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## OPINION

## Improving the evaluation of new cancer treatments: challenges and opportunities

Mace L. Rothenberg, David P. Carbone and David H. Johnson

There are, at present, ten times more anticancer drugs being tested in clinical trials than there were 15 years ago. Many of the new classes of agents, however, are predicted to work in only small subpopulations of patients, target unconventional aspects of tumour development and interact with other agents in an unpredictable manner. How can clinical trials be re-designed to accommodate the new features of targeted anticancer drugs?

In the dynamic new era of clinical cancer research, it is estimated that there are more 350 new agents that are in clinical development at present for cancer or cancer-related indications<sup>1</sup>. This is more than ten times the number of agents we had 15 years ago. Yet, along with this unprecedented opportunity, a sense of uncertainty and frustration permeates the fields of cancer treatment research and drug development. The apparently straightforward task of designing clinical trials that can clearly establish the beneficial impact of a new agent on a patient with cancer has become

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 Online links

## DATABASES

The following terms in this article are linked online to: **Cancer.gov**: [http://www.cancer.gov/cancer\\_information/breast\\_cancer|colon\\_cancer|ovarian\\_cancer|prostate\\_cancer|small-cell\\_lung\\_cancer](http://www.cancer.gov/cancer_information/breast_cancer|colon_cancer|ovarian_cancer|prostate_cancer|small-cell_lung_cancer)  
**LocusLink**: <http://www.ncbi.nih.gov/LocusLink/BRCA1|BRCA2|p53|PSA>

## FURTHER INFORMATION

**McGill Program in Cancer Genetics**:

[www.mcgill.ca/cancer/genetics](http://www.mcgill.ca/cancer/genetics)

**McGill Program in Cancer Prevention**:

[www.mcgill.ca/cancer/prev](http://www.mcgill.ca/cancer/prev)

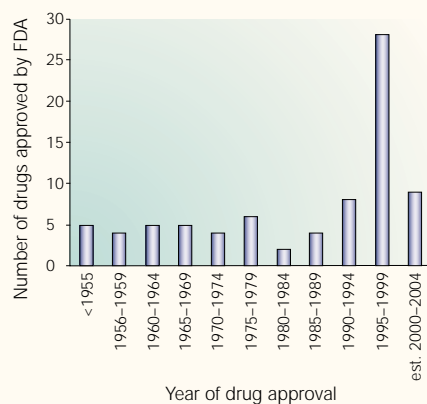
Access to this interactive links box is free online.

increasingly difficult. The problem lies in the fact that many of the new classes of agents are predicted to work only in small subpopulations of patients, affect tumours in an unconventional fashion and interact with other classical and novel agents in ways that we cannot yet predict. How can we resolve this clinical paradox and take full advantage of the opportunities for real progress that lie before us?

## The price of success

In the 1990s, there was a surge in the development and approval of new drugs for oncological indications. Thirty-six new agents were approved for the treatment of cancer and cancer-related indications in that decade — more than in the preceding 40 years (FIG. 1; and see **FDA approval statistics** in online links box). Similarly, the number of claims approved by the Food and Drug Administration (FDA) for the treatment of cancer indications during the 1990s exceeded the number granted during the preceding 40 years (FIG. 2; and see **FDA approval statistics** in online links box). Identification of exploitable molecular targets,

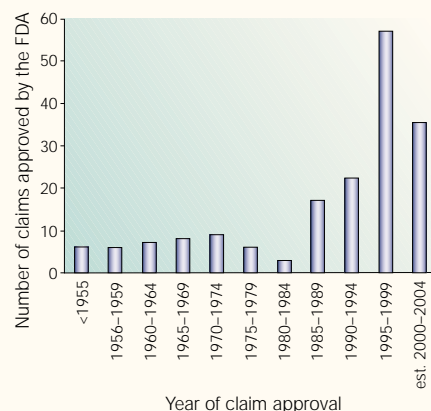
## PERSPECTIVES



**Figure 1 | Number of new drugs approved for oncological indications by the US Food and Drug Administration (FDA).** The number of new drugs approved for cancer clinical trials increased rapidly during the 1990s, and is projected to decline between 2000 and 2004. Data from <http://www.accessdata.fda.gov/scripts/cder/onctools/statistics.cfm>. est, estimated.

establishment of large-scale natural-product screening programmes, advances in rational drug design and synthesis, and refinement of high-throughput screening techniques contributed to this success. Novel therapeutics were designed to treat advanced **pancreatic cancer** (gemcitabine)<sup>2</sup>, progressive **colorectal cancer** (irinotecan)<sup>3-5</sup>, **non-small-cell lung cancer** (docetaxel)<sup>6</sup> and hormone-sensitive **breast cancer** (anastrozole, fulvestrant and letrozole)<sup>7-9</sup>.

