

REPORT TO PHYSICIANS

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Oncology

Targeting Inflammation in Cancer Prevention

Inhibition of inflammation may
disrupt the development of some
cancers in patients at high risk.

By John LeBas

Cancer prevention specialists have long sought ways to forestall cancer in people most at risk for the disease. Because chronic immune responses appear to provoke genetic aberrations and defective cell signaling that cause many types of cancer, blocking inflammation is a logical approach to cancer prevention.

Anti-inflammatory compounds have garnered much interest in the field of cancer prevention and are being widely tested, despite the somewhat rocky history of a newer subgroup of anti-inflammatory drugs known as cyclooxygenase-2 (COX-2) inhibitors. Five years ago, most testing of COX-2 inhibitors for cancer prevention was halted because of unacceptable cardiotoxicity. Since then, however, researchers have found new promise in both COX-2 inhibitors and other drugs that disrupt inflammatory pathways to cancer.

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Dr. Ernest Hawk, professor and vice president for cancer prevention at M. D. Anderson, says “targeting inflammation appears to be part of the answer” as investigators seek drugs that can block many types of cancer.

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Targeting Inflammation in Cancer Prevention

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Of the various reasons to continue testing COX-2 inhibitors and other non-steroidal anti-inflammatory drugs (NSAIDs) for cancer chemoprevention, the most important may be that inflammation appears to play a role in many cancer types that affect a large number of people. “We can’t always anticipate which type of cancer a patient might get. When people have risk factors placing them at an increased risk for a specific type of cancer, we can often suggest screening or preventive approaches targeted to that cancer type. But it would be even better if we could identify a drug that will prevent not just one type of cancer but many,” said Ernest Hawk, M.D., professor and vice president for cancer prevention at The University of Texas M. D. Anderson Cancer Center. “We are still looking for that Holy Grail, and targeting inflammation appears to be part of the answer.”

Learning from the past

The idea that inflammation leads to cancer is not altogether surprising, considering that medicine has linked an overactive or extended immune response with many ailments, including asthma, rheumatoid arthritis, and inflammatory bowel disease.

Further, it has long been known that many solid tumors arise at sites of chronic irritation. The potential sources of cancer-causing inflammation include:

- viruses, such as the hepatitis B virus (liver cancer),
- excessive stomach acid (esophageal cancer),
- sunburn (skin cancer),
- consumed irritants, such as alcohol (esophageal and liver cancers, among others) and cigarette smoke (oral and lung cancers, among many others), and
- inhaled asbestos fibers (mesothelioma).

The administration of NSAIDs for cancer chemoprevention has been most vigorously tested in patients with famil-



Preliminary findings from a phase II pediatric trial suggest that celecoxib, even at a high dose, is safe in children as young as 10 years old, at least when given for a short time.”

– Dr. Patrick Lynch

ial adenomatous polyposis (FAP). In this inherited condition, mutations of the APC gene cause hundreds or thousands of colorectal adenomatous polyps, or adenomas. FAP almost always progresses to colorectal cancer by adulthood unless a prophylactic colectomy (removal of the colon) is performed. Researchers began experimenting with COX-2 inhibitors to prevent such cancers in the 1990s after a team led by Raymond N. DuBois, now provost and executive vice president at M. D. Anderson, discovered that the COX-2 enzyme was highly expressed in colorectal adenomas and colorectal cancer.

FAP patients are a seemingly ideal group in whom to test cancer-preventing compounds. First, genetic testing and family history can clearly identify such patients as being very likely to develop a specific type of cancer. Second, both the COX-2 inhibitor celecoxib (Celebrex) and the NSAID sulindac (Clinoril) have been shown effective at reducing the number of polyps in FAP patients.

But the risk of side effects, particularly those associated with celecoxib, has slowed the wider application of NSAIDs as chemopreventive agents. After federally sponsored trials of COX-2 inhibitors were halted in 2004 as a result of the cardiotoxicity findings in one large trial, researchers sought clues to what went wrong. In a retrospective study, they learned that a small percentage of people—those with the star-3 allele of the CYP 2C9 enzyme—do not seem to me-

tabolize celecoxib as effectively, which leads to higher serum levels of the drug. As a result, such patients may be more likely to suffer side effects, and they probably are not good candidates for future research involving celecoxib, Dr. Hawk said. However, other factors may affect a patient’s risk of cardiac harm from the drug, and those would best be elucidated by larger prospective studies.

