Special Lecture

There Are No Bad Anticancer Agents, Only Bad Clinical Trial Designs—Twenty-first Richard and Hinda Rosenthal Foundation Award Lecture¹

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Abstract

Unfortunately, the vast majority (90%) of new anticancer agents designed in the laboratory never make it into routine clinical use. The hypothesis of this lecture is that many new agents fail in the clinic because the appropriate clinical trial(s) that could exploit the attributes of the new agent are not performed. An appreciation that both bench and clinical investigations are difficult endeavors should aid in improving clinical trial designs and give the best chance for new agents to be added to our therapeutic armamentarium.

Introduction

A very common story is that a basic scientist works for years and years to develop a new agent with a unique mechanism of action to treat tumor cells; but that new agent never makes it into clinical trials, or if it does, it almost always fails to make an impact on the disease.

The hypothesis of today’s lecture is that many new agents fail because the appropriate clinical trials to exploit the attributes of the new agent have not been performed. This is because of a basic uncoupling or disconnection between the bench scientist, who has worked long and hard on his or her hypothesis but who may not understand the difficulties of and creativity required for clinical trials, and the clinical scientist, who may not understand how difficult the basic discovery has been and how careful one must be before abandoning the new concept or new agent from the bench.

The magnitude of the disconnection between the bench scientist and the bedside clinician cannot be assessed solely by how many new agents don’t make it into general use in the oncology community. The percentage of agents, however, that do go to clinical trial and are adopted for clinical use is disappointingly low. Fig. 1 details the number of new agents brought into clinical trials from 1975 to 1994 and the number of those agents eventually approved for clinical use. Overall, there were 280 new agents brought into Phase 1 (dose-finding) clinical trials in patients. Only 29 of them (10%) were eventually approved for use in patients.

There are three main reasons that emerge in examining why the other 90% of new agents don’t make it into routine use. These include: (a) the toxicities of the agent were too great; (b) there was a lack of efficacy; and (c) no attention was paid to the mechanism of action of the compound when the clinical trials were designed and conducted.

In the discussion below, we will explore all three of these major reasons why new agents don’t make it into general clinical use. In addition, examples will be given of how to bypass these problems so that a greater percentage of agents brought into clinical trials will actually make it to general use.

Why Compounds Don’t Make It—Toxicities

Table 1 gives examples of severe toxicities that halted the development of several new anticancer agents. These toxicities basically stopped the development of the new agents in their tracks, in most instances, with a complete suspension of their clinical trials. However, because of the clinical activity of the agent that had been seen early on, e.g., responses to the agent paclitaxel in patients with a variety of malignancies, clinicians persisted in trying to find a way to circumvent the toxicity of paclitaxel.

The thesis is that one can circumvent toxicities of the new agent if the drug has clinical antitumor activity. Table 1 also details the methods that were used to circumvent toxicities for each of the agents.

The observation of our drug development team in San Antonio, TX, is that in dealing with the phenomenon of dose-limiting toxicities, stopping the drug and then the clinician finding a way to circumvent those toxicities, we have devised the life cycle of a new anticancer drug as shown in Fig. 2 (1). As can be seen in the figure, a drug is discovered and brought into clinical testing. Almost inevitably, a crisis in the development of the agent occurs in which either a severe toxicity is noted with the agent or no antitumor activity is noted with the agent. The agent then undergoes programmed drug death, which we like to call “pharmacoptosis.” Fortunately, methods can sometimes be developed to circumvent the toxicity of the new agent, and the agent then emerges from the state of pharmacoptosis and is rediscovered or reborn. As is noted in Table 1, this ability to reverse pharmacoptosis is a very common phenomenon.

An Example of Recovery from Pharmacoptosis Because of Toxicity—Mitoguazone. A recent example of recovery from pharmacoptosis is the redevelopment of mitoguazone. Mitoguazone was synthesized in 1898 by Thiele et al. (2). It also has the names MGBG, methylglyoxal bis(guanilhydrazone),

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methyl-GAG, and NSC-32946. The structure of mitoguazone is shown in Fig. 3. One of the intriguing aspects of mitoguazone is that it has a unique mechanism of action as an inhibitor of S-adenosylmethionine decarboxylase (3, 4). Some investigators have believed that it is also a mitochondrial interactive agent (5). It should be remembered that compounds with new and unique mechanisms of action have a better chance for non-cross-resistance with the antineoplastics already in clinical use.

