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REPORT TO PHYSICIANS

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OncoLog

Outsmarting Brain Cancer

Finally, cause for optimism in glioblastoma treatment.

By Dianne C. Witter

Dr. Charles Conrad explains how Delta-24 will be delivered intravenously to glioblastoma.

It's been called a viral "smart bomb," and with good reason. The name even has a military ring: Delta-24. Mission: eradicate glioblastomas while leaving critical nearby brain structures unscathed. The mission is even tougher than it sounds. Unlike most other solid tumors, glioblastomas are not shaped in a definitive lump; they spread into crevices within the brain, taking healthy tissue hostage as they go.

Delta-24 is a new-generation adenovirus therapy developed by researchers at The University of Texas M. D. Anderson Cancer Center. The virus targets the pathway of the retinoblastoma protein (pRb), a master regulator of cell growth that is deficient in many cancer cells. Researchers created a gene mutation in the virus that allows it to reproduce only in cells without pRb; thus, in normal cells, Delta-24 cannot replicate.

But when injected into tumor cells, the virus replicates exponentially until the cells burst, each releasing about 10,000 new copies of the virus. These copies spread out, attach to more cancer cells, and repeat the process. The virus moves, wave-like, throughout the tumor,

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Outsmarting Brain Cancer

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infecting and killing cancer cells without affecting normal cells.

On the verge of important advances

Targeting tumors with a viral smart bomb is only one of the avenues showing promise. After several decades in which no new drugs were approved for the treatment of brain tumors and survival rates remained disappointingly low, there are now a variety of promising new medical treatments in the pipeline. They come close on the heels of the U.S. Food and Drug Administration's approval in 2005 of the chemotherapy drug temozolomide for use in glioblastoma. Temozolomide, when used in addition to surgery and radiation, extends median overall survival by 2.5 months—and a few people in the early clinical trials of temozolomide are alive years beyond what was expected.

W. K. Alfred Yung, M.D., chair of the Department of Neuro-Oncology, believes temozolomide was the beginning of a positive trend in brain cancer treatment. "We are just now on the cusp of understanding much more about the molecular biology of this disease, which is leading us down some innovative and very promising avenues," he said. "For example, in addition to the Delta-24 virus, we're also looking at a peptide vaccine, antiangiogenesis agents, and epidermal growth factor receptor (EGFR) inhibitors, in addition to retooling existing chemotherapy drugs so they will cross the blood-brain barrier."

Charles Conrad, M.D., associate professor in the Department of Neuro-Oncology, adds, "I think we're going to see an explosion of new drugs for brain tumors within the next 3 to 5 years, and many of those are being developed at M. D. Anderson. We have a real optimism that advances are coming." Nationwide, only 1% to 2% of glioblastoma patients survive long-term today. Dr. Conrad believes that within 5 or 10 years, that figure will have jumped to 20% or even 30%.

Sneak peek at projects under way

Researchers at M. D. Anderson designed a vaccine that alerts the



Dr. Frederick Lang (right), professor in and director of clinical research for the Department of Neurosurgery, and **Dr. Juan Fueyo** are working to bring Delta-24 to clinical trials after finding success in the laboratory.

immune system to the presence of epidermal growth factor receptor variant III (EGFRvIII), a protein found on gliomas that is believed to drive them to spread aggressively. The vaccine contains a synthesized piece of the protein and a stimulator to activate the immune system, inciting it to mount a response, attacking the EGFRvIII and the gliomas it's attached to.

In a phase II clinical trial conducted at M. D. Anderson, glioblastoma patients whose brain tumors showed evidence of the protein on examination after surgical removal were eligible for the vaccine.

Preliminary results suggest the vaccine is significantly increasing the expected life span of patients in the study; participants have had a median overall survival of at least 18 months. Researchers found that the treatment can potentially keep the disease at bay for a period of time in up to 50% of glioblastoma patients. However, there is evidence that the tumors may eventually circumvent the vaccine, so researchers plan to combine the vaccine with chemotherapy in the current study.