Another recent analysis of 5-year data from earlier trials showed for the first time that celecoxib suppresses—but does not ablate—colorectal adenomas, meaning that the agent may need to be taken continuously to control the growths over the long term. Although that finding could help refine patient selection, it too needs to be confirmed with a large prospective study.

New research

Many of the data from celecoxib trials gathered since 2004 are preliminary or from early-phase testing, but they suggest that investigation of COX-2 inhibitors should continue.

Published data from the first large randomized phase II study of celecoxib in lung cancer prevention showed not only that the drug reduced levels of a cellular proliferation biomarker in current and former smokers, but also that no adverse cardiac events occurred. The trial was among those halted in late 2004 after the cardiac risks of celecoxib were discovered; however, it reopened 6 months later after stricter guidelines

were adopted to exclude those patients who were more susceptible to adverse cardiac events. “We learned that not only are COX-2 and the inflammation pathway important targets in lung cancer prevention, but that COX-2 inhibitors can be given safely to some patients at a high risk for lung cancer,” said Edward S. Kim, M.D., an assistant professor in M. D. Anderson’s Department of Thoracic/Head and Neck Medical Oncology and principal investigator for the lung cancer study.

Early analyses from other placebo-controlled phase II trials suggest that celecoxib may also reduce the incidence of cancer in some patients at high risk for bladder or skin cancer, though confirmatory data are needed.

Investigation of celecoxib in patients with FAP has continued as well. M. D. Anderson was the lead institution in a recent phase II pediatric trial that aimed to determine whether celecoxib can delay or prevent the need for prophylactic colectomy in children with FAP.

“Preliminary findings suggest that celecoxib, even at a high dose, is safe in children as young as 10 years old, at least when given for a short time (3 months),” said principal investigator Patrick Lynch, M.D., an associate professor in the Department of Gastroenterology, Hepatology and Nutrition. “When polyps are present, celecoxib, at least at a high dose, seems to work as well as it does in adults in shrinking or regressing adenomas.” A phase III trial is under way to see whether celecoxib can prevent the initial occurrence of adenomas in children who have APC gene mutations but who haven’t yet developed many polyps.

Investigators caution that much remains to be learned about how celecoxib affects individual patients’ risk of adverse cardiac events. “Screening for cardiotoxicity is a hard one,” Dr. Lynch said. “What we do is to exclude from trials and from non-trial use of NSAIDs those subjects who have obvious preexisting cardiovascular risk factors, such as existing cardiovascular

disease, hypertension, diabetes, and a strong family history of cardiovascular disease.”

Based on the research from the past 5 years, COX-2 inhibitors warrant further study, Dr. Hawk believes. “If it can be definitively shown through larger trials that celecoxib can blunt the incidence of cancer in at least four organs (colon, lung, bladder, and skin), and if we can refine its administration in a safe manner, then COX-2 inhibitors may be a very powerful class of compounds for cancer prevention.”

Other approaches

Of course, the strategy of interrupting inflammatory pathways to cancer may not rely solely on COX-2 inhibitors, as suggested by successful studies of other agents. Dr. Hawk was the project officer for a U.S. National Cancer Institute–led clinical trial of two older drugs, sulindac and eflornithine (an inhibitor of the enzyme ornithine decarboxylase), in patients with prior colorectal adenomas. Testing in animals had demonstrated that the drugs had synergy when given in combination, suggesting that the effective dose of each agent is lower when they are given together than when they are given separately. With lower doses, the researchers expected fewer side effects (which can include cardiotoxicity from sulindac and loss of hearing and low platelet counts from eflornithine).

Results of the phase II/III clinical trial, which included 375 patients, were far better than expected: the combination yielded a 90% reduction in the number of adenomas overall and a 95% reduction in premalignant adenomas. Moreover, no significant side effects were observed, though there was some indication of hearing loss and myocardial infarction in patients with certain cardiac risk factors. The study was published last year in *Cancer Prevention Research*.

“This was arguably the first real test of combination chemoprevention,” Dr. Hawk said. “Though there is still a potential for side effects, we think the

risk can be managed by giving this combination. Its effectiveness was almost comparable to that of a surgical approach.” Two trials are now being designed to test the combination in a larger group of patients, and a third trial of the combination plus celecoxib in patients with FAP is under way at M. D. Anderson and other institutions.

