividing cells close to the vasculature. This is a challenge for all classes of compounds, but is a particular challenge for molecularly targeted agents because modification to improve macroscopic uptake is likely to affect the selectivity and effectiveness of the targeting unless modifying groups can be added that are lost at the appropriate point in the tumor.

Selection of anticancer agents with better macroscopic uptake properties will require the use of more appropriate models than two-dimensional cell cultures. Cytotoxic agents have been developed by assessment of their cytotoxicity against panels of cell lines. However, it is not at all clear that these cell lines provide a good model for tumors, or that activity in the cells correlates with activity in the clinic (17). It has been shown that activity in three-dimensional models, especially those that include an extracellular matrix, provide a much better indicator of the likely *in vivo* activity (17). Prodrugs, and in particular those that are activated in the abnormal environment of solid tumors, are unlikely to show activity in two-dimensional cell culture that reflects their activity in humans or animals. This is known to be the case for platinum (IV) complexes (18) and for hypoxia selective drugs, although modification of the conditions can result in mimicking of the solid tumor environment to some degree (13). In addition, compounds that are selectively active against metastases are unlikely to be identified in cell culture studies.

Conclusions

The underlying principles of molecular targeting are clearly sound, and the problems discussed here are not reasons for abandoning this approach. Rather, molecularly targeted agents should be seen as one part of a broad approach to the treatment of cancer and used in conjunction with other treatments. For instance, the combination of a compound designed to activate p53 and, thereby, increase susceptibility to cytotoxic, apoptosis-inducing agents could have an enormous effect on the treatment of currently resistant cancer with cytotoxic agents. Already, some, if not most, molecularly targeted agents have been found to be more effective and to exhibit synergy when used in conjunction with one or more cytotoxic agents. For instance, bevacizumab, a vascular endothelial growth factor targeting antibody, generated a significant increase in median survival when used in combination with carboplatin and paclitaxel for the treatment of small-cell lung cancer, although at the cost of an increased number of treatment-related deaths (19).

Molecular targeting, being based on a knowledge of the genetic changes that have led to the formation of a cancer, must continue to make a contribution to drug development over the coming decades. However, it is probable that such agents alone will not be able to effectively treat most cancer and, therefore, there is a need to reassess the almost overwhelming current emphasis on molecular targeting and find ways to make better use of new and existing cytotoxic agents. At present, it is too soon to predict whether imatinib will turn out to be the exception rather than the rule. However, some signs suggest it may be, and, therefore, an overemphasis on molecular targeting has the potential to result in a further slowing in the development of new anticancer drug treatments.

Disclosure of Potential Conflicts of Interest

The author is a named coinventor on a number of patents relating to anticancer agents. He may benefit from this financially through The University of Sydney's intellectual property rule. The author has worked as a consultant for a number of companies involved in anticancer drug commercialization.

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Response

Professor Hambley made important points regarding the potential problems with targeted therapies. I will highlight the areas where we agree, because I believe that these will most likely result in near-term advances for the treatment of patients with cancer.

1. The pace of new drug approvals is too slow.
2. Human cancers are characterized by numerous genetic mutations.
3. Solid tumors are more difficult to treat than malignancies of hematopoietic origin.
4. Monotherapy will be less effective than combinations.
5. Cells grown on plastic are not ideal models for complex human cancers.
6. Drug selectivity is a relative term.
7. Both the targeted and unsupervised approaches should be pursued.
8. Drug distribution, metabolism, and uptake are critically important to the success of any therapy.

The Pace of New Drug Approvals Is Too Slow

This is especially true from the perspective of patients and their families. However, the slowing rate of return on investment does not indict the targeted approach. In fact, recent evidence suggests that inhibitors of protein kinases have a higher probability of technical and regulatory success than most other types of oncology drugs (Walker, I. EJC suppl; 6:abs35, 2008). Finally, as I argue in my accompanying article, the massive accumulation of knowledge should not be ignored in favor of returning to empirical discovery.

Human Cancers Are Characterized by Numerous Genetic Mutations

I have lectured in the past that trying to treat a metastatic carcinoma was like trying to untie the Gordian knot, and I urged my colleagues to focus on preventing the knot from being tied in the first place. It does appear, at least at first glance, that the wiring of complex human malignancies is so complex and the pathways so redundant that finding the right target or combination of targets might be a fool's errand. However, I disagree with this line of thought for many reasons, and would paraphrase the formulation of Dr. William Kaelin of the Dana-Farber Cancer Institute on the subject. Kaelin has argued persuasively that the mere presence or detection of multiple genetic abnormalities in individual tumors does not mean that each and every one of these must be corrected for a treatment to be effective. In his model, there is a hierarchy of mutations, and that correcting one or two may suffice. He has drawn an analogy to a combination tumbler style lock that must have three tumblers each showing the correct number to be opened, but by changing only one tumbler, the lock is impenetrable.

Solid Tumors Are More Difficult to Treat than Liquid Tumors

I also can provide a perspective of someone who ran a pharmacology laboratory for more than 20 years. When the hypothesis is sound, but the first few experiments fail, one should not abandon the hypothesis too soon, especially when no other equally compelling hypothesis has emerged. Rather, each experiment, whether in the laboratory or in the clinic, should be designed to provide as much information as why the experiment did not work as why it succeeded. One must never forget that one of the earliest targeted therapies, tamoxifen for breast cancer, is reason to suspect that malignancies of epithelial origin will also be amenable to a targeted, personalized approach.

Monotherapy Will Be Less Effective than Combinations

This will undoubtedly be true for targeted as well as empirically derived therapies. As we learned from the treatment of tuberculosis, targeted therapies used in combination will be the most effective approach.

Cells Grown on Plastic Are Not Ideal Models for Complex Human Cancers

True, and in fact more complex models will be needed to optimally identify new targets and predict their efficacy. It is tempting to speculate that fresh human tumors grown in short-term culture or in immunocompromised mice might be more predictive.

Drug Selectivity Is a Relative Term

Several pharmacologic principles need to be followed when thinking about drug development, including potency, efficacy, and selectivity. Potency, the concentration at which a defined effect is achieved, must be clearly distinguished from the independent variable of efficacy, the amplitude of the effect. Selectivity, the ability of a drug to hit a single target, is likely related to potency, but not necessarily related to efficacy. Although we now can routinely assay the potency of a compound against a panel of more than 200 protein kinases to determine selectivity, we should be cautious in interpreting these results. First, the assays are done using purified or partially purified enzymes, with artificial substrates, under nonstoichiometric conditions. Second, merely because a compound shows selectivity against a protein kinase, this is no guarantee that it does not inhibit (or, for that matter, activate) other proteins with similar binding sites (e.g., ATP binding folds). The maxim that all drugs are selective until they are not is a good one.

Both the Targeted and Unsupervised Approaches Should Be Pursued

I agree, but each "pursuer" should prioritize the one that they are most excited about and have the most expertise.

Drug Distribution, Metabolism, and Uptake Are Critically Important

Professor Hambley raises a key issue that is as important for targeted drug developers as it is for nontargeted drug developers. In summary, we have much to learn, and we should use all of the knowledge at our disposal to achieve our goal: the eradication of suffering from malignant diseases.

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The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

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