Unfortunately, it seems that the pace of new agent development and approval is slowing — since 2000, only five new anticancer agents



**Figure 2 | Number of claims approved for oncological indications by the US Food and Drug Administration (FDA).** The number of claims approved by the FDA for treatment of cancer indications during the 1990s exceeded the number granted during the preceding 40 years. Data from <http://www.accessdata.fda.gov/scripts/cder/onctools/statistics.cfm>. est, estimated.

have been approved by the FDA for the treatment of 21 oncological indications<sup>2</sup>. When projected out over the 5-year period of 2000–2004, this represents a 68% reduction in new drug approvals and a 37% reduction in the number of claims approved for new oncological indications, compared to the preceding 5-year period of 1995–1999 (FIGS 1 and 2). Just at the time when new insights into the molecular and genetic basis of cancer present unprecedented opportunities for the development of therapeutic agents directed at novel, potentially crucial targets for cancer treatment, why are we experiencing a decline in new drug development and approval?

Defining ‘safety’ and ‘efficacy’ Survival provides the clearest, most unambiguous demonstration of clinical benefit that is meaningful to the patient. However, as more agents are approved for second- and even third-line treatment of common malignancies, the adherence to a survival end point for registration trials for front-line use of new agents becomes increasingly problematic. The crossover design of many studies — in which the investigational agent is made available to patients who are randomized to the control arm of the study following tumour progression — coupled with the availability of active second- and third-line therapies, combine to potentially obscure any survival advantage that might be achieved with the new agent. At present, there are 41 claims that have been approved by the FDA for adjuvant or first-line treatment of cancer and 53 claims approved for second-line, third-line or palliative indications (see **FDA approval statistics** in online links box).

For these reasons, several researchers have advocated for the use of ‘time-to-tumour progression’ (TTP) as a more accurate way to isolate the effect of the new agent, and remove the confounding effect that subsequent therapies could have on survival. For a number of years, the European drug regulatory authorities have used TTP as an acceptable end point for cytotoxic drug approval, whereas the US FDA has not. However, even TTP is not without its drawbacks, including the confounding effect of ‘lead-time bias’. Lead-time bias makes one agent seem to be better or worse than it really is, based simply on the timing of tumour re-evaluation and difficulties in defining how an improvement in TTP translates into clinical benefit.

To complicate matters further, there is no standardized method of incorporating toxicity and tolerability information into

decisions regarding new drug approval. Should, for example, a new agent that improves median survival time or TTP by a statistically significant 6-week margin be approved even if it is associated with substantial rates of treatment-induced morbidity or mortality? There are no easy answers to these questions, but it is disappointing that there has not been more extensive dialogue between cancer researchers, pharmaceutical companies and regulatory agencies to address these issues.

The ‘failure’ of targeted therapies Identification and characterization of several growth-factor signalling pathways that are crucial to the establishment, local progression and metastasis of tumours brought about a shift in our expectations for cancer treatment and clinical trials. Historically, most chemotherapeutic agents were targeted against molecules that were required for the maintenance of structural and genetic integrity of the cancer cell. By contrast, many of the agents that entered into clinical evaluation in the late 1990s were targeted against growth-factor receptors and signal-transduction pathways.

It was anticipated that this would have several effects in patients with cancer. First, it was believed that the antitumour effect of agents that targeted growth-factor signalling pathways would probably be manifested as tumour stasis (cytostatic effect) rather than tumour shrinkage (cytotoxic effect). Second, it was assumed that these agents would be so specific that their effects would be limited to cancer cells and spare normal cells. A third assumption was that these agents would be so effective that they would largely supplant older, non-specific cytotoxic agents. A corollary of this assumption was that, in situations in which cytotoxic therapy was of established value, inhibition of growth-factor signalling would prove to be complementary to the effects of the cytotoxic therapy.