Meanwhile, preclinical studies at M. D. Anderson are providing new knowledge about the varied ways in which inflammation can contribute to cancer—and perhaps are laying the groundwork for future preventive therapies.

For example, it is strongly suspected that obesity increases a person’s risk of developing pancreatic cancer, but until recently, the exact mechanism of carcinogenesis was unknown. Then last year, a preclinical study by researchers at M. D. Anderson and The University of Texas at Austin showed that mice given a high-calorie diet developed more pancreatic tumors and pancreatic tumors of greater severity than mice given a restricted-calorie diet. Furthermore, the study showed that the restricted-calorie group had lower serum levels of inflammatory signaling proteins—a finding that made sense, according to the authors, because fat tissue is known to be a major source of such proteins. “Our findings suggest that calorie restriction could play a role in the prevention of pancreatic tumors caused by chronic inflammation,” said senior author Stephen D. Hursting, Ph.D., professor in M. D. Anderson’s Department of Carcinogenesis and chair of the Department of Nutritional Sciences at The University of Texas at Austin.

In another example, M. D. Anderson researchers discovered that tumor necrosis factor alpha, an inflammatory protein, can trigger blood vessel growth (angiogenesis) in breast cancers by switching off two genes that suppress tumor formation. Since angiogenesis is crucial to tumor growth, tumor necrosis factor alpha might be a therapeutic target for some breast cancers, researchers said. In mice,

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injections of the immunosuppressant rapamycin interrupted the angiogenic process, presumably by blocking the molecular signaling that switched off the tumor-suppressing genes. The group, led by Mien-Chie Hung, Ph.D., professor and chair of the Department of Molecular and Cellular Oncology, is now trying to determine whether the tumor pathway elucidated in the study helps explain why obese people may be at a higher risk of developing pancreatic and other cancers, since obese mammals have been shown to have high levels of tumor necrosis factor alpha in their fat cells.

Given the complexity of inflammation's role in cancer development, it could be that not one but many Holy Grails will someday be used to prevent inflammation from causing tumors. "I don't anticipate that any of these agents are chemotherapeutic—they aren't going to wipe out a cancer," Dr. Hawk said. "But for the prevention of certain cancers, they may ultimately prove to be very effective." ●

For more information, visit M. D. Anderson's Web site at www.mdanderson.org.

Clinical Trial in Prevention

A Phase III Placebo-Controlled Trial of Celecoxib in Genotype Positive Subjects with Familial Adenomatous Polyposis (2006-0040). Principal investigator: Patrick Lynch, M.D. The goal of this clinical research study is to learn whether celecoxib can delay or prevent the need for a colectomy in children who have familial adenomatous polyposis (FAP). Participants are randomly assigned to receive celecoxib or placebo and are followed for 5 years or until the first occurrence of either a) 20 or more polyps (> 2 mm) detected by colonoscopy or b) diagnosis of colorectal cancer. Participants must be 10–17 years old at the time of enrollment and have a genetic confirmation of FAP.

Treating Radiation Necrosis of the Brain

In a phase II trial, bevacizumab appears to stop a debilitating side effect of radiation therapy.

By John LeBas

When brain tumors are treated with radiation therapy, there is always a risk of radiation-induced necrosis of healthy brain tissue. Insidious and potentially fatal, radiation necrosis of the brain may develop months or even years after irradiation.

This poorly understood side effect can occur even when the most stringent measures are taken to avoid exposing healthy tissue to harmful levels of radiation. In most cases, radiation necrosis of the brain occurs at random, without known genetic or other predisposing risk factors. The only treatment options typically available for radiation necrosis of the brain are surgery to remove dead tissue and use of the steroid dexamethasone to provide limited symptom control. But clinicians have not found a way to stop the progression of necrosis, despite having tested a range of therapies including anticoagulants, hyperbaric oxygen, and high-dose anti-inflammatory regimens.

However, recent studies at M. D. Anderson have shown that the monoclonal antibody bevacizumab (Avastin) may be able to stop radiation necrosis of the brain and allow some of the damage to be reversed. Victor A. Levin, M.D., a professor in the Department of Neuro-Oncology and the senior researcher on the studies, said the findings suggest that radiation necrosis of the brain can be successfully managed—and perhaps even prevented—with bevacizumab or



We think aberrant production of VEGF is involved.

