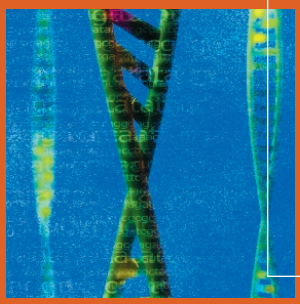
USC/NORRIS COMPREHENSIVE CANCER CENTER

FALL 2004

Cancer Center Report

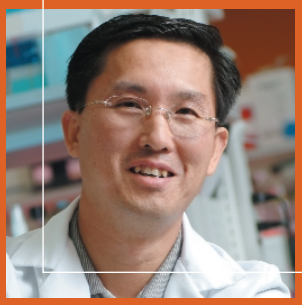





OUTSIDE THE BOX

Five cancer-fighting experts go beyond scientific boundaries to take innovative cancer research and patient care in new directions.






USC/Norris Comprehensive Cancer Center

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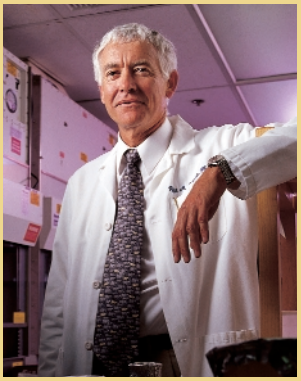
Leading Reason

Director of USC/Norris Comprehensive Cancer Center is president-elect of the American Association for Cancer Research. by Alicia Di Rado



Peter A. Jones, Ph.D., director of the USC/Norris Comprehensive Cancer Center, has become president-elect of the American Association for Cancer Research (AACR).

AACR members selected Jones for the post during the organization's 95th annual meeting in March. Jones will be installed as president at the AACR's 96th annual meeting in 2005.

Jones, Distinguished Professor of Biochemistry and Molecular Biology and Urology at the Keck School of Medicine of USC, holds the H. Leslie Hoffman and Elaine S. Hoffman Chair in Cancer Research.

"Obviously, it is a great honor to be asked to lead the premier cancer research organization not only in the United States, but in the entire world," Jones says. "This is a critical time in cancer research because the application of molecular breakthroughs to cancer treatment and prevention holds so much promise, while funding for cancer research remains flat."

Jones left his native South Africa in the 1970s to join USC as an assistant professor of pediatrics and biochemistry at Childrens Hospital Los Angeles. He took the helm of the USC/Norris Cancer Center in 1993.

When Jones first arrived at USC, little was known about what causes cancer cells to proliferate wildly, a hallmark of malignancy. Since then, knowledge of cancer has grown exponentially, especially in genetics. Jones focuses on DNA methylation, a process in which the body locks certain genes—in some cases, genes that help keep cancer in check.

Research on cancer genetics is burgeoning at USC/Norris, where Jones has concentrated on recruiting scientists in molecular genetics and translational research. His selection as AACR president-elect signals the respected stature of USC/Norris, which was among the first institutions selected by the National Cancer Institute as a comprehensive cancer center. "Heading such an important organization is very significant for us," Jones says. "It really is a testament to the strength of our program."

Jones is one of seven scientists to join the AACR's leadership this year. Officers serve terms of one year. Currently, Vanderbilt University's Lynn M. Matrisian is serving as president of the organization.

Founded in 1907, the AACR is a professional society of more than 22,000 laboratory, translational and clinical scientists engaged in all areas of cancer research in the U.S. and in more than 60 other countries. The AACR's mission is to accelerate the prevention and cure of cancer through research, education, communication and advocacy. ■

PHOTO BY S. PETER LOPEZ

For USC/Norris Hospital patients and their families and friends, afternoon tea brings a physical as well as a mental break from their treatments.

Tea not just for Two

by Jon Nalick

Offering chemotherapy patients a welcome change of scenery from their rooms, volunteers and dietary staff at the USC/Norris Cancer Hospital have established a new Friday tradition: afternoon tea.

As part of a 16-month-old program, volunteers deliver personally printed invitations to patients on the third and fourth floors, inviting them to spend some time with family, friends and their fellow patients in visitors' rooms that offer a cozy, genial atmosphere as well as china, linen tablecloths, teapots, fresh flowers, cookies and music.

Marta Shand, food nutrition director at the hospital, says the weekly program is run as a collaboration between USC/Norris Dietary Services and Volunteer Services.

Shand says that the first few times they hosted the event, staff members were unsure whether anyone would attend. But almost immediately they found themselves in a room packed with people.

Shand notes that cancer patients rarely leave their rooms except for treatment and that the new program offers a welcome respite.

Now, each Friday around 3 p.m., patients—some with I.V. poles at their sides—mingle and enjoy tea and snacks with friends and family.

The tradition was the brainchild of Shand and director of volunteer services Alicia Syres. With the help of USC senior psychology major and volunteer Jessica Lewis and donations from the USC/Norris Auxiliary, the plan to help comfort patients and families came to fruition.

The feedback from attendees was positive and immediate, Lewis says: "The thing I kept hearing was that it's a good distraction—a ray of sunshine on a cloudy day for a lot of people. The families really enjoy it."

