

# OncoLog

REPORT TO PHYSICIANS

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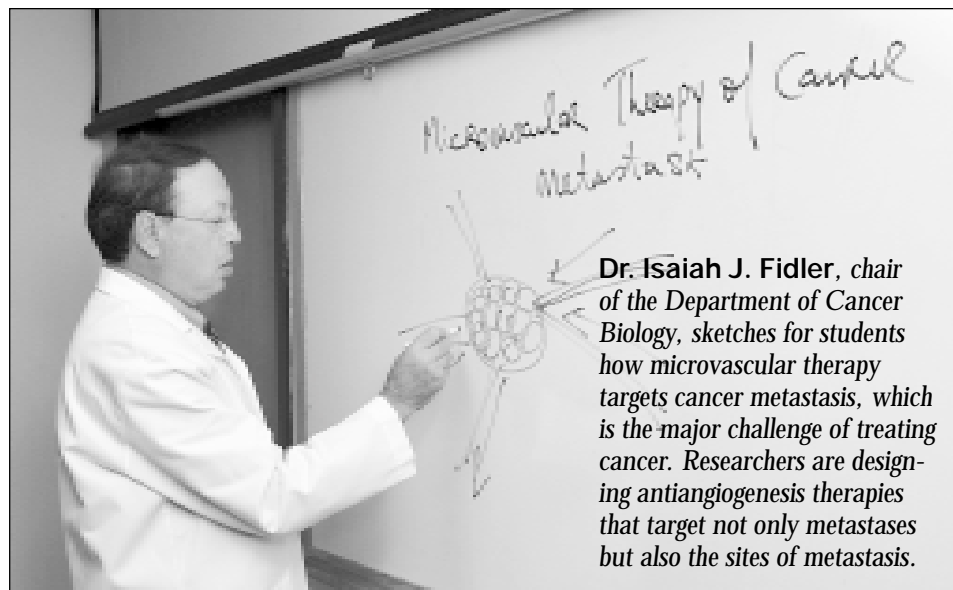
## Despite Initial Setbacks, Researchers Are Focusing on Antiangiogenic Therapy More Than Ever

by Kate Ó Súilleabháin

A few years ago, many people believed that the Holy Grail of cancer treatment had been found. Antiangiogenesis therapy was safe, elegant, and at first apparently effective. But the clinical results soon fell short of expectations. The tumors, it seemed, had found a way to circumvent even this most ingenious of treatment approaches. Despite the setbacks, however, angiogenesis remains a very tempting target, and researchers are exploring new agents and approaches to maximize the effects of antiangiogenic therapies.

### A tempting target

Unlike a normal cell, a cancer cell is genetically unstable, causing it to replicate inaccurately. As a tumor grows, this genetic infidelity results in



**Dr. Isaiah J. Fidler**, chair of the Department of Cancer Biology, sketches for students how microvascular therapy targets cancer metastasis, which is the major challenge of treating cancer. Researchers are designing antiangiogenesis therapies that target not only metastases but also the sites of metastasis.

multiple subpopulations of cells with different biological characteristics. An antitumor treatment, be it chemotherapeutic drugs or radiation, will kill most of the billion or so cells in each cubic centimeter of tumor tissue. But invariably, some cells will be resistant to the treatment. After the treatment-sensitive cells are depleted, the resistant cells may rapidly divide to re-create a tumor that is inherently resistant to the therapy.

Given the heterogeneity of malignant cells within an individual tumor,

not to mention among the various types of cancer, what common therapeutic target remains? The answer to this puzzle is surprisingly simple.

"We have searched for a uniform vulnerability among all tumor cells," said Isaiah J. Fidler, D.V.M., Ph.D., chair of the Department of Cancer  
(Continued on next page)

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# Researchers Are Focusing on Antiangiogenic Therapy

(Continued from page 1)

Biology at The University of Texas M. D. Anderson Cancer Center. "And that vulnerability is, in fact, the nonnegotiable need for oxygen." Tumor cells cannot thrive unless supplied with oxygen and other nutrients that are transported by the blood. In fact, research in Dr. Fidler's laboratory revealed that tumor cells cannot survive at distances greater than 150 micrometers from a blood vessel.