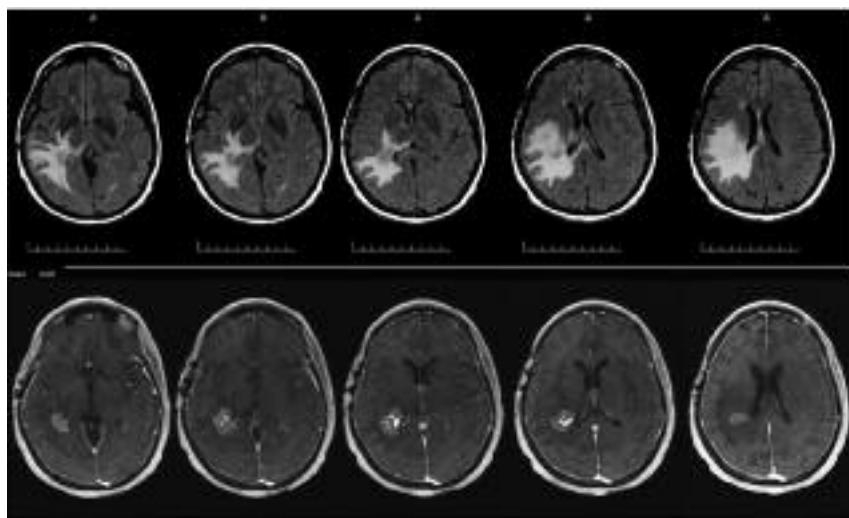
The question is, is that all that's going on?"

— Dr. Victor A. Levin

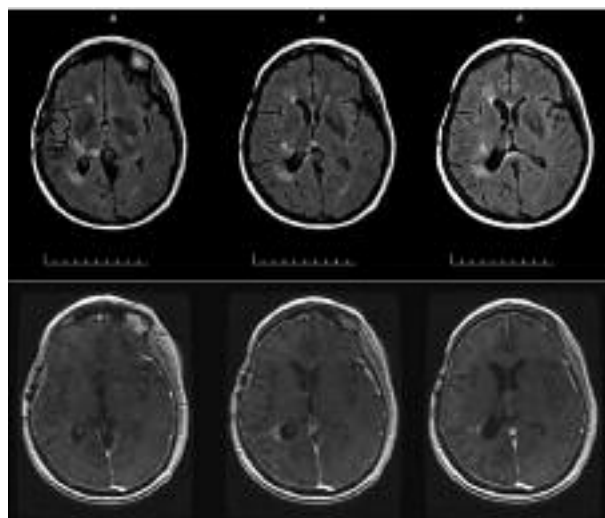
similar drugs.

The need for such a breakthrough is as old as radiation therapy for cancers in the brain. "No matter what we do or how good we do it, we know a small percentage of patients who receive radiation therapy to the central nervous system will suffer late-occurring radiation necrosis," Dr. Levin said. "We used to think it was the dose that was causing problems. Then we did a study and found that there was little to no relation to radiation dose or radiation volume—the necrosis occurred simply by chance. So it is impossible to say which patients will develop this problem; we just have to monitor them and hope for the best."

Like necrosis, the discovery that bevacizumab has an effect on necrosis can also be attributed to chance. Bevacizumab, a newer drug that prevents blood vessel growth in tumors by blocking vascular endothelial growth factor (VEGF), was originally approved in the United States for the treatment of metastatic colon cancer



PANEL 1



PANEL 2

Visualizing the effects of bevacizumab: An ongoing M. D. Anderson study has found that bevacizumab may be effective against radiation necrosis of the brain. In panel 1, magnetic resonance images show an area of necrotic tissue in a patient who received radiation therapy for a brain tumor. In panel 2, the necrosis has regressed following four doses of bevacizumab administered over several months.

and non-small cell lung cancer. An M. D. Anderson group that included Dr. Levin decided to test the drug in patients who had VEGF-expressing brain tumors. “Some of these patients also had necrosis from prior radiation therapy, and we were struck by the positive response of those patients to bevacizumab,” Dr. Levin said. “We had never seen such a regression of necrotic lesions with any other drug like we did in those patients.” The observation prompted the researchers to design a placebo-controlled, double-blind, phase II trial sponsored by the U.S. Cancer Therapy Evaluation Program in which bevacizumab would be tested specifically for the treatment of radiation necrosis of the brain.