In other research, scientists are work-

ing to identify the genes and proteins associated with gliomas to identify or develop small-molecule drugs specifically targeted to these molecular pathways. Some of the more common genetic alterations in malignant brain tumors include the *p53* tumor suppressor gene; EGFR genes that control cell growth; platelet-derived growth factor and

vascular endothelial growth factor (VEGF) genes involved in cell growth and angiogenesis; and the *PTEN* (phosphatase and tensin homologue) tumor-suppressor gene.

A number of signal-transduction inhibitors are being tested for use

in brain tumors based on these molecular signatures, including erlotinib, ZD 1839, and AEE788 (which are EGFR inhibitors) and rapamycin and RAD001 (which are mammalian target of rapamycin [mTOR] inhibitors). mTOR inhibitors regulate the way tumor cells respond to nutrients and growth factors and also control blood supply to the tumor through their effects on VEGF.

Researchers at M. D. Anderson expect to open two clinical trials of unique P13K inhibitors, PX-866 and

Some of the mice were considered clinically cured of their brain tumors."

— Dr. Juan Fueyo

BEZ-235, in glioblastoma patients in 2008. The agents are expected to offer several advantages, including significantly reducing the dose-limiting toxicity common with P13K inhibitors. The agents will be tested in combination with existing small-molecule drugs such as erlotinib and sorafenib, with the expectation of blocking multiple pathways.

Glioblastomas are highly vascularized, and the vascular system is thought to have a key role in their progression—which has led investigators to look increasingly at using antiangiogenic agents. “The antiangiogenic drug bevacizumab is one of the most promising agents being studied right now,” said Dr. Yung. “We’ve seen very good early responses in studies combining it with the chemotherapeutics irinotecan or erlotinib.”

“Most chemotherapy drugs have not traditionally had success in brain tumors due to their inability to cross the blood-brain barrier, which actively pumps out cytotoxic drugs as fast as we put them in,” said Dr. Conrad. With an improved understanding of the biology of the blood-brain barrier, researchers have developed a way to retool existing chemotherapies so that they will penetrate this barrier. This could be achieved through modification of the chemical structure or using carrier peptides or antibodies. For instance, M. D. Anderson researchers re-engineered the chemotherapy agent doxorubicin to cross the blood-brain barrier. Phase I trials of the resulting agent, RTA744, have shown encouraging results—including one patient with complete resolution of his tumor. Another agent under development is 2-deoxy-d-glucose, which inhibits the glycolysis process that brain tumors depend on for energy.

And then there is the new generation virus, Delta-24. Researchers were excited by the degree of success they had when testing Delta-24 in mice. “The virus completely eradicated some glioblastomas, a response that had never been seen before,” said Juan Fueyo, M.D., associate professor in the Department of Neuro-Oncology, who developed the treatment in collaboration with his wife

and colleague, Candelaria Gomez-Manzano, M.D., assistant professor in the Department of Neuro-Oncology. “We found only empty cavities and scar tissue where the tumors had been. Some of the mice were considered clinically cured of their brain tumors.”

It’s a big finding, albeit in very small subjects. Recently, the researchers found even more promising news about Delta-24. They showed that, in addition to killing tumor cells, the virus can target and eliminate the actual stem cells that initiate the growth of glioblastoma. “These cells are highly resistant to chemotherapy and radiation, and they fuel the re-growth of the tumors after

surgery,” said Dr. Fueyo. “We have to be cautious about extrapolating the results from animal studies, but the tumors grown from these cells closely resemble human tumors, so we’re very optimistic and excited to begin clinical trials.”

Glioblastoma is the most common, and most deadly, of brain cancers. If the results seen in mice turn out to be indicative of the results in humans, Delta-24 may ultimately prove to be an important new therapy for human glioblastomas. The Brain and Spine Center at M. D. Anderson expects to begin enrolling patients in the first clinical trial of the new viral therapy this fall.

