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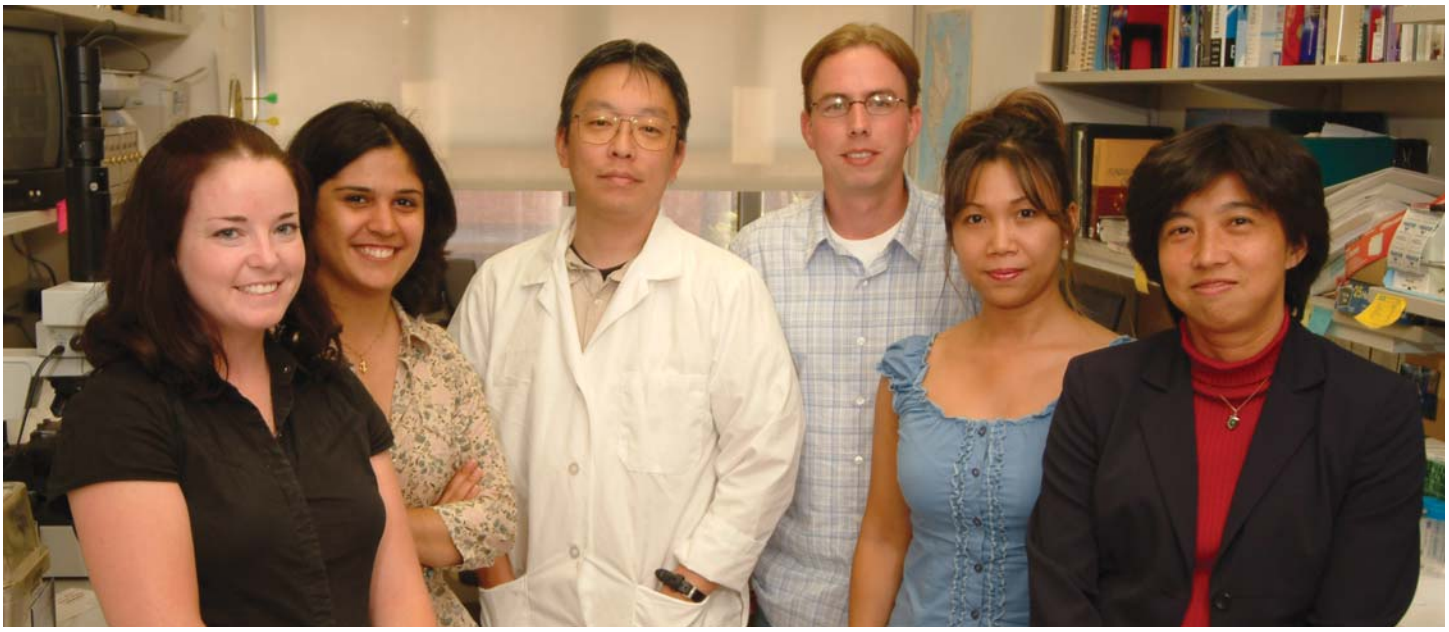
CLARK UROLOGICAL CENTER

NEWSLETTER

EXPERIMENTAL APPROACH TO PROSTATE CANCER DIAGNOSIS SHEDS NEW LIGHT, COULD GUIDE FUTURE TREATMENT

Unlike PSA, Technique Shows Where Tumor Cells Have Metastasized



Lily Wu, MD, PhD (right), with her research team, from left to right: Breanne White (graduate student), Arpi Setrak (graduate student), Makoto Soto (postdoctoral fellow), Jeremy Burton (graduate student), and Mai Johnson (research associate).

A Clark Urological Center research team is continuing to make exciting progress in its development of a new system for diagnosing and treating advanced prostate cancer.

Despite advances in prevention and early detection, approximately 40,000 men die of prostate cancer in the United States each year, largely due to the inability to cure the disease once it has metastasized. Nearly one in five newly diagnosed patients present with metastatic disease. These patients can be treated successfully with hormone deprivation for a certain period of time, but eventually the treatment fails to produce a response. This hormone-refractory disease progression is signified by surging prostate-specific antigen (PSA) levels, though the PSA test doesn't reveal specific information about where the cancer has spread.

But last year, a UCLA team headed by Lily Wu, MD, PhD, captured the attention of prostate cancer researchers and clinicians with a paper published in the peer-reviewed journal *Nature Medicine*. Dr Wu's team engineered a virus capable of identifying prostate cancer cells based on the PSA protein, and attached the substance that makes fireflies glow to enable tracking of the virus's activity through an imaging technique. After injecting the specially equipped virus into mice grafted with human prostate tumor, the researchers found that the beaming substance illuminated prostate cancer cells both in primary tumors and in distant metastases that were too small to cause symptoms or appear on conventional detection scans.