These findings followed the discovery by Judah Folkman, M.D., and his colleagues at Children's Hospital Boston that pathologic angiogenesis, the process by which a malignant tumor develops new vessels, is the primary means by which cancer cells spread. Tumor cells migrate by using these vessels, which also supply the primary tumor with oxygen and other nutrients. The isolation of certain compounds that inhibit angiogenesis in mice fueled hopes of a cure for cancer. However, researchers soon found that angiogenesis can occur via any combination of multiple molecular signaling pathways, a characteristic termed "redundancy."

"We're dealing with a multifactorial process," said Roy S. Herbst, M.D., Ph.D., an associate professor in the Department of Thoracic/Head and Neck Medical Oncology and codirector of the Clinical Trials Working Group. "There are now almost 20 known proangiogenic factors that are made by the tumor cells, stromal cells, or lymphocytes, which stimulate endothelial cell growth," he said. The division of endothelial cells, which line vessels, is blocked by antiangiogenic agents. But preventing these cells from multiplying may require targeting several molecules simultaneously—a daunting enterprise, considering the differences in expression and signaling among the various molecules governing angiogenesis in different cancers.

Far from being discouraged, however, researchers are focusing more than ever on agents that target the tumor vasculature. At least four major proteins and their receptors and signaling pathways commonly govern angiogenesis in solid tumors: platelet-derived growth factor, epidermal growth factor, vascular

endothelial growth factor (VEGF), and fibroblast growth factor (basic and acidic). Therapies that either target these molecules or block their signaling pathways should be effective in preventing solid tumor growth and metastasis by preventing the formation of new vessels.

"Angiogenesis inhibition in the clinic is an even more challenging area than it was a few years ago," Dr. Herbst said. "We're trying to target angiogenesis using any number of different compounds." Dr. Herbst and his team are conducting a phase I/II trial of bevacizumab—a monoclonal antibody that targets VEGF and is the first antiangiogenesis agent to receive Food and Drug Administration approval—in combination with erlotinib in patients with non-small cell lung cancer. These data were presented at the 2004 Proceedings of the American Society of Clinical Oncology.

Other drugs targeting proteins important in angiogenesis are under study at M. D. Anderson. The Phase I Clinical Trials Working Group is exploring a number of investigational

## Dynamic Contrast-Enhanced Magnetic Resonance Imaging Predicts Response to Antiangiogenesis Agents

by Kate Ó Súilleabháin

**H**ow do oncologists measure vascular growth, the target of angiogenesis inhibitors? Although researchers have relied on surrogate markers of angiogenesis, such as circulating levels of the proangiogenic molecules basic fibroblast growth factor and vascular endothelial growth factor, these levels may be more useful for predicting the response of certain patients than as a surrogate indicator of response to an agent. Assistant Professor Michael O'Reilly, M.D., of the Division of Radiation Oncology, said, "Most studies that have looked at changes in circulating

levels of proangiogenic factors haven't shown any meaningful correlation with response." Indeed, the changes are sometimes contrary to what is expected because blocking certain molecules with angiogenic inhibitors can cause the tumor to produce more of that molecule.

To measure therapeutic response and predict outcomes, researchers at The University of Texas M. D. Anderson Cancer Center have begun to use dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), a computer-enhanced modality that relies on a special algorithm to estimate blood flow. DCE-MRI is overseen in both patients and laboratory animals by

Edward Jackson, Ph.D., an associate professor in the Department of Imaging Physics.

According to Donald Podoloff, M.D., the head of the Division of Diagnostic Imaging, "The ability to measure blood flow enables us to see changes in tumor vascularity, which occur at a much earlier stage in the treatment of tumors than does shrinkage of tumor mass as measured with a ruler. This should lead to earlier assessment of response or failure of a particular drug."