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Clinical Trials in Glioblastoma

- A Phase II/III Randomized Study of CDX-110 Vaccine with Radiation and Temozolomide in Patients with Newly Diagnosed Glioblastoma Multiforme (2007-0263). Principle investigator (PI): Morris Groves, M.D. The goal of this clinical research study is to compare the effectiveness of giving temozolomide with a CDX-110/GM-CSF vaccine combination to giving temozolomide by itself in patients with glioblastoma multiforme.
- A Randomized, Factorial-Design, Phase II Trial of Temozolomide Alone and in Combination with Possible Permutations of Thalidomide, Isotretinoin and/or Celecoxib as Post-Radiation Adjuvant Therapy of Glioblastoma Multiforme (2004-0662). PI: Mark Gilbert, M.D. The goal of this clinical research study is to learn if temozolomide, when given alone or in combination with thalidomide, isotretinoin, and/or celecoxib, is effective in treating newly diagnosed glioblastoma multiforme in patients who have already been given radiation therapy.
- Phase I Trial of Conditionally Replication-Competent Adenovirus (Delta-24-RGD) for Recurrent Malignant Gliomas (ID01-310, pending activation). PIs: Charles Conrad, M.D., and Frederick Lang, M.D. The goal of this clinical research study is to find the highest safe dose of Delta-24-RGD4C that can be injected directly into brain tumors and into surrounding infiltrative normal brain. A second goal is to study the effects of the drug on brain tumor cells.
- Phase III Trial Comparing Conventional Adjuvant Temozolomide with Dose-Intensive Temozolomide in Patients with Newly Diagnosed Glioblastoma (RTOG0525). PI: Mark Gilbert, M.D. The goal of this clinical research study is to compare two dose schedules of temozolomide treatment in patients with brain tumors. Researchers want to find out if increasing the intensity of temozolomide treatments after radiation will improve response. Researchers will study whether the response to temozolomide and the overall outcome depend on whether the tumor cells express the *MGMT* gene.
- Phase II Single Arm Trial of VEGF Trap in Patients with Recurrent Temozolomide-Resistant Malignant Gliomas (NABTC06-01). PI: John de Groot, M.D. The goal of this clinical research study is to find out if VEGF trap can help control glioblastoma multiforme or anaplastic glioma that has recurred. The safety of VEGF trap will also be studied. ●

Outsmarting Brain Cancer

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In this clinical trial, Delta-24 will be injected into brain tumors through a surgically implanted catheter. After 2 weeks, the tumors will be surgically removed and examined. In future studies, however, the virus may be delivered to the tumors via mesenchymal stem cells, which would effectively serve as a Trojan horse for the virus. Researchers at M. D. Anderson have discovered that these stem cells preferentially home in

The antiangiogenic drug bevacizumab is one of the most promising agents being studied right now.”

— Dr. Yung

to tumors, even if a tumor exists in the unique environment of the brain. By concealing the virus inside the stem cells, it could be carried directly to the tumor without detection by the immune system and, once inside, destroy it.

Looking forward

Glioblastoma is a formidable foe, and researchers say the key to outwitting it won't come from one drug or one treatment; it will take a variety of approaches and an arsenal of next-generation drugs and therapies. “We need to attack multiple pathways at one time to outsmart the cancer cells,” said Dr. Yung. “So, in addition to identifying new drugs, we need to test different treatments in combination to find the optimal approach.”

For now, though, Dr. Yung stresses that there are many more options available to brain tumor patients than in the past. “We now have a wide range of trials using different approaches and targeting different types and stages of the disease; there's something for everyone,” he said. “There are many things we can do to increase a patient's chance of survival and quality of life.

“Most importantly, we can offer more hope,” he said. ●

For more information, call the Brain and Spine Center at 1-877-632-6789 or visit www.mdanderson.org/care_centers/brainspinal.

Protecting the Heart

Careful monitoring, early intervention can limit cardiotoxicity from cancer therapies.

By Karen Stuyck

Hearth disease is one of the most common treatment-limiting side effects of cancer therapy. Monitoring patients for heart damage and managing the anticancer therapy to minimize cardiovascular complications are the keys to dealing with the problem, according to M. D. Anderson cardiologists.

Preventing treatment-related heart problems in cancer patients is especially important today, said Daniel Lenihan, M.D., associate professor in the Department of Cardiology and director of clinical research in cardiology. “Cancer

treatment has become so much more effective that, in many cases now, living with cancer resembles managing a chronic disease like diabetes or high blood pressure,” he said. American Cancer Society statistics indicate that the 5-year survival rate for all cancers has substantially increased in the past 20 years, from 51% for patients diagnosed between 1975 and 1977 to 66% for patients diagnosed between 1996 and 2002. “We don't want our patients to survive cancer and then die of a heart problem that might have been avoided.”