With the single exception of imatinib (Gleevec), none of these predictions proved true when evaluated in clinical trials (TABLE 1). Tumour regressions were reported in clinical trials of several of these new agents, including epidermal growth-factor-receptor (EGFR)-targeted therapies<sup>10,11</sup>. Normal tissue toxicity was observed in trials involving matrix metalloproteinase (MMP) inhibitors — arthralgia developed in patients who were treated with marimastat and prinomastat, whereas thrombocytopenia developed in patients who were treated with tanomastat<sup>12</sup>. Despite pronounced effects in preclinical models,

angiogenesis inhibitors did not have discernable efficacy when administered as single agents in patients with advanced cancer<sup>13</sup>. And lastly, the idea that complementary mechanisms of activity would

translate into improved outcome when growth-factor inhibitors were integrated into established cytotoxic regimens has not been born out. In fact, targeted therapies have failed to improve survival in

nearly twenty-four Phase III clinical trials (TABLE 1). How could we have been so far off in our predictions? What changes are needed to help us avoid similar outcomes in the future?

Table 1 | Outcome of Phase III trials of targeted therapies

Agent	Control	Cancer	Clinical setting and tumour status	Effect of targeted therapy	References
<b>Matrix metalloproteinase inhibitors</b>					
Marimastat	Gemcitabine	Pancreatic	First-line therapy, locally advanced and metastatic	No survival benefit	26
Marimastat	Placebo	Gastric	Non-progressive following surgery or first-line therapy, locally advanced and metastatic	No survival benefit	17
Marimastat	Placebo	Glioblastoma	Locally advanced, unresectable cancer	No survival benefit	27
Marimastat	Placebo	Small-cell lung	Limited or extensive stage, following response to first-line therapy	No survival benefit	28
Marimastat + Gemcitabine	Gemcitabine	Pancreatic	First-line therapy, locally advanced and metastatic	No survival benefit	29
Marimastat + Carboplatin	Carboplatin	Ovarian	Locally advanced and metastatic	No enhancement of response rate	27
Marimastat	Placebo	Breast	Non-progressive following first-line chemotherapy for metastatic disease	No survival benefit	30
Marimastat	Placebo	Colorectal	Unresectable liver metastases	No survival benefit	31
Marimastat	Placebo	Glioblastoma	Unresectable multiforme	No survival benefit	32
Prinomastat + Gemcitabine/ Cisplatin	Gemcitabine/ Cisplatin	Non-small-cell lung	Unresectable locally advanced and metastatic	No survival benefit	33
Prinomastat + Carboplatin/ Paclitaxel	Carboplatin/ Paclitaxel	Non-small-cell lung	Unresectable locally advanced and metastatic	No survival benefit	34
Prinomastat + Mitoxantrone/ Prednisone	Mitoxantrone/ Prednisone	Prostate	Metastatic, hormone refractory	No survival benefit	35
Tanomastat	Gemcitabine	Pancreatic	First-line, locally advanced and metastatic	Worse survival	36
Tanomastat	Placebo	Small-cell lung	Limited or extensive stage, following response to first-line therapy	Worse survival	37
BMS-275291 + Carboplatin/ Paclitaxel	Carboplatin/ Paclitaxel	Non-small-cell lung	First-line, locally advanced and metastatic	Accrual complete, results pending	
Neovastat	Placebo	Renal cell	Locally advanced and metastatic	Accrual complete, results pending	
<b>Epidermal growth-factor receptor inhibitors</b>					
Gefitinib + Carboplatin/ Paclitaxel	Carboplatin/ Paclitaxel	Non-small cell lung	First-line, locally advanced and metastatic	No survival benefit	38
Gefitinib + Cisplatin/ Gemcitabine	Cisplatin/ Gemcitabine	Non-small-cell lung	First-line, locally advanced and metastatic	No survival benefit	39
Erlotinib + Carboplatin/ Paclitaxel	Carboplatin/ Paclitaxel	Non-small-cell lung	First-line, locally advanced and metastatic	Accrual complete, results pending	
<b>Farnesyltransferase inhibitors</b>					
R115777 + Gemcitabine	Gemcitabine	Pancreatic	Locally advanced and metastatic	No survival benefit	40
<b>Angiogenesis inhibitors</b>					
Bevacizumab + Capecitabine	Capecitabine	Breast	Second- or third-line metastatic	No survival benefit	41
Semaxanib (SU5416) + Irinotecan/ 5-Fluorouracil/ Leucovorin	Irinotecan/ 5-Fluorouracil/ Leucovorin	Colorectal	First-line metastatic	No survival benefit	42

The patient selection paradox. Although it is tempting to attribute these disappointing results to inactive drugs brought forward on the basis of faulty preclinical models, it is important to acknowledge other factors that are likely to have contributed to the apparent clinical 'failure' of these agents.