"We're trying to assess the effectiveness of these new agents using markers of blood flow, and we're showing that blood flow decreases with time," said Roy S. Herbst, M.D., Ph.D., an associate professor in the Department of Thoracic/Head and Neck Medical Oncology and codirector of the Clinical Trials Working Group. Using DCE-MRI to estimate drug efficacy represents an improvement over traditional marker



**Dr. Michael O'Reilly** (looking through the microscope), an assistant professor in the Division of Radiation Oncology, and **Dr. Roy S. Herbst**, an associate professor in the Department of Thoracic/Head and Neck Medical Oncology, have built mouse models of lung cancer metastasis that show that lung cancer metastases behave differently from the primary tumor. These findings could help researchers determine which angiogenesis inhibitors are optimal for metastatic sites versus the primary tumor.

compounds in patients with advanced solid tumors.

### Maintenance therapy

Dr. Herbst stresses a combinatorial approach involving angiogenesis inhibition along with other novel treatments, conventional chemotherapy, and/or radiotherapy. "Cancer is going to be treated as a chronic disease," he said. With the use of antiangiogenic agents as maintenance therapy, it is hoped that cancer can be controlled in the same way that medications are used to control hypertension and high cholesterol levels. "There are so many different mutations in cancer that we'll certainly have to individualize the therapy from time to time based on a patient's particular tumor. Are we going to cure everyone with metastases? No, very few. But we hope to knock it down to its minimal bulk with chemotherapy and radiation therapy, which still have their important role. Perhaps these inhibitors can then be used as maintenance," said Dr. Herbst. Given that the side effects of antiangiogenesis agents have been

minimal and that many are orally administered, prescribing them as maintenance therapy for outpatients is plausible.

But Dr. Fidler notes that targeting new vessels may not be enough. By the time most patients enter a clinical trial of an angiogenesis inhibitor (or any new treatment), their tumors are resistant to conventional therapy, are large, and have an established vasculature. "Inhibiting angiogenesis after it has already taken place is like closing the door on the barn after the horse has escaped," Dr. Fidler noted. Shrinking or destroying a tumor may require therapy that is not only antiangiogenic but also antivascular, targeting the existing vessels rather than endothelial cell turnover or new vessel growth.

### "Seed and soil"

Clearly, the major challenge in treating cancer is not eradicating the primary tumor (which can be treated with radiation or surgery) but eradicating metastases, which are usually already present at the time of the initial diagnosis. The ability of a cell to metastasize is proportional to its genetic instability, making the cell populations of metastases even more heterogeneous than those of primary tumors—and hence more difficult to treat. Therefore, researchers are designing therapies that target not only metastases but also the sites of metastasis, an approach that harkens back to Stephen Paget's "seed and soil" hypothesis of 1889. After observing that some cancers favored certain sites of metastasis over others, Paget maintained that metastasis can occur only if the cancer cell (the "seed") finds a favorable microenvironment at the site of metastasis (the "soil," or host). Researchers now understand that metastatic cells usurp homeostatic mechanisms that govern host physiologic processes because the host cells secrete growth factors that prompt tumor cell replication. Therefore, whereas traditional cancer therapies target the "seed," new approaches target the "soil," making the sites of

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analyses of tumor biopsy specimens, which are not only invasive but also subject to sampling bias.

In the laboratory, Drs. O'Reilly, Herbst, and Jackson, as well as Roger E. Price, Ph.D., an associate professor in the Department of Imaging Physics, are using antiangiogenesis agents to compare the results of DCE-MRI with those of tumor biopsy and resection in mice. "Once the tumor has shrunk, the imaging shows very dramatic differences between control animals and animals treated with angiogenesis inhibitors," Dr. O'Reilly said. "But we're looking for something early on the DCE-MRI scans that is going to predict response." To find this early indication of response, researchers are implanting tumors into mice and then treating them with angiogenesis inhibitors, either alone or in combination with radiotherapy. Before the tumors have sufficient time to shrink (five to seven days after treatment), DCE-MRI

and tumor biopsy or resection are performed. The changes on DCE-MRI are compared with the results of immunohistochemical staining. "Our hope is that the data we get from the invasive strategies will help us validate the noninvasive ones," said Dr. O'Reilly.

In addition, researchers at M. D. Anderson can now precisely quantify an inhibitor's effect on endothelial cells. "If endothelial cells are dying at twice their usual rate but growing at twice their usual rate, the net effect is zero," Dr. O'Reilly pointed out. "So we've come up with what we call an angiogenesis index: a ratio of endothelial cell proliferation and apoptosis. Many [studies] look only at apoptosis, and I think that misses half the story." ●

FOR MORE INFORMATION, contact Dr. O'Reilly at (713) 563-2300, Dr. Podoloff at (713) 745-5153, or Dr. Herbst at (713) 792-6363.