Chemotherapy and even newer biological and targeted cancer therapies can weaken a patient's heart. A study by M. D. Anderson cardiologists, published in the June 29, 2004, issue of the journal *Circulation*, reviewed the effects of 29 anticancer agents and concluded that every class of cancer drugs can potentially damage the heart.

One of the most problematic

Liza Sanchez, RCS, and Dr. Daniel Lenihan study a cardiogram for signs of chemotherapy-induced cardiotoxicity.



classes of anticancer drugs is the anthracyclines/anthraquinones, which include doxorubicin, widely prescribed for breast cancer, lymphoma, and other cancers. These drugs can cause irreversible chronic heart failure or left ventricle damage, said Edward T. H. Yeh, M.D., professor in and chair of M. D. Anderson's Department of Cardiology. The mechanism is thought to be direct myocardial injury due to formation of free radicals. Patients given these drugs need to be closely monitored for early signs of heart problems, he said, to limit any cardiotoxicity.

Other chemotherapy agents have a variety of toxic effects on the heart. If the total dose is high, cisplatin and cyclophosphamide may produce problems ranging from hypertension to chronic heart failure. Antimetabolites, such as 5-fluorouracil, can cause ischemia that, if untreated, can lead to heart attacks.

The newer targeted therapies, designed to attack only cancer cells, may also cause cardiotoxicity. Monoclonal antibody drugs, such as bevacizumab, cetuximab, and rituximab, produce significant infusion reactions, such as hypertension or hypotension, in some cancer patients. Antihistamines, acetaminophen,

steroids, and slow infusions may prevent or minimize such reactions. Careful monitoring for hypotension is recommended for patients who have pre-existing cardiac disease. If recognized early enough, these blood pressure changes can be easily treated, Dr. Yeh said.

Recent research has provided useful information for treating these therapy-related heart problems. "Before we just recognized that people were at risk for a heart problem, but now we've refined who's at risk," Dr. Lenihan said.

Cardiotoxicity can occur in any cancer patient, though elderly patients or those who already have pre-existing illnesses such as heart disease or diabetes have the highest risk. This damage to the heart can occur during treatment or months afterward.

It's important that cardiologists and oncologists work together both to prevent cardiotoxicity from occurring during cancer treatment and to treat any heart problems that do appear, Dr. Lenihan said. He and other physicians in the Cardiopulmonary Center often consult with the cancer center's oncologists or cardiologists outside of M. D. Anderson. They may be asked to evaluate such issues as a new cancer patient's risk of cardiovascular disease or how to minimize the effects of cancer therapy for a patient with pre-existing heart disease.

Depending on the individual case, they might recommend adjusting the patient's heart medications throughout the course of chemotherapy, since chemotherapy typically affects blood pressure. A patient's heart treatment might also have to be changed because of impending cancer therapy.

For instance, a stent should not be implanted because anticoagulants, which are necessary because clots otherwise may form in the stent, are contraindicated during chemotherapy. Instead, Dr. Lenihan said, he would probably recommend maximizing medical therapy to manage the heart problems.

Other patients might require going off clopidogrel, a blood thinner, for a period of time before having cancer surgery since the drug could adversely affect their ability to clot. "The timing

can be critical," Dr. Lenihan said. "We want to minimize the time a patient is off that medication because we understand how important it is."

Educating other physicians about new management techniques to limit toxicity during cancer treatment is also vitally important, he said. He and other M. D. Anderson physicians have given presentations at the Heart Failure Society of America to inform cardiologists about guarding against heart problems during cancer treatment.

Last February, the first Cardiology and Oncology Partnership symposium, held at M. D. Anderson and chaired by Dr. Lenihan, offered health professionals a comprehensive review of cardiovascular complications related to cancer therapy. A second conference will be held next May in conjunction with Memorial Sloan-Kettering Cancer Center in New York.