**Target specificity.** Targeted therapies should work only when the target is present. For agents such as tamoxifen and trastuzumab, expression of the oestrogen or **ERBB2** (also known as HER2/neu) receptor, respectively, is required to achieve antitumour effects. However, this same relationship does not seem to hold true for all 'molecularly targeted' agents — probably due to an incomplete understanding of the non-targeted biological processes that are affected by these agents. There is a growing body of literature that suggests that EGFR-targeted therapies have similar effects in cells or tumours with high, intermediate or low levels of EGFR expression<sup>10,14,15</sup>. Furthermore, the potentiation of antitumour effects when EGFR inhibitors are combined with classical cytotoxic agents could be mediated by pathways that function completely independently of EGFR<sup>16</sup>. Future studies are required to address whether tumour expression of activated EGFR is a necessary prerequisite for benefit from these agents, and whether this relationship is the same when EGFR-directed agents are used alone, or in combination with other therapies. In addition, these studies will also need to evaluate non-targeted pathways to determine their contribution to the observed antitumour effect. DNA expression array and proteomic analysis will facilitate this kind of exploratory investigation.

**Disease stage.** MMPs are key enzymes involved in local tumour growth, tissue invasion, angiogenesis and the establishment of tumour metastases<sup>12</sup>. Most preclinical studies have focused on the role of MMPs in the early stages of cancer progression and metastases, in which MMP inhibition seems to have its greatest effect. Unfortunately, clinical trials of MMP inhibitors were conducted almost uniformly in patients with advanced, metastatic disease, and all have failed to show any beneficial effect on patients<sup>12</sup> (TABLE 1). It is possible that these same trials — conducted in patients with earlier stages of disease — could have had different outcomes. Unfortunately, failure to show antitumour activity in the advanced disease setting, combined with regulatory and economic disincentives that discourage drug development in early-stage patients, have resulted in a number of sponsors abandoning

further clinical development of MMP inhibitors. Although provocative results have been observed in some subsets of patients treated with MMPIs<sup>17</sup>, it remains to be seen whether any new, large-scale clinical trials will be undertaken to evaluate these leads in a prospective, more definitive fashion.

**Molecular characterization of host and tumour.** Technologies now exist that allow us to characterize tumours in great detail. They range from simple immunohistochemistry of protein expression, to pharmacogenetic testing to determine the expression levels of genes that are associated with antitumour effects and/or metabolism, to more sophisticated techniques such as cDNA microarray or proteomic analysis, which can identify molecular fingerprints associated with tolerability or response to therapy<sup>18,19</sup>. The common thread in all of these approaches is that they use patient samples to provide information about the effects of a new drug. Increased use of these resources could be the single most significant improvement that we can make in the design of clinical trials of new anticancer agents. The ultimate goal would be the development of accurate and reproducible predictive models, based on patient and tumour characteristics.

The information generated by these types of studies could be of as much, if not more benefit, in understanding the reasons behind the failure of a new agent in a clinical trial as it would be in refining our understanding and application of agents that already show clinical efficacy. Rather than impeding the development of a new drug, careful evaluation of patient samples could actually reduce trial size and cost, and speed development of new therapies<sup>20</sup>. Rather than limiting the projected market for a new drug, molecular characterization could actually increase the range of indications it can be used to treat. For example, although imatinib was originally designed to inhibit **ABL** tyrosine kinase in patients with chronic myelogenous leukaemia, it was also found to inhibit the tyrosine kinase activities of **platelet-derived growth factor** and **c-KIT**. As a result, imatinib is the first effective treatment for patients with gastrointestinal stromal tumours (GISTs)<sup>21,22</sup>.

**Patient cohorts.** Eligibility for most therapeutic trials is based on clinical characteristics such as tumour type, stage of disease and number of prior therapies. Whereas these factors have some degree of influence on drug activity, molecular characterization of the host and tumour can identify those patients that are most likely to benefit from the therapy. This approach has already been

applied to a limited degree and, in addition to the examples cited above, has resulted in the identification of correlations between enzyme expression levels in the tumour and response to 5-fluorouracil in patients with gastrointestinal malignancies<sup>19,23</sup>. Analysis of expression levels of detoxifying enzymes in patients with acute lymphoblastic leukaemia can be used to determine which will respond best to mercaptopurine therapy<sup>24</sup>.