## Antiangiogenic Therapy

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metastasis inhospitable for cancer cells.

### Preclinical models

The “seed and soil” hypothesis is guiding the development of mouse models to study different sites of metastasis in human lung cancer and other malignancies. Researchers at M. D. Anderson use a mouse model of lung cancer that closely resembles the disease in humans: a single tumor grows and expands within the lung and then spreads into the mediastinum and lymph nodes. In another mouse model designed to study brain metastasis of lung cancer, the same tumor cells are injected into the carotid artery, the main artery leading to the brain.

“We’ve also developed models of bone metastases, and we’re now trying to develop models of different bones because lung cancer that spreads to the femur can behave very differently from lung cancer that spreads to the spine,” said Michael O’Reilly, M.D., an assistant professor in the Division of Radiation Oncology. “So we’re now trying to identify any differences between different bone microenvironments.” Supporting the “seed and soil” hypothesis, the data show that lung cancer growing in the brain behaves differently from lung cancer growing in the lung, as shown by unique patterns of production of proangiogenic molecules and different apoptotic indexes. Thus, angiogenesis inhibitors that are optimal in the primary organ may not be optimal in the metastatic site.

Dr. O’Reilly stated, “The ultimate goal is to translate the findings in these animals into the clinic and see if there are correlations [between animals and humans]. If we can figure straightforward ways to optimize antiangiogenesis therapies in the animals, we can optimize ways to kick off this therapy in patients.” ●

FOR MORE INFORMATION, contact Dr. Fidler at (713) 792-8580, Dr. Herbst at (713) 792-6363, or Dr. O’Reilly at (713) 563-2300.

# “Smart Bombs”: Targeted Therapies Home in on Increasingly Well-Defined Targets

by Katie Prout Matias

**F**or those who treat patients with cancer, the crux has always been finding ways to destroy cancerous cells without harming healthy cells. The first so-called targeted cancer therapy was actually chemotherapy; many chemotherapeutic agents were designed to attack the metabolic processes of actively dividing cells based on the concept that cancer cells divide more rapidly than normal cells. But chemotherapy also kills many normal cells, causing unwanted toxic effects. These days, targeted therapy has come to mean much more specific agents than chemotherapy that are designed to zero in on ever more precise targets.

“The idea has always been if we could get therapy that is directed towards specific pathways and mechanisms that cause cancer, these therapies would be much less toxic and maybe more effective than the current therapies we use,” said Jack A. Roth, M.D., who is the chair and a professor in the Department of Thoracic and Cardiovascular Surgery and a professor in the Department of Molecular and Cellular Oncology at The University of Texas M. D. Anderson Cancer Center.

Targeted therapies have a variety of pathways to aim for, including angiogenic, cell cycle, and apoptosis

pathways as well as growth-promoting proteins. Monoclonal antibodies can block such proteins from promoting cancer growth by binding to their receptors on the cancer cell’s surface. Small molecules use those same receptors to worm their way inside the cell and interrupt its molecular activity.

“We want to attack that pathway more with a smart bomb than with the cluster bombs we’ve been using,” said Roy S. Herbst, M.D., Ph.D., an associate professor in the Department of Thoracic/Head and Neck Medical Oncology and codirector of the Clinical Trials Working Group.

### Gene therapy

Other targeted therapies focus on replacing missing or damaged genes, several hundred of which are important to carcinogenesis and thus potential targets. Unlike monoclonal antibodies and small molecules, which go through a lengthy and complicated process of being discovered and tested in the laboratory and formulated into functional agents, the genes used in gene therapy come ready-made. “We don’t have to reformulate them. We don’t have to make them soluble. We don’t have to make them digestible. We just have to get them to the tumor, that’s all,” said Dr. Roth, who is also director of the W. M. Keck Center for Cancer Gene Therapy. “Once you get the delivery system in hand, then you’ve got a whole library of hundreds of genes that you can choose from, and you can deliver more than one of those genes.”