Mitoguazone was first given to patients in the early 1960s, usually on a chronic (e.g., daily × 30 days) schedule (6, 7). Antitumor activity was noted in patients with leukemia and lymphoma (6–8). However, the major toxicity of mucositis (and other severe toxicities) caused all clinical trials with the agent to be stopped. Therefore, despite clinical activity, all clinical trials with mitoguazone were discontinued (the drug underwent pharmacoptosis).

The key to the rebirth of mitoguazone was new scientific knowledge from pharmacokinetic studies performed in the late 1970s and early 1980s (and reconfirmed recently) that mitoguazone had an extremely long plasma half-life of >5 days (9–11). With this new understanding, it was clear that the schedule of daily administration of mitoguazone could have been responsible for the side-effect profile (severe mucositis and myelosuppression secondary to toxicity on rapidly turning over cells in the mucous membranes). Based on this new knowledge, weekly and every other week schedules of administration were devised (12, 13). Using these dosing schedules, mucositis became an unusual side effect with the agent, and antitumor activity was noted in patients with Hodgkin's disease, non-Hodgkin's lymphoma, head and neck cancer, endometrial cancer, prostate cancer, and esophageal cancer (12–16). Despite that activity, there was still little interest in mitoguazone until the emergence of non-Hodgkin's lymphoma in patients with AIDS.

AIDS-related non-Hodgkin's lymphoma was first reported in 1982. It is usually a disease with aggressive histologies (large-cell immunoblastic and small-cell non-cleaved), has a high incidence of central nervous system involvement, accounts for 12–16% of all AIDS-related deaths, and there is no standard treatment for patients who have progressed on first-line therapy (17, 18). The average survival for patients who have progressed on first-line therapy is 63 days (19). Polyamines are elevated in patients with lymphoma 4.0–5.3-fold compared with normal volunteers (20, 21); therefore, an agent like mitoguazone, which

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**Table 1** Agents in which severe toxicities halted their development and methods used to circumvent those toxicities (and reverse pharmacoptosis)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Toxicity</th>
<th>Method to circumvent toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin/Daunomycin</td>
<td>Congestive heart failure, neurotoxicity</td>
<td>Dose limitation, dexrazoxane</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Neurotoxicity</td>
<td>Dose limitation</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Renal toxicity, ototoxicity, emesis</td>
<td>Hydration, antiemetics</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Anaphylactic shock</td>
<td>Steroids and other premedication</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Fluid retention</td>
<td>Steroids</td>
</tr>
<tr>
<td>CPT-11</td>
<td>Diarrhea</td>
<td>Antidiarrheals</td>
</tr>
<tr>
<td>Fludarabine phosphate</td>
<td>Blindness</td>
<td>Dose limitation</td>
</tr>
</tbody>
</table>

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Fig. 1 Total number of different agents in Phase I trials per year (■), and number of those agents eventually approved (□).
inhibits the synthesis of polyamines, was an attractive agent to try against the disease. In addition, mitoguazone was interesting to try because: (a) the agent already had documented activity in patients with non-AIDS-related non-Hodgkin’s lymphoma (12, 13); (b) the agent causes minimal myelosuppression and other toxicities on the new schedule (12, 13); and (c) mitoguazone crosses the blood brain barrier, as evidenced by high concentrations in brain tumors (22).

Recently, Levine et al. (23) reported the results of a Phase II trial of mitoguazone given at a dose of 600 mg/m² on days 1, 8, and then every 2 weeks, in patients with AIDS-related lymphoma. In that study, she treated 35 patients with AIDS-related lymphoma, all of whom had failed on prior regimen and 17 of whom had failed 2–6 prior regimens. Twenty-four (80%) of the patients had a CD4 count of <100/dl. There were three patients who attained a complete response, plus three who attained a partial response for an overall response rate of 6 of 35 or 17% (95% confidence interval, 4.7–29.6%; Ref. 23). A second study in a similar population has confirmed that response rate (24).

The toxicities associated with the use of mitoguazone on the days 1, 8, and then every 2 weeks schedule were minimal, with only an 8% incidence of grades 3 and 4 mucositis. The lesson learned from the further development of mitoguazone is that new knowledge regarding the basis for toxicity with a compound (in this case, its clinical pharmacology) can lead to a different way of using that compound that avoids the toxicities and allows its antitumor activities to be exploited.