The program now has three volunteers who host the weekly event—Lewis, Jane Morita and Julie Sullivan. In addition, Ruth Dunn, a 94-year-old USC/Norris volunteer, makes sachets from lavender she grows in her own garden for each patient attending the teas.

Volunteers interested in assisting the program should call Alicia Syres, director of volunteer services, at (323) 865-3169.

UNLOCK and roll

By unlocking specific genes in cells, the drug zebularine slows tumor growth.

by Lori Oliwenstein

A novel anti-cancer drug that inhibits a process known as DNA methylation is preferentially taken up by tumor cells as compared to normal cells, according to a group of researchers led by scientists from the Keck School of Medicine.

In addition, this drug—a methylation inhibitor called zebularine—is better at inhibiting cell growth and promoting gene expression in cancer cells, notes Peter Jones, Ph.D., director of the USC/Norris Comprehensive Cancer Center and the principal investigator on the study. In a study of zebularine's effect on the rate of division of cancer cells, Jones and his colleagues showed that zebularine slows growth by as much as 68 percent in cancer cells, but only by 21 percent or less in normal cells.

These findings were reported in the August 2004 issue of *Cancer Cell*.

DNA methylation—the addition of a methyl group to a stretch of DNA, which can lock, or silence, that gene—can play an important role in the development of cancer. If methylation silences a gene that normally would control cell growth or prompt the cell to commit suicide, then the cell will grow unchecked—the hallmark of cancer.

"The concept that the silencing of genes is a critical part of the cancer process is a major conceptual advance in this field," Jones says. "Realizing that, it becomes very important to find keys to unlock those silenced genes."

Methylation and its effects are reversible. In the *Cancer Cell* study, Jones, M.D./Ph.D. student Jonathan Cheng, and graduate student Christine Yoo—along with colleagues from the National Cancer Institute, the University of Miami School of Medicine and Aarhus University Hospital in Denmark—looked at the effects zebularine had on a panel of seven different human tumor cell lines, and compared them to its effects on four different cell lines of normal human fibroblasts, which are cells that produce collagen fibers and retain an ability to differentiate and grow. The difference between tumor cells and normal fibroblasts is that the growth of tumor cells tends to continue unchecked.

What the researchers found was that, in all seven cancer cell lines, treatment with zebularine slowed tumor-cell growth by anywhere between 32 and 68 percent. The fibroblasts showed only a 12 to 21 percent slowdown. Much of the difference, Jones notes, comes from the way zebularine is preferentially taken up by the cancer cells. Zebularine appears to bring about this change by demethylating specific genes in the cells—in particular, the p21 gene.

"Our results demonstrate that zebularine can be selective toward cancer cells and may hold clinical promise as an anticancer therapy," the researchers wrote.

Eric Selker of the University of Oregon first discovered zebularine's inhibition of DNA methylation in experiments on a filamentous fungus, says Cheng, who is one of the first authors on the *Cancer Cell* paper. "And we have since shown that it can work the same way in mammalian cells," Cheng adds.

In a previous study published in the *Journal of the National Cancer Institute* in March 2003, Jones and Cheng showed that zebularine can reduce the size of tumors in mice even when given orally, and that it does this tumor-whittling by turning on tumor suppressor genes that had been turned off through methylation. "This was the first time this type of drug has been able to reactivate silenced genes through oral administration," Jones notes.

This new study not only adds to the optimism surrounding zebularine that was generated by the earlier research, but also creates a renewed sense of hope that, because zebularine is not taken up by cancer and normal cells at the same rate, the drug will be less side-effect laden than other anticancer therapies.

This work was supported by a grant from the National Institutes of Health. ■

Structural breakpoint

by Lori Oliwenstein

Keck School researchers link unusual DNA structure to cancer.

USC researchers have discovered an unusual DNA structure in the chromosomes of lymphocytes that appears to create a so-called "fragile site" on the chromosome and to predispose cells carrying it to develop a common form of non-Hodgkin's lymphoma.

"This is the first disease ever to be associated with a deviation from the Watson-Crick helix," says Michael R. Lieber, M.D., Ph.D., Keck School of Medicine professor of pathology and biochemistry, the Rita and Edward Polusky Chair in Basic Cancer Research and the study's principal investigator.

The paper was published in the March 4 issue of *Nature*.

Lieber and his colleagues at the USC/Norris Cancer Center had previously used similar techniques to uncover the first new, stable structure in DNA, which was associated with an antibody-production process called class switching. This structure, however, looks different from the previously described structure and is further distinguished by being associated with cancer.

The fragile site in question is located on the Bcl-2 gene on chromosome 18. Bcl-2 is a gene that normally plays a role in blocking apoptosis, or cellular suicide. When it is over-expressed, however, it results in a form of B-cell lymphoma (hence the name Bcl) called follicular lymphoma.

The fragile site found on the Bcl-2 gene is the most common fragile site in all of cancer, according to Lieber.

"That one break site, which is only about 120 base pairs long, is responsible for 4 percent of all cancers," he says.

To cause follicular lymphoma, the fragile site on chromosome 18 must experience a break, and then trade bits of DNA with chromosome 14. This is a well-known phenomenon in the world of oncology research and treatment, and is called the 14:18 translocation.