Finding an effective and safe delivery system for gene therapy is, however, the tricky part.

### Viral and lipid vectors

Viruses are often used as a type of Trojan horse to deliver normal versions



By injecting mice with millions of human mesenchymal stem cells transduced with an adenovirus carrying interferon- $\alpha$  and interferon- $\beta$ , a team led by **Dr. Michael Andreeff**, chief of the Section of Molecular Hematology and Therapy, successfully halted the growth of leukemias, ovarian and brain tumors, and lung metastases of melanomas and breast cancer in the mice.

of a defective gene to the cancer cell. Older systems of gene delivery were based on retroviruses, or RNA viruses, which are hard to produce and do not grow very well in artificial conditions. Along with other researchers at M. D. Anderson, Dr. Roth chose instead to use adenoviruses to deliver gene therapy. These viruses are much more robust than retroviruses, are easier to grow, and can be engineered to be selectively taken up by cancer cells but not by normal cells, he said.

In a phase II trial, the results of which were published in the January 2003 issue of *Clinical Cancer Research*, Dr. Roth and his colleagues treated 19 patients with nonmetastatic non-small cell lung cancer with six weeks of radiation therapy and three intratumoral injections of an adenoviral vector carrying the p53 gene, which is mutated or altered in more than half of all human cancers, including 40% to 70% of non-small cell lung cancers.

They found that the therapy was well tolerated and that 12 patients had a major response: one complete response and 11 partial responses.

Dr. Roth said, "We found that gene therapy was safe, that serious adverse events occurred very rarely, and that there was evidence of programmed cell death. We also saw evidence that certain other genes that we expected to be activated by the presence of p53 gene were being activated, that the gene was highly expressed in the cancer, and finally, that in some cases shrinkage of the tumor actually occurred. When gene therapy was combined with radiation therapy, this tumor shrinkage occurred in a very high percentage of patients." According to Dr. Roth, p53 gene therapy is now in phase III studies, primarily in head and neck cancer.

Another method of delivering genes to cancer cells involves using lipids to coat or surround—and thus disguise—molecules of DNA. "I like to think of them as artificial viruses," said Dr. Roth.

Lipid vectors have at least one advantage over viruses, however. They can be delivered systemically without causing an immune response. Dr. Roth noted that this allows lipid vectors to overcome one of the major obstacles of gene therapy: treating metastases. "If you directly inject [the genes] into just a single tumor, you're not affecting the metastatic disease," said Dr. Roth. "By using some of these other delivery systems, I'm talking about primarily nonviral systems, you can inject intravenously."

### Stem cells

Another approach to the problem of delivering genes and other anticancer biologic agents directly to metastases is the use of stem cells.

Mesenchymal stem cells are nonhematopoietic, unspecialized cells that the body calls to areas of injury to build connective tissue for wound repair. Tumors, including metastases, cleverly use this system to build up normal tissue, which the cancer needs as a support matrix; the cancer attracts the stem cells by sending out signals, and the stem cells migrate to the cancer.

A team of investigators at M. D. Anderson is using this stem cell signaling behavior to beat the tumors at their own game. By taking mesenchymal stem cells from human bone marrow, transducing them with an adenovirus carrying human interferon- $\alpha$  and interferon- $\beta$ , and intravenously injecting millions of the genetically engineered stem cells into mice, Michael Andreeff, M.D., Ph.D., chief of the Section of Molecular Hematology and Therapy and director of research in the Department of Blood and Marrow Transplantation, and his team—Frank Marini III, Ph.D., an assistant professor in the department, and Frederick Lang, Jr., M.D., an associate professor in the Department of Neurosurgery—have found a way to get biologic agents directly to the cancer's metastases.

The group's research, which was presented at the 2003 meeting of the American Society of Hematology and the 2004 meeting of the American Association of Cancer Research, showed that this technique halted the growth of leukemias, ovarian tumors, brain tumors, and lung metastases of melanomas and breast cancers in mice. In fact, 70% of the mice with one kind of ovarian tumor were cured. In mice with metastatic breast and melanoma tumors, cancer growth was nearly eradicated, and survival was prolonged.