The trial is small, having accrued 13 of a planned 16 patients, and is limited to those with progressive symptoms, lower-grade primary brain tumors, and head and neck cancers. But the results have been unlike anything the researchers have seen before in radiation necrosis therapy. All of the patients receiving bevacizumab responded almost immediately to treatment, with regression of necrotic lesions evident on magnetic resonance images, while none of the patients receiving the placebo showed a response. The results were striking, and all of the patients who switched from placebo showed a response to bevacizumab as well. So far, responses have persisted over 6 months even after the end of bevacizumab treatment.

Side effects seen in the trial so far included venous thromboembolism in one patient, small vessel thrombosis in two patients, and a large venous sinus thrombosis in one patient. Dr. Levin is unsure whether the side effects were caused by therapy or the radiation necrosis itself. “We’re also not absolutely sure what is causing the positive effects against the radiation necrosis,” he said. “We presume it’s related to the release of cytokines like VEGF, since bevacizumab

is very specific and only reduces VEGF levels. We think aberrant production of VEGF is involved with radiation necrosis of the brain, and the fact that even short treatment with bevacizumab seems to turn off the cycle of radiation damage further confirms the central role of VEGF in the process.”

The multidisciplinary research team has also postulated that radiation therapy damages astrocytes, a cell type involved in various brain functions, and causes them to leak VEGF. This leaked VEGF might then cause further damage to brain cells and further leakage of VEGF. “It gets to be a very vicious cycle,” Dr. Levin said. “The question is, is that all that’s going on?”

Dr. Levin hopes that the answers to that question and others may lead to preventive measures against radiation necrosis, beyond what is already done to control the development of radiation itself. Perhaps bevacizumab can be given in low doses before radiation or intermittently afterward to reduce VEGF levels and protect the brain from abnormally high levels of the protein. He hopes such approaches can be tested in future studies. “Just the fact that bevacizumab works has helped us understand so much more about what happens in radiation necrosis,” he said. “Everything we’ve tried up until now has been a brick wall.” ●

For more information, call Dr. Levin at 713-792-8297.

Brain Necrosis At a Glance

Current techniques for irradiating brain tumors are highly targeted to maximize the radiation dose delivered to cancer cells while minimizing the dose to healthy cells. However, radiation injury is still a possibility with any radiation therapy. Brain tissue that suffers such an injury can die off months or years after treatment—a late-occurring, potentially fatal side effect known as radiation necrosis.

Symptoms of radiation necrosis of the brain include:

- headache
- neurocognitive problems
- motor function problems
- dementia

Aside from palliative surgery and palliative steroid therapy, no standard treatment exists.

Preclinical Studies Reveal Effectiveness of Therapies for Pediatric Cancers

Researchers in the Children's Cancer Hospital at M. D. Anderson recently reported preclinical results for anti-cancer approaches in neuroblastoma and acute myelogenous leukemia, potentially paving the way for new clinical treatments.

All of the agents tested in the studies, which were presented last month at the 22nd annual meeting of the American Society of Pediatric Hematology/Oncology (ASPHO), are either in trials for other cancers or may begin early clinical testing this year. "We hope that these agents will one day make it to our pediatric patients, who often run out of new treatment options," said Patrick Zweidler-McKay, M.D., Ph.D., senior investigator on the studies and an assistant professor in pediatrics.

Neuroblastoma

In one study, a glycolysis inhibitor named 3-BrOP was shown to starve neuroblastoma cells by blocking the cells' ability to derive energy from sugar. 3-BrOP reduced human tumor growth in mice by more than 75%. The researchers found that neuroblastoma cells are much more dependent on

have efficacy against glioblastoma, colon cancer, lymphoma, and acute leukemia.

Another neuroblastoma study presented at ASPHO targeted the tumor by inhibiting its blood supply. In this study, investigators used the mobilizing agent AMD3100 and unexpectedly found that it disrupted tumor growth by reducing the number of tumor blood vessels. Daily treatment with AMD3100 reduced tumor growth in mice by more than 75%.