"Of all the chromosomal fragile sites in cancer, this is the first one where we've actually understood why it's fragile," Lieber says. "And it's because of this molecular quirk in the Watson-Crick helix."

Follicular lymphoma is the second-most-common form of non-Hodgkin's lymphoma, with somewhere between 13,000 and 22,000 cases being diagnosed each year, generally in older individuals. The five-year survival rate is about 75 percent.

Lieber credits this and related discoveries in his lab to a technique developed in conjunction with the USC/Norris laboratory of his wife, Chih-Lin Hsieh, Ph.D., associate professor of biochemistry and molecular biology and urology at the Keck School of Medicine. "It's called the bisulfide method," Lieber explains. "It's based on the fact that when you treat DNA with bisulfide, the cytosine bases of the DNA undergo a transformation. But they only undergo that transformation if they're in a single-stranded region. If they are in the normal double-stranded configuration, they do not undergo the transformation. So this has allowed us to pinpoint areas of DNA that are not arranged in a double helix and to explore them."

There is plenty of work left to be done before the fragile site is fully understood, says Sathees Chukkurumbal Raghavan, Ph.D., a research associate in the Lieber laboratory and the paper's first author. "While we know it deviates from the standard helix, we don't know what the base pairing is at the fragile site."

Lieber is equally unsure as to whether this finding will have a therapeutic application down the road. "It's important to know how and why cancer begins," he says. "And this is an important step to understanding why the break is happening and why the chromosomes are swapping arms.

"We already knew that this translocation throttles the Bcl-2 up, making the cell invincible—and making it a good cancer cell. But nobody knew why it was happening. Now we are beginning to understand."

Lieber's work is funded by the National Institutes of Health. ■

by Alicia Di Rado and Lori Oliwenstein

OUTSIDE THE BOX

Five cancer-fighting experts go beyond scientific boundaries to take innovative cancer research and patient care in new directions.

What went wrong?

Cancer patients know that somehow, for causes they cannot pin down or explain, something went awry in their bodies to cause the disease that has so changed their lives.

While patients try to make some sense of it all, scientists ask the same question, but for a very different reason. For investigators and physicians, the answers to the enduring mystery—what makes cancer start and thrive—holds the key to beating back malignancy.

A new corps of cancer-fighting experts at USC/Norris Comprehensive Cancer Center is tackling the cancer whodunit with scientific zeal and an infectious curiosity. These five new faculty members will build on the advances made by researchers already at USC/Norris, while expanding innovative research programs in new directions.

Cathie T. Chung, M.D., Ph.D., exclusively cares for patients, bringing the latest discoveries to bear in the treatment of breast cancer. Basic scientists Judd Rice, Ph.D., and Woojin An, Ph.D., perform the laboratory research that makes medical advances possible. Allen Yang, M.D., Ph.D., and Ana Aparicio, M.D., straddle both domains, balancing patient care in hematologic and genitourinary cancers with basic research.

CATHIE T. CHUNG, M.D., PH.D.

Soon, instead of a single, cell-blasting chemotherapy for all cancer patients, a variety of molecular "smart bombs" will partner with chemotherapy to disrupt the many mechanisms at the heart of each individual's cancer.

Oncologists have already started to add some of these therapies to their toolbox, says Cathie T. Chung, M.D., Ph.D., assistant professor of medicine at the Keck School of Medicine and the newest breast cancer specialist at the Harold E. and Henrietta C. Lee Breast and Ovarian Center at USC/Norris.

Chung is especially interested in biological therapies, treatment methods that interfere with how cancer develops and grows. Probably the best-known example of such therapies is Herceptin.

Herceptin targets only aggressive cancer cells that have lots of human epidermal growth factor receptor 2 (HER2) proteins on their surface; traditional chemotherapy blasts all fast-growing cells, cancerous and healthy ones alike.

Just like Herceptin, new biologic therapies will battle certain cancer types because they go after precise characteristics that make that cancer tick. Chung believes researchers have a plethora of targets in cancer cells to explore for the next Herceptin-like drugs.

Chung is enthusiastic about bringing research from the lab bench to fruition through clinical trials at USC/Norris. "The breast oncol-

ogists at Norris already have a large number of clinical trials here: They have a track record," she says, holding a list of about 30 current breast cancer trials. "I'd like to expand on that—do trials of some new biologics and new small molecules."

Although Chung exclusively treats patients, she is no stranger to the lab. As a scientist at the National Institutes of Health, she focused on signal transduction research in the study of alcoholism and drug abuse and infectious diseases.

Still, she yearned to see how science came alive in patients—so she returned to academia, graduating from George Washington University's medical school. Cancer seemed a natural direction to follow: "Oncology was where great science was being done," she says.

After stints at UC San Francisco and Stanford University, Chung moved to USC/Norris, where she hopes to make a difference by bringing her research background to patient care.

"Today, in oncology, to be an innovator, you can't rely on pure basic science or pure clinical science," she says. "Oncologists need to be a real merger of the two to fight cancer."

ALLEN YANG, M.D., PH.D

One minute Allen Yang, M.D., Ph.D., is an oncologist, caring for patients with leukemia.

The next, he is a basic scientist, exposing cancer cells in his lab to an experimental drug that may soon join medicine's cancer-fighting arsenal.