After the presentation of this lectureship, the Phase II data on the activity of mitoguazone in patients with AIDS-related non-Hodgkin’s lymphoma, presented to the Food and Drug Administration Advisory Committee, and the Committee recommended against its approval based only on Phase II data. A randomized Phase III trial to further support its efficacy was recommended by the Food and Drug Administration, and plans are being made to conduct that study. The drug has not yet emerged from pharmacoptosis.

Why Compounds Don’t Make It—Lack of Efficacy
A second reason new agents don’t make it into routine clinical use is no efficacy (or a supposed lack of efficacy). Many investigators would argue that the reason we have so many compounds that make it into clinical trials that have poor to no activity in the clinic is the poor (nonpredictive) preclinical systems we have for selecting those agents (25, 26). Our thesis in San Antonio is that in our clinical trial designs, we are asking the drug to do more clinically than it did preclinically. For example, take the hypothetical new drug “difungomuctane” (not a real drug), which inhibits tumor growth to the degree noted in Fig. 4.

As can be seen in Fig. 4, difungomuctane clearly causes tumor growth delay. However, can we really expect this drug to shrink tumors in patients when all it does in animal systems is slow down tumor growth? Again, the theory is that with our current clinical trial designs, we are asking our drugs to do more clinically than they do in preclinical systems. Perhaps new clinical trial end points besides shrinkage of patients’ tumors are needed to assess the antitumor activity of some new agents.

An Example of Recovery from Pharmacoptosis Because of Supposed Lack of Antitumor Activity. Gemcitabine (LY 188011, difluorodeoxycytidine; dFdC) is a nucleoside with the structure shown in Fig. 5. The compound was synthesized by Hertel et al. (27) with tumor growth delay documented in several animal models and human tumor xenograft models including X5563 melanoma; 6C3HED lymphosarcoma; L1210, P388, and P1543J leukemia; and the CX-1 and LX-1 xenografts (28–30). In addition, the agent had a broad spectrum of antitumor activity against human tumor colony-forming units taken directly from patients and growing in soft agar (31). Activity was particularly impressive against breast, non-small cell lung, ovarian, and pancreatic cancer colony-forming units.

Phase I trials were conducted with gemcitabine beginning
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in 1987 (32, 33). The daily \( \times 5 \), 30-min infusion schedule gave a maximally tolerated dose of only 9 mg/m\(^2\), with hypertension and flu-like symptoms being the dose-limiting toxicities. On the every 2 weeks schedule, over 0.5–4 h, the maximally tolerated dose was 3600 mg/m\(^2\). Dose-limiting toxicities included neutropenia and flu-like symptoms. In that study, we noted one patient with pancreatic cancer with clinical improvements including less pain, an improved performance status, and weight gain. Based on that observation as well as observations from other groups, a Phase II trial of gemcitabine was conducted by Casper et al. (34, 35). In that study, 43 patients with advanced pancreatic cancer with no prior chemotherapy received doses of gemcitabine ranging from 800-1250 mg/m\(^2\) weekly \( \times 3 \) repeated every 28 days. Five partial responses were noted for an overall response rate of 13%. Toxicities were mild. What was striking was that, despite the overall low incidence of partial response (only 13%), there was a far greater percentage of patients who reported improvements in their pancreatic cancer-related symptoms, i.e., pain, weakness, and weight loss. Because virtually no chemotherapy has been shown to impact the symptoms of pancreatic cancer, it was decided to design a clinical trial with gemcitabine to determine, in a controlled setting, whether that agent decreased the symptoms associated with advanced pancreatic cancer. This thinking was a departure from usual oncology clinical trial designs, where typical end points are either tumor shrinkage (complete or partial responses) or survival. However, in other areas of drug development, other end points are always used in clinical trials. For example, the end point for a clinical trial for a new antiarrhythmic agent is control of arrhythmias, not survival. The end point for the clinical trials of a new antihypertensive is control of blood pressure, not survival. New end points in clinical trials in patients with advanced cancer may also be in order. One of those end points could be whether the new therapy improves the

tumor-induced problems that bother the patient. In the case of pancreatic cancer, the things that bother the patient include pain, weakness, and a declining performance status and weight loss (36, 37). If a new treatment could improve those symptoms for a patient, we postulated that the new treatment would give them clinical benefit and should be made available to them.