In a third study focusing on neuroblastoma, researchers tested a novel multi-kinase inhibitor, vandetanib. "By itself, vandetanib inhibited neuroblastoma tumor growth in mice by two-thirds and decreased blood vessel formation around the tumors," said Peter Zage, M.D., Ph.D., an assistant professor in pediatrics and the investigator who presented the findings. "When vandetanib was combined with 13-cis-retinoic acid (CRA), the impact on tumor growth was even greater." Mice treated with the combination of vandetanib and CRA, a drug used to treat severe acne, had an 86% reduction in tumor growth.

CRA was previously known to differentiate neuroblastoma cells into benign cells when used in combination therapies, though it has no direct action against the cancer. A first-in-children phase I clinical trial of the vandetanib-CRA combination is now open at M. D. Anderson for children whose neuroblastoma has relapsed.

The findings of the neuroblastoma studies are important because current therapies have limited effectiveness. Neuroblastoma is the most common



“Now that we have found a new, targetable growth pathway in acute myelogenous leukemia, we may be able to use AZ23 to treat the disease.”

— Dr. Patrick Zweidler-McKay

extra-cranial solid tumor in children, and nearly two-thirds of those children are diagnosed after the disease has metastasized.

Leukemia

In another study involving mice harboring human acute myelogenous leukemia cells, a novel tropomyosin receptor kinase inhibitor named AZ23 was shown to reduce the levels of circulating leukemia cells by more than half within 1 week. Meanwhile, in mice treated for 4 weeks, the leukemia was eradicated and remained undetectable in 60% of the mice for several months. Importantly, the researchers found that AZ23 was more effective against human acute myelogenous leukemia cells that express high levels tropomyosin receptor kinase A, a nerve growth factor receptor, which could guide treatment with the drug in the future.

Pediatric acute myelogenous leukemia has a cure rate of only 50%, compared with the more common acute lymphoblastic leukemia, which is cured in 80% of pediatric patients. As with neuroblastoma, new treatments for acute myelogenous leukemia are badly needed, and thus investigators are encouraged by the preclinical results seen with AZ23. "Now that we have found a new, targetable growth pathway in acute myelogenous leukemia, we may be able to use AZ23 to treat both children and adults with the disease," said Dr. Zweidler-McKay. ●

For more information, call Dr. Zage at 713-792-6624 or Dr. Zweidler-McKay at 713-563-5394.

“When vandetanib was combined with 13-cis-retinoic acid, the impact on neuroblastoma growth was greater.”

— Dr. Peter Zage



glycolysis for energy than normal cells, which explains why the 3-BrOP was effective. The agent, developed at M. D. Anderson, has previously been shown to



Protect and Check Your Skin

Skin cancer is the most common type of cancer in the United States, with more than 1 million cases diagnosed each year. By age 65, 40%–50% of Americans will have had at least one skin cancer, according to estimates by M. D. Anderson Cancer Center.

Fortunately, you can do a lot to protect yourself and your family from skin cancer. It's especially important to think about skin safety during the sunny days of summer, since sunburn is the single greatest risk factor for all types of skin cancer.

The three types

There are three main types of skin cancer: basal cell carcinoma, squamous cell carcinoma, and melanoma. All three can usually be cured when found and treated in their early stages.

Basal cell carcinoma, which accounts for more than 90% of skin cancers, usually shows up as a small, pink bump or patch on the head or neck, although it may appear on any part of the body. It is a slow-growing cancer but should be treated as early as possible.

The less common **squamous cell carcinoma** can resemble basal cell carcinoma. However, squamous cell carcinomas are usually more scaly and rough and are often found on the head, neck, ears, lips, and backs of the arms and hands. Squamous cell carcinomas can also develop around scars or ulcers. This cancer type is more likely to grow deeply within the skin or spread to other parts of the body than basal cell carcinoma.

Melanoma is rarer still, but it is much more dangerous than basal cell carcinoma and squamous cell carcinoma. Left untreated, melanoma is likely to spread to other organs and eventually kill. Melanoma will usually first ap-

pear as a dark or colored mole with an irregular border.