Balancing his research time with his patient-care time can be tough. "But there are advantages in both worlds," Yang says. "And the advances you make in one benefit the other."

Yang already has his lab up and running at USC/Norris. On the clinical side, he is developing a program to offer trials of investigational therapies, based in epigenetics, to patients with hematologic malignancies that have resisted traditional medications.

Not bad for someone who started out as a student of the very physicians and scientists he works with today at USC/Norris.

Yang attended medical school at USC, where he enrolled in the rigorous M.D./Ph.D. program. While learning to treat patients, he also delved into the basic science behind cancer's inner workings. He joined the lab of USC/Norris Director Peter Jones, Ph.D., a DNA methylation pioneer. The DNA methylation field was in its infancy, and Jones became Yang's trusted mentor.

In 2001, Yang joined leukemia experts at the M.D. Anderson Cancer Center in Houston. There, he began working with decitabine, an experimental methylation-inhibiting drug he first studied in Jones' lab. Scientists knew decitabine seemed to fight blood cancers, but it was hard to tell how well it worked from patient to patient and why.

Yang developed a sensitive test to show how strongly decitabine stifled DNA methylation in each patient. The valuable test provides insight into how the drug acts, and Yang hopes it will help oncologists use decitabine effectively in the future.

Much of that work will go on at USC/Norris. "I've come to the hub of the epigenetics universe," Yang says enthusiastically, rattling off a list of prominent epigenetics researchers based at USC. And he is excited about the research prospects.

His first set of experiments pair decitabine with hydroxyurea to see if the drugs work even better in combination.

"We're also testing new demethylation drugs, and existing drugs that seem to be methylation inhibitors," he says. "Once we figure out how these are inhibiting methylation, we can then try to make them more potent.

"There's a lot of work to be done."

ANA APARICIO, M.D.

"If you're an oncologist, people seem to think, 'how depressing,'" says Ana Aparicio, M.D., a native of Madrid, Spain and assistant professor of medicine at the Keck School of Medicine. "But oncology really is one of the areas where you can make the most difference in people's lives."

One reason for this bright outlook may lie in new classes of medications that draw on recent epigenetics research findings.

"These drugs are five years—or even less—away," Aparacio says.

She should know; she conducted some of the drugs' first clinical trials at USC/Norris, evaluating them in patients with melanoma, breast cancer and other solid cancers.

When not treating patients—she specializes in genitourinary cancers, such as malignancies of the bladder—Aparicio conducts research within the

PHOTOS BY DON MILICI

lab of DNA methylation expert and Cancer Center Director Peter Jones, Ph.D. She is interested in drugs called histone deacetylase (HDAC) inhibitors, which might form an especially dynamic duo with demethylation drugs. HDAC inhibitors seem to create cancer roadblocks—such as deterring tumors from growing new blood vessels to feed themselves, while encouraging damaged, potentially cancerous cells to annihilate themselves.

On their own, demethylation drugs are intriguing, too.

For one, she says, demethylation drugs such as decitabine are surprisingly more effective in low doses than high ones. That means researchers need to do some homework through clinical trials, studying how various doses of the drugs affect tumors in patients.

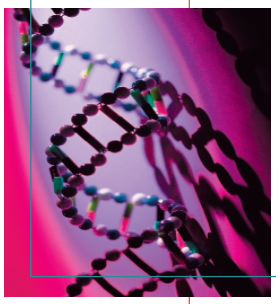
"But the problem with solid tumors, such as breast or colon cancer, is that you can't keep going in and testing a person's cancer cells to see how active the drugs are in their body," she explains. "You need to find another way."

So Aparicio is seeking out convenient biomarkers—tests that can be done on blood or saliva—that signal how well the drugs are fighting solid tumors during treatment. It is a perfect assignment for someone who admits to being "curious about everything."

"The research simply makes me a better oncologist," Aparicio says. "You need to understand the drugs you're working with to apply them better in the clinic."

EPIGENETICS PRIMER

Epigenetics is like putting in earplugs.



Everyone with healthy ears can hear. But plug the ears, and sounds go unheard. The ears are still there—still functioning—but they are kept from doing their job.

In the same way, a fully functioning gene may be silenced or locked. The gene is still functional, but it is kept from doing its job. This silencing is at the core of epigenetics.

Genes can be silenced through methylation. In this process, a chemical tag called a methyl group attaches to the surface of a DNA strand. It acts as a stop sign, marking a part of a DNA strand—a genetic sequence—that should be ignored.

In most cases, that works well. It helps cells healthfully grow, mature and function. But sometimes, methyl groups become attached to parts of DNA that should be active. In these cases, methylation may silence a genetic sequence that keeps cells from growing out of control. The result: cancer.

Genes can also be silenced another way.

DNA does not normally exist as the naked double helix so familiar to many people. In a cell, DNA coils tightly around proteins called histones, forming a complex substance known as chromatin. When histones are tagged with acetyl groups, or acetylated, chromatin is open and genes are potentially active; but when histones are not chemically tagged, or deacetylated, the chromatin condenses and genes are held captive in silence.

Today, researchers are trying to better understand methylation and histone deacetylation and develop drugs that interfere with or counteract their effects.