Applying this strategy in designing new clinical trials for anticancer agents would result in smaller sample size, increased odds for patient improvement and improve the discovery of drugs that have important antitumour activity. This is not a hypothetical situation — allelic loss of chromosome 1p in patients with anaplastic oligodendroglioma, which is associated with durable response to chemotherapy and improved survival in recurrent tumours than in newly diagnosed tumours<sup>25</sup>. Evaluation of a new agent in an unselected group of patients with newly diagnosed anaplastic oligodendrogliomas might therefore result in rejection of an agent that could be highly effective in the patients that carry this specific genetic deletion<sup>20</sup>.

Obstacles to genetic profiling. Breast cancer patients have benefited for decades from characterization of hormone-receptor expression levels in tumours, and, more recently, of **ERBB2** expression levels, in determining their suitability for treatment with therapeutics targeted against these receptors. Unfortunately, misperceptions surrounding genetic testing have prevented us from reaping the full benefit of detailed characterization of normal and tumour tissue using newer technologies, such as cDNA microarray analysis. What is even more unfortunate is that these misperceptions have been promulgated by government agencies as well as local institutional review boards under the guise of protecting patient privacy — up to and including patients who are rapidly approaching the end of life or have died of their disease. In fact, adequate measures to protect patient privacy are in place and function very effectively — we are not aware of a single case of genetic discrimination that has emerged as a result of information obtained in a cancer clinical trial. Most cancer patients are, in our experience, willing and even eager to have their tumours and normal tissue evaluated for genetic characteristics that could be associated with response and outcome. Removing regulatory barriers to tissue collection and allowing this data to be correlated with clinical outcome

Table 2 | Sources of support and oversight for cancer drug studies

Agency	Department or division	Web site	Responsibilities
National Cancer Institute (NCI)	Cancer Therapy Evaluation Program	ctep.cancer.gov	Reviews, approves and monitors clinical trials using NCI-supplied investigational drugs
	Developmental Therapeutics Program	ntp.nci.nih.gov	Reviews, approves and provides assistance in investigational drug screening formulation, production and toxicological assessment
	Office of Extramural Research	grants1.nih.gov	Reviews, approves and funds clinical and translational research studies
Food and Drug Administration	Center for Drug Evaluation and Research	www.fda.gov/cder	Reviews investigational new drug (IND) applications and allows human testing to proceed; reviews new drug applications (NDAs) and approves new drugs for specific indications
	Office of Orphan Products Development	www.fda.gov/orphan/	Reviews, approves and funds grants for clinical trials to evaluate investigational drugs for limited populations and/or rare diseases
Office for Human – Research Protections		ohrp.osophs.dhhs.gov/	Establishes policies and procedures for protecting the rights and safety of all research involving human subjects; certifies and oversees all IRBs (see below)
Universities and Medical Centers	Institutional Review Board or Independent Ethics Committee	Various	Reviews, approves and monitors all clinical and translational research at an institution to ensure adherence to federal policies protecting the rights of human research subjects
NCI-Designated Cancer Centers	Scientific Review Committee		Reviews, approves and monitors all clinical and translational research performed at that centre for scientific merit and integrity

— especially on archival samples, to answer questions that were not predictable at the outset of the trial — will improve our understanding of drug responses.

#### Coordinating support

In cases of industry-sponsored studies, pre-clinical research, clinical development and post-marketing clinical trials are often managed by entirely different departments within a company — each of which is focused on its own area of responsibility. This is unfortunate, as laboratory correlative studies become an increasingly integral part of all phases of clinical trials involving an investigational new agent. The National Cancer Institute (NCI) has done an excellent job of recognizing the need for better coordination of laboratory and clinical studies by establishing a Clinical Trials Study Section to fund this type of coordinated research. In FY2002, the NCI's Clinical Trials Study Section funded 19 investigator-initiated R01 and R21 grants with a total of approximately US \$7 million.

Although an important accomplishment, the execution of this concept has run into problems, due to the lengthy grant review and funding process that often results in funding that is 'out of sync' with the clinical trial — often, the trial was already initiated, or sometimes completed, before funding could begin. In the present climate, it makes little sense for the clinical trial to be reviewed and approved by one review panel and the laboratory correlative studies by another. The problem has been compounded when the therapeutic agent has not yet been available, and a third proposal had to be written and independently reviewed for production and testing of the drug.

Improved mechanisms are therefore needed to expedite the review and funding process for clinical translational research and coordinate the initiation of the clinical trial with the initiation of research grant support. Besides simply speeding up the process, another option would be to provide cancer centres with flexible blocks of funding that

could be rapidly allocated to such translational research projects, based on local peer review at that institution, with periodic federal programmatic review. Supplemental funding made available for clinical-translational research studies within Specialized Programmes of Research Excellence (SPORE) is a step in the right direction.