To determine whether gemcitabine gave clinical benefit to patients with advanced pancreatic cancer, the clinical trial outlined in Fig. 6 was designed. As can be seen in that figure, to be eligible for the study, patients had to have advanced pancreatic cancer which was symptomatic (e.g., patients with pain of \( \geq 20 \) on the Memorial Pain Assessment Card (38); patients required more than 10 mg of morphine sulfate or equivalent to control their pain; and patients had to have a Karnofsky Performance Status of \( \geq 50 \) but \( \leq 80 \)). Patients were randomized to receive either weekly treatment with 1000 mg/m\(^2\) of gemcitabine or weekly treatment with 600 mg/m\(^2\) of 5-fluorouracil. The study was single blinded, e.g., the patients did not know which of the two agents they were receiving. The end points of the study included: (a) clinical benefit (improvement in pain, performance status, or weight gain measured with a rigorous algorithm using the Memorial Pain Assessment Card scored by the patient), analgesic consumption recorded by the patient, and performance status and weight measured by the research nurse (39); (b) response rate (conventional partial or complete responses; Ref. 40); (c) TTP\(^4\) (which should correspond to the end point of tumor growth delay noted with gemcitabine in animals); (d) overall survival; and (e) 1-year survival (to allow detection of the minor percentage of patients whose tumors were sensitive just like in a human tumor cloning assay), which corresponds to the tail of the survival curve.

As reported recently, the study included 126 patients (63 per arm; Refs. 41 and 42). Table 2 summarizes the findings. It is noteworthy that the response rates for both arms were low. Pancreatic cancer is a difficult disease to evaluate because of the effects of prior surgery or prior radiation therapy to the tumor bed and pancreatitis/phlegmon associated with the tumors.

Twenty-four % of the patients who received gemcitabine

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\(^4\) The abbreviations used are: TTP, time to tumor progression; DFMO, difluoromethylornithine (eflornithine); ODC, ornithine decarboxylase.

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\[ \text{Structure of gemcitabine.} \]

\[ \text{Fig. 5} \]

\[ \text{Fig. 6 Design for definitive trial of gemcitabine in patients with advanced symptomatic pancreatic cancer.} \]
Table 2  Summary of results of randomized trial of gemcitabine versus 5-fluorouracil (5-FU) for treatment of patients with advanced pancreatic cancer∗

<table>
<thead>
<tr>
<th>Parameter</th>
<th>5-FU arm</th>
<th>Gemcitabine arm</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical benefit</td>
<td>4.8%</td>
<td>23.8%</td>
<td>0.0022</td>
</tr>
<tr>
<td>Response rate</td>
<td>0%</td>
<td>5.4%</td>
<td>0.077</td>
</tr>
<tr>
<td>TTP (mo)</td>
<td>1.0</td>
<td>3.2</td>
<td>0.0002</td>
</tr>
<tr>
<td>Survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (mo)</td>
<td>4.41</td>
<td>5.65</td>
<td>0.0025</td>
</tr>
<tr>
<td>One year</td>
<td>2%</td>
<td>18%</td>
<td></td>
</tr>
</tbody>
</table>

∗ Burris et al. (42).

had clinical benefit versus 5% of the patients who received 5-fluorouracil (P = 0.0022). This has now been reported in other trials (43, 44). The TTP (which corresponds best to the tumor growth delay in animals) was also significantly better. Of additional note and importance is that median survival and 1-year survival were significantly better for the gemcitabine-treated patients. This finding helped validate the use of our clinical benefit parameter as a clinically meaningful end point. Also importantly, the side-effects profile of gemcitabine was not significantly different from the profile of 5-fluorouracil, except that more transfusions were required in the patients receiving gemcitabine, and neutropenia was also more common. However, the gemcitabine patients also lived longer to obtain those transfusions or to develop neutropenia.

The gemcitabine example is provided to document that if a new agent produces tumor growth delay in a preclinical model, we should strive to use a tumor growth delay end point (e.g., TTP) in our clinical trials. Above all, we should strive to match our clinical trial end points to what has been found in preclinical models. Only then will there be a true and fair clinical test for that new agent. This will be particularly important as our new molecular biology gives us new agents that are growth-modulating agents rather than cytotoxic agents that shrink established tumors (see below).