JUDD RICE, PH.D.

Judd Rice, Ph.D., regularly peers into the tangled mess of DNA, proteins and enzymes that fill a cell's nucleus and are the lynchpins in the development of cancer. And yet, he remains notably optimistic.

Perhaps that is because Rice believes in the potential that lies in the pioneering work he and other scientists at USC/Norris are doing on epigenetic gene regulation—the turning on and off of genes by chemical modifications to structures in the nucleus.

In a cell that is not currently dividing—which is most cells, most of the time—DNA is a component of chromatin, a mix of proteins and nucleotides in the cell's nucleus.

The DNA is wrapped around a core of proteins called histones; DNA plus a histone protein is called a nucleosome, and it is the way nucleosomes are strung together—whether their structure is tight or loose, for instance—that determines whether the wrapped DNA is able to be physically reached and read by the cell's protein-producing machinery.

"What I'm trying to do is to understand better just how nucleosome structure is regulated, and the effect that has on translation and transcription of DNA," Rice says.

Specifically, Rice studies the "tails" of the histone proteins, which tend to stick out of the bundled-up nucleosome and into the nucleus itself, and serve as lightning rods for an epigenetic process known as methylation—the addition of a methyl group to a stretch of protein or DNA. Rice and his colleagues have shown that changes in chromatin structure due to histone tail methylation can vary depending on where the methyl group is placed—or even what enzyme places it there.

For now, Rice's laboratory, located in the Zilkha Neurogenetic Institute pending completion of the Harlyne J. Norris Cancer Research Tower, is working to understand the biological significance of these modifications.

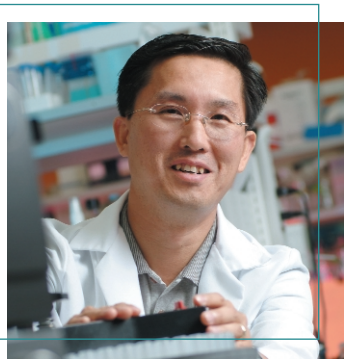
"My ultimate goal," he says, "is not only to understand how these enzymes and protein modifications are important to normal development, but to also understand how dysmodifications lead to certain diseases—cancer, in particular."

WOOJIN AN, PH.D.

As a biochemist and molecular biologist, Woojin An, Ph.D., focuses mainly on the inner workings of cells—specifically, on the exposed bits of protein and DNA that play key roles in determining which genes get expressed and which proteins are produced in the human body.

Like his colleague, Judd Rice, Ph.D., An studies chromatin and the way DNA is wound tightly around histone proteins and then, ultimately, unwound to be translated into enzymes and other proteins for the cells to use. An mainly focuses on decoding the transcriptionally active role played by the histone tails that stick out of these bundles in the cell's nucleus.

These histone tails, An explains, are studded with chemical tags of methyl groups, acetyl groups and/or phospho groups. These chemical changes are important to determine what happens to the rest of the histone-and-DNA complex—whether it relaxes and unwinds, exposing long stretches of DNA to transcription machinery, or whether it curls up into ever-tighter tangles, making gene transcription virtually impossible.



An says these post-synthetic changes to the histone tails "act as signals, letting the transcription machinery know to gather at that site so gene transcription can take place."

An is looking specifically at the way the tumor-suppressor protein p53 activates gene transcription that promotes cell-growth arrest for damaged DNA repair.

In the June 2004 issue of the journal *Cell*, An demonstrated that p53 not only calls in one protein that can place an acetyl group on the histone tail, but also two different proteins that place a methyl group on the histone tail—and they do so in a very specific order.

An's next step is to determine what happens at the cellular level when p53, the most frequently mutated gene in human cancers, does not work with various histone modifications. "It's important to know how different histone modifications are functioning in the normal cell," An says. "But it's equally important to find out what happens when p53 is mutated, as it is in 50 percent of human cancers. Most of the genes p53 affects play an important role in stopping cell growth or promoting cell death. If p53 can't do its job, then the cell is in trouble. And we need to know exactly how all p53-responsive genes are controlled by chemical modifications of histones." ■

Positive Outcome

David Penson combines expert care with deep compassion to treat men undergoing radical prostatectomy.

by Jon Nalick

For David Penson, M.D., M.P.H., simply curing a patient's cancer is not enough.

The physician-researcher, who joined the Keck School of Medicine last spring, of 2004, studies quality-of-life issues and says he has learned from his patients a simple truth: "Sometimes the cure is worse than the disease."

David Penson, M.D., M.P.H.

Depending on factors such as the age of the patient and experience of the physician, about 60 percent of men who undergo radical prostatectomy to treat their cancer suffer permanent erectile dysfunction and 5 to 10 percent suffer incontinence, Penson says.

As a result, many men trade their cancer for a new set of problems that often they—and sometimes even their physicians—are reluctant to discuss. As associate professor of urology and preventive medicine at the Keck School of Medicine, Penson's research aims to provide a better understanding of what happens to men after treatment and how to plan for and mitigate potential side effects.

"In my research, it became clear that as physicians, we were curing their cancer, but we weren't necessarily making their lives better. Our goal as physicians should be to leave patients at least as good as how we found them—but without their illness," he says.