Through Collaborative Research and Development Agreements (CRADAs) and Clinical Trial Agreements (CTAs), the NCI has provided access to investigational new drugs from industry. In return, the Cancer Therapy and Evaluation Program (CTEP) of NCI works with independent investigators to generate scientifically rigorous clinical and laboratory-clinical translational trials to help evaluate drugs. This has been a very successful programme — especially when the trials involved testing the investigational drug as a single agent or in combination with a commercially available agent. The process, however, does not work as well when the proposed trial involves the use of multiple investigational agents from different sponsors — even if CRADAs or CTAs are in place with each individual sponsor. Although this might seem to be a relatively uncommon situation, clinical trials involving immunotherapy, in which one or more adjuvants must be administered to stimulate the immune response to a tumour vaccine, encounter this problem with distressing regularity.

Although it is hoped that the NCI could be an effective mediator and resolve concerns over proprietary information, this has proven to be more difficult than anticipated. As a result, the development of very promising immunotherapeutic regimens has been slowed or, in some cases, discontinued altogether. Resolution of this problem will not be easy. Accommodations will have to be made by all parties involved. Sponsors must be willing to assume the risk of associating their compound with another agent that might be ineffective or toxic, accept a certain degree of loss of confidentiality and recognize that they might have little or no control over decisions to discontinue the development of a partner compound. These concerns could be effectively addressed, and even overcome, if this risk was shared. Regulatory agencies could make accommodations to focus primarily on data from regimens taken forward for registration rather than on regimens that had been tested and abandoned. Research and funding agencies could provide assurance that a potentially effective component of a combination regimen would not be abandoned, even if it lost support from the sponsor. Fortunately,

progress is being made and CTEP has obtained permission from ten pharmaceutical companies to use their investigational new drugs in combination with those from another sponsor.

Another obstacle to the efficient conduct of translational research is an increasingly burdensome network of federally mandated agencies involved in the oversight of clinical research. For example, an NCI-funded, investigator-initiated clinical trial involving an experimental drug must obtain separate approval from at least five different sources (TABLE 2). Although each one of these was created with a specific purpose in mind — for example, protection of human subjects involved in research or the provision of financial support of meritorious research projects — their domains have expanded to the point that each one overlaps with the other. Directives issued by one might — and often do — conflict with another. Although a single authority responsible for both the oversight and support of clinical research might not be possible, better appreciation of the complexity of this system and its adverse impact on translational research should prompt closer coordination of efforts.

#### Conclusions

This is an extraordinary time in cancer treatment research. There have never been greater opportunities to translate new insights in cancer biology into therapeutic advances. Yet few effective new treatments have emerged from these targeted therapies. Although part of this can be attributed to limitations in our knowledge of molecular and systems biology of cancer, many of the most daunting obstacles are of our own making. These problems include application of new agents in inappropriate clinical settings, in unselected patients, and without a clear understanding of the role of the putative target in mediating the antitumor effect. Collection of tissue from patients at time points that correspond with maximal pharmacodynamic or clinical effect will provide the best opportunity to gain insight into the reasons agents work or, more commonly, don't work.

The scientific, ethical, financial and administrative obstacles to this are formidable, but not insurmountable. What it will require is a clearly articulated, comprehensive policy that is designed to coordinate basic and clinical cancer treatment research. Development of such a policy would need to involve government agencies, including those that are involved with cancer research funding, drug approval and human research

protection, non-governmental experts in legal and ethical issues surrounding human research, the pharmaceutical industry, basic and clinical cancer researchers, and cancer patient representatives. Such a commission would need to carry sufficient authority to ensure that recommendations that emerge from this panel would have a reasonable likelihood of influencing policy and practice among all stakeholders. Until such an effort is undertaken, we will not be able to reap the full rewards of translating the significant advances that have been made in the laboratory to improved therapies for our patients.

**Mace L. Rothenberg, David P. Carbone and David H. Johnson are at the Vanderbilt-Ingram Cancer Center, 777 Preston Research Building, Nashville, Tennessee 37232-6307, USA. Correspondence to M.L.R. e-mail: mace.rothenberg@vanderbilt.edu**

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 Online links

## DATABASES

The following terms in this article are linked online to:

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**LocusLink:** <http://www.ncbi.nlm.nih.gov/LocusLink/>  
ABL | EGFR | ERBB2 | KIT | platelet-derived growth factor

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