Cardiologists and oncologists, Dr. Lenihan said, may have different perspectives or focuses, but cancer patients with heart problems can only benefit from a partnership between the two medical specialties and multi-disciplinary management of their treatment.

Dr. Lenihan is also involved in research to detect cardiotoxicity after chemotherapy earlier than commonly used monitoring techniques. One of his M. D. Anderson studies used cardiology-specific blood tests—cardiac biomarkers B-type natriuretic peptide and troponin—to identify cardiotoxicity earlier than standard methods.

The preliminary study will be repeated in a more definitive fashion at other institutions, Dr. Lenihan said. He is hopeful that this research will help identify chemotherapy-related heart problems "at the onset of the problem so that we can devise ways to prevent it from becoming a real issue.

"Right now, we just respond to problems after they develop, but our research using biomarkers gives a mechanism to react much sooner and devise a treatment strategy to limit or prevent such toxicity." ●

For more information, call askMD Anderson at 1-877-632-6789 or visit www.mdanderson.org/care_centers/cardiopulmon.



Study Examines Diet, Breast Cancer Recurrence Risk

Researchers have discovered that a diet very high in fruits, vegetables, and fiber and extremely low in fat neither reduces the risk of breast cancer recurrence in women nor increases the chance for survival any more than the nationally recommended five servings a day of fruits and vegetables.

The Women's Healthy Eating Living (WHEL) Study, whose results were published in the July 18 issue of the *Journal of the American Medical Association*, enrolled more than 3,000 women previously treated for early-stage breast cancer. The comparison group (1,551 women) followed a standard "five-a-day" healthy diet, was given written material regarding a healthy lifestyle, was offered four cooking classes during the first year, and received bimonthly newsletters. In contrast, the intervention group (1,537 women) adopted a diet low in fat, high in fiber, and with twice the daily servings of fruits and vegetables; these women were intensively monitored with frequent phone counseling sessions, were offered 12 cooking classes during the first year, and received monthly newsletters.

No statistically significant difference emerged in either the breast cancer recurrence or death rates in the two groups. During the study, 518 of the women—256 (16.7%) from the intervention group and 262 (16.9%) from the comparison group—had a recurrence of their breast cancer, or developed a second primary tumor. A total of 315 women, 155 (10.1%) from the intervention group and 160 (10.3%) from the comparison group, died during the study.

M. D. Anderson Cancer Center enrolled 380 breast cancer survivors. Lovell Jones, Ph.D., professor in the Department of Health Disparities and the study's principal investigator at M. D. Anderson, said the study's results were extremely surprising.

"The WHEL's findings are pivotal

because we always assumed that we were not eating enough fruits and vegetables and the more we ate, the more protected we would be against cancer," Dr. Jones said.

However, he cautioned, "With these findings, it is imperative that we not discount the importance of a healthy diet and its role in cancer prevention. It is important to remember that our control group was eating the recommended guidelines for fruits and vegetables."

Differing interim results have been seen in another trial, the Women's Intervention Nutrition Study, which concluded that reducing dietary fat intake was marginally associated with longer relapse-free survival of breast cancer patients. However, the WHEL Study was not designed as a comparison investigation.

"The WHEL's findings are pivotal because we always assumed that we were not eating enough fruits and vegetables and the more we ate, the more protected we would be against cancer."

— Dr. Lovell Jones

Dr. Jones explained that the WHEL Study also did not address whether a low-fat diet high in fiber, fruits, and vegetables would alter the risk of primary breast cancer; it did not take into account what participants were eating prior to their enrollment into the study, healthy or not; and the outcome of the study could have been impacted by the improvement of breast cancer therapy over the past decade.

Except with women of color, Dr. Jones said, "We made more strides in the treatment of breast cancer in the last 10 years than we had in the 25 years before that. It is very possible that we are seeing the impact of better therapy on both sides of our study." ●

Pancreatic Cancer Gene Therapy Shows Promise in Preclinical Study

A liposome-delivered gene therapy developed at M. D. Anderson has been shown to selectively kill pancreatic cancer cells in mice while leaving healthy tissue unharmed. Researchers say the results show promise for more effective treatment of pancreatic cancer—which has a five-year overall survival rate of less than 4%, making it one of the deadliest forms of the disease.