He says that learning how to do that better is one of the reasons he chose to join the Keck School and the USC/Norris Comprehensive Cancer Center.

"I looked at USC and the Norris and I saw a place that is really dedicated to treating cancer patients and whose nursing staff and urological department are simply terrific," he says. "I'm looking forward to being able to maintain my surgical skills while helping build a major clinical research program in the department."

Penson's current research projects include a National Cancer Institute (NCI) study that he began while he was an assistant professor of urology at the University of Washington and staff urologist at the VA Puget Sound Healthcare system, both in Seattle. The study follows 750 men who were diagnosed with prostate cancer in 1995. The men have completed quality-of-life surveys at regular intervals since their diagnoses, which Penson says will let new prostate cancer patients and their physicians know more about which therapies work best, how often cancer recurs and what to expect regarding long-term side effects. He also is a member of the Prostate Cancer Outcomes Study initiated by the NCI in 1995 that tracks 3,300 men nationwide.

Penson's dedication to research, surgery and patient care issues is crucial, he says, to help fight a cancer that afflicts as many as 200,000 American men each year. Penson says, "I'm looking forward to expanding my research, increasing and sharing my knowledge, and maintaining and improving my surgical skills—all of this so that my patients and others won't have to decide between cancer and possible disability." ■

PHOTO BY DON MILICI

DETERMINED PROGRESS

As head of oncology, Jeffrey Weber has a goal to keep the division at the lead in the fight against cancer. by Jon Nalick

Jeffrey Weber, M.D., Ph.D.

When Jeffrey Weber, M.D., Ph.D., the Lucy and Berle Adams Chair in Cancer Research, and associate professor of medicine and microbiology at the Keck School of Medicine, assumed the post of chief of the Department of Medicine's oncology division in February, he set his sights on a single goal: increased growth for the division.

Adding new faculty members and the clinical and research space they need to work, he says, is required for the division to remain an engine for progress in the fight against cancer. In an effort to bring his goal closer to reality, Weber says, the division has gained three new recruits in 2004 and plans to add two more in 2005.

"Failure is not an option," Weber says, in part because of the crucial leadership role the division plays at the USC/Norris Comprehensive Cancer Center: The division accounts for more patients seen than any other division at the Norris Hospital, as well as most of the cancer center's funded clinical trials.

"Our success has a ripple effect on the whole center," he says.

A nationally known scientist in cancer immunology, Weber focuses his research on melanoma tumor vaccines as well as drugs that enhance the immune system's response to tumor cells and those that attack tumor cells in patients with high-risk and metastatic melanomas.

Weber says he was drawn to the treatment of melanomas because it provides the purest test of the efficacy of immunologic cancer treatments: "If immunologic approaches are going to work, they are going to work in this field."

The National Cancer Institute (NCI) is hoping he is right: It just provided Weber with a $2.5 million grant for a 75-patient study of an antibody booster to aid melanoma patients.

Peter Jones, Ph.D., director of USC/Norris, calls Weber an especially appropriate choice to lead the division, praising his extensive expertise in clinical trials.

"Dr. Weber is a well-funded researcher with major grants from the National Institutes of Health, the National Cancer Institute, the Beckman Foundation and other key organizations committed to the fight against cancer. With his experience in clinical trials and his demonstrated leadership, he possesses the skills and the drive to help propel the division to even greater success," Jones says.

Weber received his doctorate. in molecular cell biology from Rockefeller University in New York and his medical degree from New York University School of Medicine. Following an internship and residency at the University of California at San Diego, he completed a fellowship and became the senior investigator in tumor immunology at the NCI. Weber joined USC/Norris in 1995.

Weber says that within 10 years, he expects the division to grow to include as many as 16 members and serve as a major national leader in translational research.

"We have to move beyond the classic paradigm at this campus of strength in clinical medicine to strength in clinical research and lab research," he says. "Research, and the ability to translate novel laboratory findings into effective treatments, will determine progress in the fight against cancer in the years to come." ■

PHOTO BY DON MILICI

A monoclonal antibody drug for advanced colon cancer partners with standard therapies to raise response rates.

Colorectal cancer patients in clinical trials at USC/Norris Comprehensive Cancer Center are helping to unveil a new generation of anti-cancer drugs that are less toxic and more specific than ever before.

Patients with advanced, metastatic colorectal cancer are the first to test these new therapies, called monoclonal antibody drugs, which aim their attack strictly at cancer cells—rather than also harming healthy cells in the process, as traditional chemotherapies do. Results have oncologists so optimistic that they have begun testing monoclonal antibodies together with standard therapies in patients with earlier-stage cancers, trying to pack more punch into initial therapy and increase the chance of cure.

Many of these experimental drugs are under study at USC/Norris and the Keck School of Medicine.

"These monoclonal antibody drugs are exciting because they have been developed as targeted therapies to selectively inhibit tumor cells, without affecting healthy cells; therefore, they are less toxic and are perfect partners for chemotherapies," said Keck School medical oncologist Heinz-Josef Lenz, M.D., who has led many of the studies at USC/Norris.

Consider the story of cetuximab.