Why Compounds Don’t Make It—Attention Is Not Paid to the Mechanisms of Action of the Compound

When attention is not paid to the mechanism of action of a new compound, our clinical trials often do not exploit that mechanism of action, which usually leads to failure of the compound in the clinic. As noted in Fig. 7, I refer to this as “preclinical-clinical uncoupling.” Table 3 gives some examples of preclinical-clinical uncoupling. As can be seen in that table, regardless of the mechanism of action of the agent, the only parameter we have used to determine whether to continue development of a new agent has been to assess whether the compound causes complete tumor shrinkage (100% disappearance of the tumor lasting at least 1 month) or a partial response (≥50% disappearance of tumor lasting at least 1 month). This nearly total neglect of the mechanism of action probably has led to discontinuing the development of many new agents that, had their mechanism of action been remembered and our trials designed to measure that mechanism, may have been successful in the clinic.

An Example of an Agent Recovering from Pharmacoposis Because of Attention Paid to Its Mechanism of Action.

DFMO has the structure shown in Fig. 8. The compound has a unique mechanism of action, i.e., the irreversible inhibition of ODC (45, 46). ODC is becoming a more interesting target in both the areas of cancer treatment and in cancer etiology and, hence, in cancer prevention. More specifically, ODC has been found to be up-regulated in the tissues of several premalignant conditions, including cervical intraepithelial neoplasia (47), colon polyps (48), and others (49). Manni et al. (50) have found that ODC is up-regulated in patient breast cancer tissue, and elevation of the expression of ODC in that tissue is of greater significance for a poor prognosis than is the estrogen receptor status or the number of positive lymph nodes. Finally, of great interest, is that Auvinen et al. (51) have reported that ODC is an oncogene. Transfection of the ODC gene into NIH 3T3 cells causes transformation of the cells.

As noted above, DFMO is an irreversible inhibitor of ODC. DFMO blocks the promotion step of carcinogenesis in several animal models including breast, colon, bladder, skin, and prostate models (52–55). Unfortunately, the initial clinical trials with DFMO developed the agent as a standard anticancer agent with escalation to the maximally tolerated dose of the agent. Toxicities noted with doses of ≥20 g/m2/day of DFMO included thrombocytopenia, nausea and vomiting, leukopenia, anemia, diarrhea, high frequency hearing loss, and in some cases, metabolic acidosis (56, 57). After those studies, DFMO was abandoned (underwent pharmacoposis) by most investigators.

A breakthrough in the use of DFMO was a study by Love et al. (58) who performed a clinical trial to attempt to exploit the mechanism of action of DFMO, the inhibition of ornithine decarboxylase. They conducted a study to determine the smallest dose of DFMO that could be used to inhibit ornithine decarboxylase by carefully performing skin biopsies on the patients. They found that a dose of 0.5 g/m2/day (one-twentieth the daily dose used in prior cytotoxic approach studies) inhibited ornithine decarboxylase. Also, importantly, they noted that no toxicity was seen at that dose level. This finding fostered additional clinical trials because DFMO could now be used as a chemoprevention agent.

The field of chemoprevention has changed substantially over the past few years because there are now histological changes that are regarded as premalignant. These premalignant changes include cervical intraepithelial neoplasia (CIN III), actinic keratosis, colon adenoma, ductal carcinoma in situ of the breast, previously resected superficial bladder cancer, atypical squamous metaplasia/dysplasia in the lung, oral dysplastic leukoplakia, and prostatic intraepithelial neoplasia. The goal in chemoprevention now is to reverse those premalignant changes.
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To date, three clinical trials have correctly used low doses of DFMO to inhibit ODC. Mitchell et al. (47) have recently published their work demonstrating that DFMO could substantially reduce (in 52% of patients) cervical intraepithelial neoplasia (CIN-III, a substantial risk factor for the development of cervical cancer) after only one month of use. Meyskens et al. (60) have clearly documented that low doses of DFMO can suppress polyamine content in colorectal biopsy specimens as preparation for their randomized trial of a nonsteroidal, anti-inflammatory agent plus DFMO versus the nonsteroidal agent alone in patients with a history of recurrent colorectal polyps. The end point for this study will be the number of polyps that recur per unit of time.

Last, but not least, is a trial published by Alberts et al. (61), who randomized 44 patients with actinic keratoses (a premalignant skin condition) to receive either DFMO cream or a placebo cream. This randomized, double-blinded trial showed a significant decrease in actinic keratoses with three months of use of the DFMO cream, whereas there was no decrease with the placebo cream (61). There was a reduced spermidine:spermine ratio in the skin biopsies from the patients receiving DFMO, indicating that DFMO was inhibiting the ODC. This is a proof of principle that inhibition of the ODC by DFMO resulted in a clinically measurable decrease in the number of actinic keratoses after only a short period of application.