Unlike viral vectors, stem cells are not likely to be rejected by the body. Furthermore, Dr. Andreeff found that the stem cells were attracted to all kinds of cancer, anywhere in the body, and left healthy cells untouched; in one of his studies of glioma in mice, which was conducted in collaboration with Dr. Lang, only the cancer took up the stem cells, and the rest of the brain was not affected.

"These cells, after a few days, were only in the tumor and produced drugs

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## “Smart Bombs”

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only in the tumor. So we expect very few, if any, side effects,” said Dr. Andreeff.

### Antiangiogenesis therapy

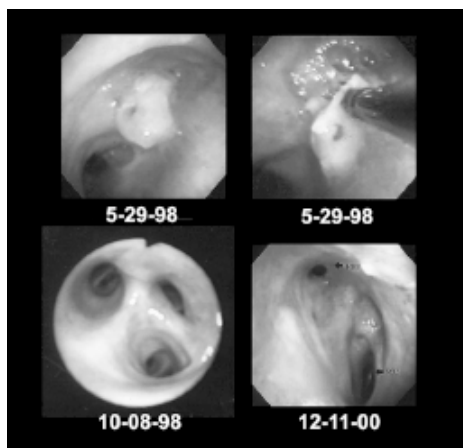
Much hyperbole has surrounded targeted therapy that focuses on attacking angiogenic pathways by which cancer cells send signals to surrounding tissue to stimulate the formation of new blood vessels, which are needed for tumor growth and metastasis. Part of the attractiveness of targeting angiogenesis is that it is common to all tumors, as opposed to many other pathways, which may be present in one tumor but absent in another.

“Angiogenesis is the final common pathway. Here you have an approach that is not dependent on any one mutation. It’s universal to solid tumors,” said Dr. Herbst.

However, many of the antiangiogenic agents tested since Judah Folkman, M.D., pioneered the concept 30 years ago have failed. “The downside is that the tumors have redundant pathways, so as a tumor gets more invasive and grows, it can make different proangiogenic factors. So if you’re only blocking one pathway, the tumor might escape,” Dr. Herbst said.

The hunt continues for more effective agents to combat the 20-plus factors that promote tumor blood vessel growth. In 2002, \$9.2 million was awarded to M. D. Anderson from the National Cancer Institute to support antiangiogenesis research projects. More than 30 antiangiogenic compounds are being tested in humans around the world; six of them are being studied at M. D. Anderson in lung cancer alone.

In the first phase I/II clinical trials combining two investigational targeted agents for the treatment of non-small cell lung cancer, Dr. Herbst and others at M. D. Anderson treated patients with a combination of bevacizumab and erlotinib. The median survival was 9.3 months compared with the expected 6 months for controls, and there was a 21% response rate among 23 patients with recurrent stage IIIB or IV lung cancer. These findings were presented at the 2004 Proceedings of the American Society of Clinical Oncology.



*In a phase II trial led by Dr. Jack A. Roth, chair and professor in the Department of Thoracic and Cardiovascular Surgery, 11 of 19 nonmetastatic non-small cell lung tumors partially responded to treatment with six weeks of radiation therapy and three intratumoral injections of an adenoviral vector carrying the p53 gene. Shown here, one patient’s right upper lobe tumor responded completely to the therapy; 29 months after treatment, there was no pathologic evidence of tumor.*

In another study at M. D. Anderson, patients with non-small cell lung cancer were treated with gefitinib, a small molecule epidermal growth factor receptor tyrosine kinase inhibitor. This study, which was presented at the 2003 annual meeting of the American Society of Clinical Oncology, found that patients treated with chemotherapy followed by gefitinib as a maintenance therapy had slower recurrence of their lung tumors compared with controls. Gefitinib, which has been approved by the Food and Drug Administration for the treatment of metastatic lung cancer, is currently being tested or awaiting testing in brain, head and neck, breast, and prostate cancers at M. D. Anderson.

However, not all findings related to gefitinib have been promising. Dr. Herbst was one of the researchers on a phase III trial in which gefitinib was used in combination with paclitaxel and carboplatin in 1,037 chemotherapy-naïve patients with advanced non-small cell lung cancer. The results, which were published in the March 2004 *Journal of Clinical Oncology*, showed

that gefitinib provided no additional benefit over chemotherapy alone.