With 40 patients in all, USC/Norris had the largest number of participants in a recent expansive, multi-center clinical trial of cetuximab, known by the trade name Erbitux. The United States Food and Drug Administration approved this monoclonal antibody drug in February as an option for patients whose colorectal tumors do not respond to standard chemotherapy.

PHOTO BY S. PETER LOPEZ

Inner Workings

by Alicia Di Rado

Lenz presented findings from the trial, one of the largest trials to date of a monoclonal antibody drug in advanced colorectal cancer, at this year's annual meeting of the American Society of Clinical Oncology.

The nearly 350 patients with advanced metastatic colorectal cancer in the study had already received at least two previous rounds of chemotherapy (irinotecan and oxaliplatin), but their cancers remained.

When trial participants were given cetuximab, about 12 percent of them saw their tumors shrink by more than 50 percent. Participants survived about 7 months. That may not sound like a lot, but patients in such trials have cancer that already has spread and is difficult to fight successfully.

"A response rate of over 10 percent is impressive," said Lenz, especially since only about 10 to 15 percent of these patients responded to the advanced treatment regimen known as FOLFOX (5-fluorouracil, leucovorin and oxaliplatin) in second-line therapy.

Scientists created cetuximab specifically to interfere with the workings of a cancer cell. It is a sort of manufactured version of the antibodies used by the immune system to protect the body. In this case, cetuximab battles something called epidermal growth factor, a substance that cancer cells often need to develop and grow.

Oncologists can test cancer cells to see if they are positive for epidermal growth factor receptors (EGFR); if so, it means that the cancer cells are especially fueled by the growth factor, and would be expected to respond well to a treatment targeting the substance.

But interestingly, Lenz saw responses in two of nine patients whose tumors had tested negative for EGFR. As a result, investigators have launched a new trial—including a site at USC/Norris—that will evaluate cetuximab in EGFR-negative tumors. Lenz believes that today's immunohistochemistry techniques might not be sensitive enough to accurately determine all tumors' EGFR status.

One of the promising aspects of cetuximab and its fellow monoclonal antibody drugs is that the drugs often partner well with other standard therapies and act together to raise response rates higher than expected. Take Avastin, for instance. "Avastin alone has barely any effect, but in combination with chemotherapy, it significantly increases response and survival—without increasing toxicity," says Lenz, director of the gastrointestinal oncology program at USC/Norris.

Another bright spot, according to Lenz, is that the drugs may be offered on their own to seniors or others who are too sick to withstand traditional chemotherapy's side effects. The drugs also may work together with standard chemotherapies so well that they may shrink tumors once considered inoperable to a point at which surgeons actually may remove them successfully.

Scientists created cetuximab specifically to interfere with the workings of a cancer cell.

Cetuximab is not alone on the USC/Norris clinical trials docket of monoclonal antibodies and experimental colorectal cancer drugs, either, Lenz noted.

USC/Norris is offering clinical trials of experimental drugs so new they are often still known by their developmental monikers, a mix of numbers and letters denoting their pharmaceutical origin. They include EPO906 (also called epothilone B), BAY 43-9006, SU11248 and an SB compound, as well as Velcade and novel vaccines.

Lenz was evaluating cetuximab back when it was still known as C225, so he has seen it from its beginnings to its entry into the market for patients. "This is an exciting drug," he said, "with more efficacy in the third line than oxaliplatin has in the second line. It has almost no toxicity, and in combination with chemo, it shows synergism. The first data in combination with FOLFOX showed a response rate of 82 percent.

"These sorts of advances give us great reasons to be optimistic for our patients and increase the number of patients we cure."

For more information about clinical trials at USC/Norris, the research of oncologist Heinz-Josef Lenz, M.D., or any of The Doctors of USC, call 1-800-USC-CARE (1-800-872-2273).

Harlyne J. Norris Research Tower Underway

Constuction crews work into the evening on the foundation of the Norris Research Tower.

After a lengthy permit process, USC broke ground in June 2003 on the Harlyne J. Norris Cancer Research Tower. The first challenges were high water levels in the site, soil issues and maintaining state earthquake safety compliance. Plans involve drilling more than 260 footers into bedrock at depths of 45 to 80 feet. These footers will be filled with concrete and rebar and will be secured into the foundation slab. The process is so complex that construction of the floors will not begin until June 2005. Completion of the building is set for January 2007.

Meanwhile, recruitment of scientists to fill the building is underway, with many new recruits occupying temporary space in the Zilkha Neurogenetic Institute building.

This new structure joins the original USC/Norris building and the Norman Topping Research Tower to complete a trio of structures that will combine world-class research and leading-edge clinical trials with high-caliber, compassionate patient care.

For live, ongoing Web cam coverage of the construction, log on to www.buildingcams.rsconstruction.com/.

Angels West Raises $91,000

Angels West continues its support of USC/Norris cancer research. The group raised $91,000 in unrestricted funds through this year's activities.

With Irene and Milt Golden as the driving force, Angels West, a non-profit group of volunteers, started with seven couples in 1967; today they number 200. In 1992, they directed their support to USC/Norris, and they have raised more than $2 million to support young scientists and their research. The funds are raised through myriad activities such as sales of entertainment books, See's candies, memorial and tribute gifts, and Festival of the Arts tickets.