The new therapy, named VISA-BikDD, uses a gene-based targeting agent, or promoter, that is known to be active in pancreatic cancer but not healthy tissue. The promoter was made more active with the addition of a regulatory gene sequence and a two-step transcriptional amplification system.

Finally, researchers added an engineered version of the *Bik* gene (known as *BikDD*) to the promoter and packaged everything in a liposome for intravenous delivery to the cancer.

According to laboratory findings, the gene activity was minimal or absent from healthy cells and even cell lines from other cancers. However, in pancreatic cancer, the *BikDD* gene forced cell death in all lines tested, resulting in prolonged survival, tumor shrinkage or eradication, and inhibition of metastasis. And, because the selectivity of the therapy was so strong, virtually no toxicity occurred. The findings were reported recently in the journal *Cancer Cell*.

"This looks like a promising approach to gene therapy for pancreatic cancer, and we are working to bring it to a clinical trial," said co-author James Abbruzzese, M.D., professor in and chair of the Department of Gastrointestinal Medical Oncology. A phase I trial could be ready to open in less than two years.

Senior author Mien-Chie Hung, Ph.D., professor in and chair of the Department of Molecular and Cellular Oncology, is leading a team that continues to research ways to tailor the gene expression vehicle so that it can target other cancers or even other diseases. ●



Recognize the Signs of Ovarian Cancer

While ovarian cancer is the deadliest of the gynecological cancers, if it is detected early, it can frequently be successfully managed and treated.

Unfortunately, ovarian cancer is too often diagnosed in its later stages, when it has already spread beyond the ovaries. Last year 15,000 women in the United States died from this relatively rare disease, which accounts for only 3% of all cancers among women.

The prognosis is much better when the disease is caught while it is limited to the ovaries. The survival rate among women diagnosed with early-stage ovarian cancer is more than 90%, according to M. D. Anderson's Ovarian Screening Clinic.

The six symptoms

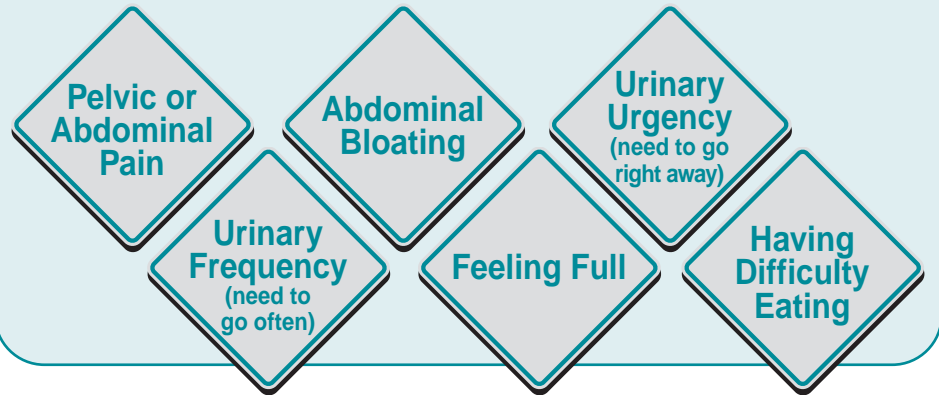
A problem in detecting the disease is that early symptoms are often overlooked because they're vague and resemble those of more common ailments. To help women identify ovarian cancer, researchers at the University of Washington recently determined six specific symptoms of the disease (see box).

The study's lead researcher, Barbara Goff, M.D., reported that while all women have these symptoms occasionally, they should be brought to a doctor's attention if "it's something new to you and it persists for more than a couple of weeks and occurs almost daily or every day." In the study, published in the journal *Cancer*, most women with ovarian cancer reported experiencing at least one of these symptoms and usually had them 12 or more times per month.

Other possible indications of ovarian cancer include changes in bowel habits; persistent gastrointestinal complaints such as gas, nausea, and indigestion; and unexplained weight loss or gain.

Health professionals at the M. D. Anderson Gynecologic Oncology

The following symptoms are often the result of something less serious than ovarian cancer. But if you are experiencing one or more of these symptoms frequently for the first time, tell your gynecologist.