### The status quo

The gefitinib study highlights the fact that despite promising research results, many targeted therapy agents are not very clinically effective. Response rates typically fall between 10% and 20%, in part because these agents are so narrow in their therapeutic index that they help only small subgroups of patients.

Furthermore, lasting responses are rare. Tumors often become resistant to targeted drugs that block only one pathway, likely because cancer cells have several pathways they can use to achieve the same function.

“If you look at an integrated circuit on a circuit board for a computer, that gives you some understanding of how these various pathways interact with each other,” Dr. Roth explained. “It’s probably going to turn out to be not just one pathway and one target but various groups of pathways or targets that need to be interrupted before we are going to make a difference therapeutically.”

For better results, most agents will need to be combined with conventional therapies, such as chemotherapy and radiation therapy, or with other targeted therapies to affect as many pathways as possible.

The hope that a single targeted therapy will replace conventional treatment and eliminate toxic effects has yet to become reality. Better mechanisms are needed for testing and developing the millions of chemicals that could be used as targeted therapy compounds and for pinpointing which agents will work in which patients. Dr. Roth noted that using targeted therapies to get rid of toxic side effects of more systemic therapies “is the utopia, but I don’t think we are very close to that. I think that chemotherapy, surgery, and radiation are going to be treating cancer patients for a long time.” ●

FOR MORE INFORMATION, contact Dr. Roth at (713) 792-7664, Dr. Herbst at (713) 792-6363, or Dr. Andreeff at (713) 792-7260.





# Understanding Angiogenesis

**T**he human body has a remarkable ability to repair itself. It has countless mechanisms to fight viruses and bacteria, to recover from infections and fevers, and to heal cuts and punctures, but one mechanism we seldom think about is angiogenesis, or the body's ability to grow new blood vessels.

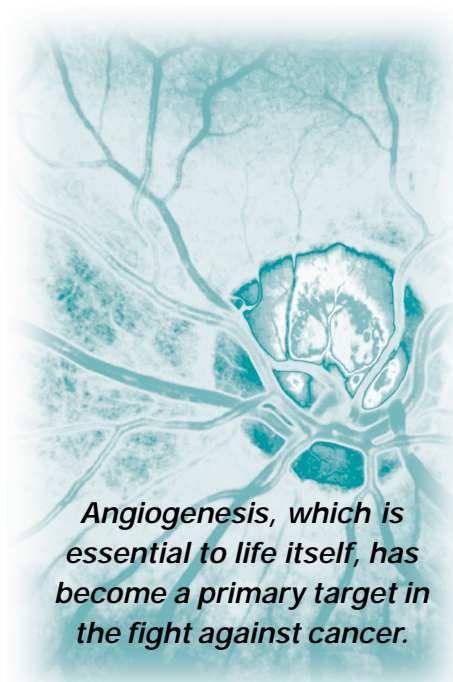
## All tissues need blood

All of the tissues of the body—including skin, cartilage, and bone—must have a constant supply of blood, which provides oxygen and nutrients essential to survival. Any time, from conception until death, that blood vessels are damaged, special proteins and molecules called growth factors go to work at the site of the damage to promote the development of new blood vessels.

Ironically, angiogenesis, which is essential to life itself, has become a primary target in the fight against cancer. Tumors also need a reliable blood supply to survive, and the same angiogenic factors that help maintain vital tissues also help maintain cancerous tissues.

## Understanding the process

Scientists have been working for years to understand the mechanisms that control angiogenesis. They have discovered that both healthy tissues and tumors naturally produce proteins and molecules that either promote or inhibit angiogenesis. Experiments on mice have been performed to determine whether angiogenesis is triggered by the tumor itself or by the surrounding host tissue. The findings proved that tumors initiate angiogenesis by releasing growth factors into the surrounding tissue, in a sense ordering the tissue to start making blood



*Angiogenesis, which is essential to life itself, has become a primary target in the fight against cancer.*

vessels. For a tumor to grow, it must release more angiogenesis-promoting factors than inhibiting factors into the surrounding tissue.