Autumn Soiree benefits Sheldon Fund

Marsha Cohen and son, David Sheldon.

The Autumn Soiree at the Braemar Country Club in Tarzana, Calif., featured a buffet dinner, silent auction and live entertainment to benefit the David Sheldon Memorial Fund.

The Cohen, Sheldon and Tanner families established the David Ian Sheldon Memorial Fund in April 1997 with the assistance of Angels West, a non-profit volunteer organization of the USC/Norris. Prior to his death in 1997, David Sheldon was a patient of Dan Douer, M.D., director of the Bone Marrow Transplantation (BMT) Program at USC/Norris.

The fund will continue to be used to purchase much-needed research equipment for the BMT Research Laboratory, under the guidance of Douer. The fund previously purchased six major pieces of equipment, totaling nearly $45,000, each bearing David Sheldon's name.

Step Up Women's Network Wellness Bag Program

The Step Up Women's Network has established a new program for women at the USC/Norris Cancer Hospital. The group has provided wellness bags to be distributed to new female patients who are admitted to the hospital. The bags vary, but may include items such as yoga mats and videos, nail polish, DVDs, slippers and beauty products. According to the Step Up Women's Network, patient reaction has been wonderful and patients greatly appreciate the bags and the efforts of Step Up.

To fill the wellness bags, the volunteers at Step Up solicited individuals and companies related to health or beauty to provide goods that will give a lift to women while in the cancer hospital.

For more information regarding the Wellness Bag Program, call Sondra Malatesta at (323) 865-0725.

Glassick Estate gives $2.4 million for Research

Elsie Glassick made a gift through her estate that will benefit cancer research at the USC/Norris Comprehensive Cancer Center.

As fervent USC supporters, Elsie Glassick and her late husband, Bill Glassick, a graduate of the USC Marshall School of Business, attended many USC football games at home, as well as away. She would watch recaps of the game and then sit down to write a letter to one of the coaches, articulating her analysis of the plays. Reading the *Daily Trojan* sports page was especially enjoyable to her.

In later years, Elsie Glassick, who lived in Orange County, regretted that she could no longer attend the USC football games, but she continued to watch them on television.

Glassick's ties to USC/Norris were cemented many years ago when she established a gift annuity to benefit cancer research. She felt strongly that there should be competition on the football field but cooperation in cancer research to find a cure for this devastating disease.

NORRIS NEWS

For more information about any of the events listed below, contact Brittany Gac at (323) 865-0648.

11th Annual Scott Parker Golf Classic

The 11th Annual Scott Parker Golf Classic on Aug. 23, 2004 returned to its original tournament site at Riviera Country Club in Pacific Palisades, Calif. Players participated in the putting and Par 3 contests, while teams competed for the top prizes for the day.

Funds from the Golf Classic benefit prostate cancer research at the USC/Norris Comprehensive Cancer Center. Special thanks to Ashworth Inc. and Color Me Graphics for their continued support of this event.

Parker Golf Classic participants (l-r) Mike Tudor, Gary Lieskovsky, M.D., Ron Parker, Don Aragon, and Tom Dolan, who was the winner of the putting contest.

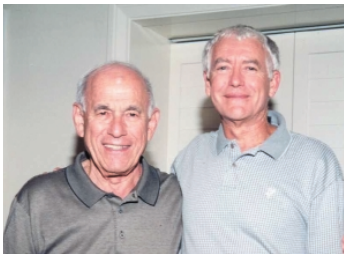
Fiesta of the Spanish Horse

On May 8, 2004, the Los Angeles Equestrian Center in Burbank opened its doors for the "Fiesta of the Spanish Horse" to benefit cancer research at the USC/Norris Comprehensive Cancer Center. This unique, multi-breed horse show provided an entertaining evening complete with live mariachi and Latin music, dancers, food vendors and a silent auction. More than $8,600 was raised for USC/Norris research.

Swing Against Cancer Golf Tournament

The first Swing Against Cancer Golf Tournament took place May 3, 2004 at El Caballero Country Club in Tarzana, Calif. The tournament raised almost $90,000 for unrestricted cancer research. Many thanks to the wonderful committee that made this tournament a success.

Mark your calendar for the second annual tournament on April 18, 2005.



Jerry Hollander (left), chair of the committee for the Swing Against Cancer Golf Tournament, and Peter Jones, Ph.D., director of USC/Norris, prepare to distribute awards to the tournament winners.

Take-A-Hike

Expedition Inspiration hosted the 9th Annual Take-A-Hike on Oct. 2, 2004 at Paramount Ranch in Agoura, Calif. to benefit breast cancer research at USC/Norris Comprehensive Cancer Center and UCLA Jonsson Cancer Center. Téa Leoni served as honorary chair for the event. Nearly 1,000 people gathered for hiking, refreshments, entertainment and a silent auction.

Funds raised for USC/Norris were directed to Michael Press, M.D., Ph.D., the Harold E. Lee Chair in Cancer Research and co-director of the Breast Cancer Research Program. He is investigating molecular genetic alterations in breast cancer and their role in prevention and treatment.

Actress Téa Leoni models "The Inspiration Bracelet," whose sales proceeds benefit breast cancer research at USC/Norris and UCLA Jonsson.

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