Protect yourself

Fortunately, you can greatly reduce your risk of all types of skin cancer simply by protecting yourself from the sun's damaging ultraviolet (UV) radiation. Here are a few tips:

- **Avoid the sun as much as possible, especially between 10 a.m. and 4 p.m., when the sun's rays are strongest.** If you are outside, try to stay in the shade. People with fair skin who freckle or sunburn easily are at a higher risk of skin cancer than others and should be especially careful.
- **Use sunscreen and lip balm with a sun protection factor (SPF) of at least 15.** Make a habit of applying sunscreen, even on overcast days. Thirty minutes before going outside, apply sunscreen generously (using a palm's worth) to your hands, feet, the tops of your ears, the back of your neck, your face, and other exposed skin. Reapply sunscreen often if you are swimming or perspiring.
- **Wear protective clothing, such as a wide-brimmed hat, a long-sleeved shirt, and pants.** Sporting goods stores sell clothes that have built-in UV protection, which makes them even more effective against sun damage. To protect your eyes, wear sunglasses that filter out UV radiation.
- **Pay special attention to your children—much of our lifetime sun damage occurs in childhood.** Apply sunscreen to children 30 minutes before they go outdoors. Teach them the shadow rule: If your shadow is shorter than you, the sun's rays are at their strongest, and extra precautions should be taken. Infants



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should never be exposed to direct sunlight.

- **Don't use sunlamps or tanning beds.**

Check yourself

In addition to limiting your sun exposure, M. D. Anderson Cancer Center recommends that you give yourself a monthly skin exam after a shower or bath, using both a full-length mirror and a hand-held mirror. Learn where your birthmarks, moles, blemishes, and freckles are and what they look and feel like. Check yourself from head to toe, including your back, scalp, genitals, and between the buttocks.

During these self-exams, check for anything that has changed, such as the size, shape, texture, or color of a mole or freckle. Also, look for areas of scaliness, itching, bleeding, or tenderness.

Contact your doctor if you see any odd-looking skin, sores that won't heal, or changes in a mole or freckle. It may be your chance to nip skin cancer in the bud. ●

For more information, talk to your physician, or:

- visit www.mdanderson.org/; under "Cancer Types," look for "Skin Cancer"
- call askMDAnderson at 1-877-632-6789

OncoLog, May 2009
K. Stuyck

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IN BRIEF

Overexpressed Protein Could Be Targeted in Osteosarcoma

A protein known to be highly expressed in bone metastases is also active in osteosarcomas, M. D. Anderson researchers have discovered. The finding suggests that osteosarcomas may be treatable with therapeutic agents that shut down the protein, known as interleukin-11 receptor alpha (IL-11- α).

Using a mouse model, the researchers determined that IL-11- α was present at high levels in primary osteosarcomas and osteosarcomas that had spread to the lungs. However, the protein was absent from normal bone and lung tissues. Immunohistochemical staining of human tissues provided further evidence that IL-11- α is highly expressed in primary and metastatic osteosarcomas as well as the blood vessels feeding them.

To test whether osteosarcomas in the mice would take up therapy targeting IL-11- α , the researchers intravenously administered phages (virus-like particles) containing an IL-11- α ligand. The phages were selectively taken up by the tumors but not healthy tissue. "Our findings indicate that therapeutic targeting of IL-11- α may yield anti-tumor, anti-metastasis, and anti-angiogenesis effects in osteosarcoma," said Valerae O. Lewis, M.D., the study's senior author and associate professor and chief of the Department

of Orthopedic Oncology at M. D. Anderson. The findings, published in the journal *Cancer Research*, are also important because researchers have identified very few proteins in primary osteosarcoma that might be targeted by therapeutic agents.

Finding an effective molecularly targeted therapy for osteosarcoma, the most common primary tumor of the bone, would be a long-needed breakthrough in treatment. Current chemotherapeutic agents for osteosarcoma are toxic to the nerves, heart, kidneys, and auditory system, which limits their use. About 30% of osteosarcoma patients die from the disease.

"Targeting of IL-11- α may yield therapeutic effects in osteosarcoma."

— Dr. Valerae O. Lewis

A therapeutic agent targeting interleukin receptor expression is now undergoing preclinical testing in osteosarcoma. Investigators hope the agent, developed at M. D. Anderson and named BMTP-11, shows efficacy against primary bone tumors and can quickly be moved to clinical testing. BMTP-11 will also soon begin phase I clinical testing in patients with bone metastases from prostate cancer. Preclinical testing showed that the agent induced cell death in such metastases. ●

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