How Can We Measure a Clinical Effect of a New Compound That Is Not a Cytotoxic Agent?

The developments in molecular biology and the identification of new targets provide challenges to both the bench and the clinical investigator (62). There are new antisense molecules, farnesyl transferase inhibitors, telomerase inhibitors, kinase inhibitors, angiogenesis inhibitors, and many other molecules that are likely to be growth-modulating and that will not cause immediate tumor shrinkage. One way to test a growth-modulating agent is to conduct a randomized trial, as was done for gemcitabine, with end points of time-to-tumor progression and 1-year survival. However, is there a way we can tell early in its development whether an agent has any promise (before conducting the randomized Phase III trial)? One way that might be used to obtain an early lead as to whether a growth-modulating agent is having an effect is outlined in Fig. 9. Our hypothesis is that if the new agent has an antitumor effect, it will change the natural history of the disease. Therefore, we will use the patient as his/her own control. As can be seen in Fig. 9, period B is the TTP on the new agent. Period A is the TTP on the treatment the patients received just before the new agent was started. Given the natural history of cancer, it would be shorter that the TTP on the new agent would be shorter than the TTP on a prior regimen. Therefore, if the TTP on the new agent (period B) is greater than the TTP on the prior therapy (period A) it is likely the new agent is having an effect on the natural history of that patient’s tumor. In Fig. 9, we suggested a 33% improvement; however, that value is arbitrary. Although not yet tested prospectively, the use of a patient as his/her control may be a way to determine whether a growth-modulating agent is having a clinical effect before the randomized Phase III trial is launched.

Summary of Lessons Learned

What lessons have we learned to increase the percentage of our agents that make it in the clinic? The first lesson is to avoid pharmacoptosis (programmed drug death). If the new agent shows toxicities in the clinic but has hints of antitumor activity, be persistent and find a way to circumvent that toxicity.

The second lesson is for the correct clinical trial design to mimic the preclinical activity of the agent. For a growth-modulating agent, a suggested clinical trial design would be:

\[ \text{Standard agent + Placebo} \]

\[ \text{Standard agent + new agent} \]

with end points of TTP and 1-year survival.

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**Table 3** Examples of preclinical-clinical uncoupling

<table>
<thead>
<tr>
<th>What is seen preclinically</th>
<th>What we are measuring clinically</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The agent inhibits angiogenesis</td>
<td>Partial or complete tumor shrinkage</td>
</tr>
<tr>
<td>2. The agent prevents metastases</td>
<td>Partial or complete tumor shrinkage</td>
</tr>
<tr>
<td>3. The agent induces apoptosis</td>
<td>Partial or complete tumor shrinkage</td>
</tr>
</tbody>
</table>

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**Fig. 8** Structure of DFMO.

**Fig. 9** A method for early determination as to whether a new agent is having a modulating effect on tumor growth. 

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**Structure of DFMO.**

\[
\begin{align*}
\text{CH}_2_2 & - \text{CH} - \text{CH}_2 - \text{CH}_2 - \text{C} - \text{COOH} \\
\text{H}_2\text{N} & - \text{CH}_2 - \text{CH}_2 - \text{NH}_2
\end{align*}
\]
The third lesson is to take advantage of the mechanism of action of the new agent when designing a clinical trial. For an angiogenesis inhibitor, use a minimal residual disease model such as:

```
  put patient in best remission (minimal residual disease)  Angiogenesis inhibitor
  Placebo
```

with end points of TTP or recurrence-free survival.

The fourth lesson (for the preclinical scientist) is to demand better trial designs for your molecule! The fifth lesson for my clinical colleagues and myself is to take it upon ourselves to personally give new agents the best mechanism-of-action-based trial design we possibly can.

Conclusion

In conclusion, I would like to thank all of the patients, mentors, and colleagues who have made this work possible. San Antonio is the birthplace of Texas freedom, and we always say, "Remember the Alamo!" From this lectureship, I would like you to remember that both bench investigations and clinical investigations are difficult endeavors and that we need to appreciate both of them as important sciences. Remembering that will keep our clinical trial designs optimal and provide the best clinical development of a new idea or a new agent from the bench.

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References

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D D Von Hoff


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