The fact that tumors also produce angiogenesis inhibitors happens to be very important in explaining metastasis, which is the spread of cancer to other parts of the body and the main reason for cancer-related deaths. Frequently, tiny, microscopic metastases in areas of the body far away from the primary tumor will remain inactive for years and begin to grow only after the primary tumor is removed. This happens because the primary tumor has been releasing angiogenesis inhibitors into the bloodstream, and when these inhibitors are gone, the microscopic tumors begin to grow. Cancer researchers hope that by preventing angiogenesis, they can prevent these microscopic metastases from growing. Furthermore, if a tumor has not metastasized, or spread to other areas, and has been effectively treated with antiangiogenesis agents, metastasis is much less likely to occur because fewer blood vessels are available to spread cancer cells from the tumor.


## Fighting angiogenesis


The almost two dozen angiogenesis inhibitors currently being tested work in many different ways. Some block the growth of vascular endothelial cells, which are the primary cells in blood vessels. Another category of angiogenesis inhibitors indirectly attacks endothelial cell growth. Others are designed to interfere with the signaling that takes place between tumor cells and cells in the surrounding tissue, preventing a tumor's order to produce blood vessels from ever reaching the host tissue. Yet another category includes angiogenesis inhibitors with different mechanisms of action that are not completely understood.

## Looking to the future

The science of stopping tumor angiogenesis is relatively new, and there are many unanswered questions. What are the short-term and long-term side effects of antiangiogenesis therapies? Will cancer cells adapt to render antiangiogenesis drugs ineffective? How long will these treatments last? These questions and others are now being addressed in clinical trials, which you can read about on the National Cancer Institute Web site (<http://www.nci.nih.gov/clinicaltrials/developments/anti-angio-table>). ●

*For more information, contact your physician or contact the M. D. Anderson Information Line:*

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and outside the United States.

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## DiaLog

### Gene Therapy for Cancer: Safety First

**Jack Roth, M.D.**  
Chair, Department of Thoracic  
and Cardiovascular Surgery



Gene therapy was originally conceived as a technique to treat patients with inherited monogenic disorders. These patients would receive a normal copy of the defective gene to be expressed in the patient's cells and produce a normal protein. Recognizing that this radically new method of treatment would require monitoring, the National Institutes of Health established the Recombinant DNA Advisory Committee (RAC) to provide scientific oversight for all gene therapy clinical trials. The RAC, as well as the Food and Drug Administration, provides stringent public review of scientific and safety issues related to clinical gene therapy.

Most gene therapy clinical trials have involved cancer patients because many defective genes are potentially involved in cancer and expression of the normal gene in the cancer cell arrests the cell's growth or leads to its death. Only short-term expression of the gene is required to accomplish this. To deliver the normal gene, these trials frequently use viruses rendered defective so that they cannot cause disease. These clinical trials are among the safest ever conducted in cancer patients. No deaths have been associated with the administration of cancer gene therapy agents in hundreds of patients, and the rate of serious adverse events is less than 5%, a safety

record far superior to that seen in initial clinical trials of chemotherapy agents.

Among the safety concerns expressed at the time these clinical trials began was the possibility that the virus or gene would mutate or that the virus would be transmitted from the patient to others. Extensive studies have shown that neither of these events occurs. Unfortunately, one death has been associated with gene therapy. It occurred in a noncancer clinical trial in which the vector was infused directly into the patient's liver, which was diseased as a result of the underlying genetic disorder. The patient's death was probably caused by an inflammatory response triggered by viral proteins. In another trial, two infants receiving gene therapy for severe combined immune deficiency (SCID) developed leukemia. The mechanism behind this occurrence probably involved the integration of the retroviral vector next to a gene that, when activated, can cause cell proliferation in association with the gene being delivered, which is known to have cancer-causing potential in rapidly dividing cells. Both children were successfully treated for leukemia and have been cured of SCID by the gene therapy. These unfortunate events led to extensive discussions and studies, which hopefully have contributed to enhancing the safety of all gene therapy clinical trials in the future.

Despite our best efforts, unforeseen adverse events can occur with any investigational agent, and the incidence of these in future gene therapy clinical trials cannot be predicted. However, to date, cancer gene therapy has one of the best safety profiles of any cancer treatment.

## OncoLog

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