Center say that a woman with any of these ongoing symptoms should discuss them immediately with a gynecologist. A full physical and gynecological exam can help determine the cause. If abnormalities are detected, special blood tests and ultrasound can be used to look for ovarian masses.

Even if you are frequently experiencing symptoms, ovarian cancer is still unlikely. More probable are a number of common illnesses, such as irritable bowel syndrome, which a doctor can rule out before checking for ovarian cancer.

There are currently no adequate screening tests for ovarian cancer, though there are some clinical trials of screening techniques at M. D. Anderson open to women at average or high risk for ovarian cancer. Ovarian cancer screening at M. D. Anderson's Gynecologic Oncology Center typically involves a discussion of your medical history and family background; a physical and a pelvic exam; a transvaginal ultrasound, a radiologic procedure that provides a picture of the ovaries; and a CA-125 blood test. Color-flow Doppler ultrasound, which measures blood flow in the ovarian vessels, may also be performed.

If you are diagnosed with ovarian cancer, surgery is the next step. During surgery, doctors will confirm the diagnosis and stage of the disease and remove the cancerous tissue from the ovary and surrounding areas. Usually the fallopian tubes, uterus, and one

or both ovaries are removed. Most patients will later receive chemotherapy to kill any remaining cancer cells.

Risk factors

The exact causes of ovarian cancer are not known, but women may be at increased risk for the disease if:

- Their mother, sister, or daughter had ovarian or breast cancer.
- They themselves have had breast, endometrial, or colon cancer.
- They have a history of infertility or used fertility drugs.
- They are of Ashkenazi Jewish heritage.
- They have a mutation or abnormal change in the *BRCA1* or *BRCA2* genes. This would indicate susceptibility to breast and ovarian cancers.

For more information about the disease or ovarian cancer screening, go to www.mdanderson.org/diseases/ovarian. ●

For more information, talk to your physician, or:

- call askMDAnderson at 1-877-632-6789
- visit www.mdanderson.org.

November 2007

K. Stuyck

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M. D. Anderson Cancer Center

DiaLog Advancing Drug Design in Academia

By Garth Powis, D.Phil.

Better. Faster. Cheaper. These three words best describe why the discovery and development of drugs in academic research settings just makes good sense.

Drug development is a multi-billion-dollar industry in the United States and around the world, yet an average of only four new cancer drugs are developed per year by big pharmaceutical companies—each costing approximately \$800 million and taking anywhere from 8 to 14 years of work. And this is only for cancers with large patient populations. Orphan cancers are typically overlooked in drug development efforts because the market is deemed too small to be profitable. But this is where we, in academia, can step up to the plate and use our knowledge, resources, and expertise.

Our estimates indicate that we can develop drugs at a small portion of the cost and time it takes for pharmaceutical companies to do so. As an academic institution, we can lead the effort to discover and develop novel drugs and to pursue innovative clinical trials for cancers with fewer patients. We are better equipped to develop agents faster, cheaper, and more innovatively because we don't face the same obstacles as big pharmaceutical companies—namely, to meet requirements of profitability and market share. We can take the initiative and pursue new ideas, whereas industry may close down a drug

program not because it isn't viable but because it isn't profitable.

In the last 5 years, M. D. Anderson has brought a remarkable 13 drugs to clinical trial, and another six are slated for clinical trials in the coming year. Another 12 agents are in the developmental pipeline. Through M. D. Anderson's Pharmaceutical Development Center, we are able to carry out nearly every aspect of pre-clinical cancer drug development—from antitumor testing and pharmacokinetic studies to state-of-the-art assay development and toxicology studies, FDA meetings, and Investigational New Drug preparation and filing. Ultimately, it is our patients—and all cancer patients—who benefit from these new drugs and treatments.

Our goal is not to become a drug company, but to enable and encourage our investigators to rapidly bring innovative findings to the point where they can be tested clinically. This approach provides patients with access to therapeutic options that otherwise do not exist and allows investigators to develop agents that will be tested in our own phase I and II clinical trials—enabling us to more quickly bring cancer drugs to patients. ●



Dr. Powis is director of the Center for Targeted Therapy and professor in and chair of the Department of Experimental Therapeutics.

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