"The current state of the art for detecting advanced stages of prostate cancer is serum PSA," notes Dr Wu. "But when the PSA rises, we have no good way to determine where the disease is recurring. Being able to see where cells have metastasized through imaging would provide clinicians with a powerful tool."

The success of the experimental diagnostic approach also suggested that the researchers might be able to take an important additional step: developing a virus that could not only light up the prostate cancer, but one that could also deliver a therapeutic gene designed to kill the prostate cancer cells while sparing the surrounding healthy ones.

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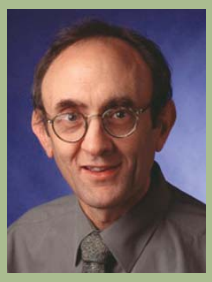
Urology Briefs



Said

Jonathan Said, MD, professor of pathology and laboratory medicine and chief of the Division of Anatomic Pathology at UCLA, recently received a joint appointment in the Department of Urology. Dr Said has become an important collaborator within the department in the area of genitourinary cancers, particularly prostate cancer. In fact, he has a key role in the department's UCLA SPORE in Prostate Cancer grant, a five-year award from the National Cancer Institute that designates UCLA as a center of excellence for prostate cancer care research, and requires an extremely strong pathology core, which Dr Said leads.

Mark Preston vanBree, MD, an intern and resident in the UCLA Department of Urology from 1989 to 1995, died May 30, 2003, from a cardiac arrest. He was 46. After graduating with honors from George Washington University Medical School, Dr vanBree came to UCLA, where he met his future wife Rebecca, a nurse. They had two daughters and, following completion of his training, settled in Wilson, N.C., to join a urology practice in 1995. Earlier this year, Dr vanBree was elected president of the Wilson County Medical Society. The faculty and staff of the UCLA Department of Urology remember Dr vanBree as a talented and compassionate physician, and extend condolences to his family.

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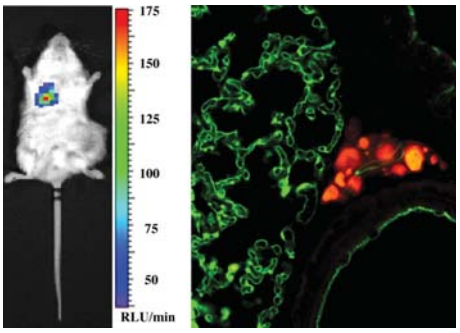
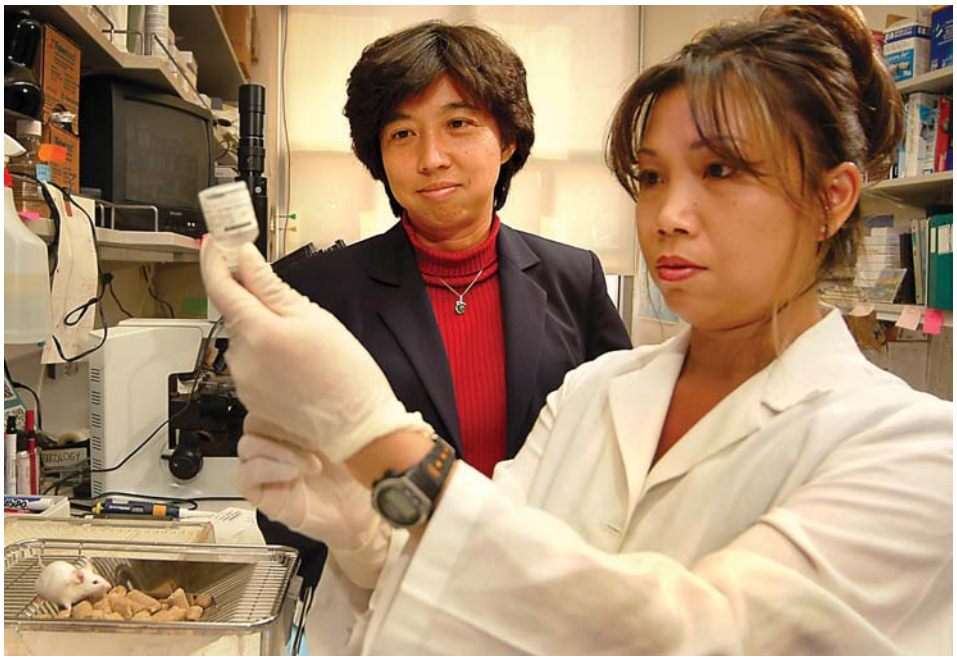
Having provided proof of principle with the *Nature Medicine* paper, Dr Wu's team is following up with larger studies, funded by the National Cancer Institute, U.S. Department of Defense and California Cancer Research Program, to link the diagnostic approach with a therapeutic component. Dr Wu's research group has ramped up the strength of its gene delivery system significantly, achieving 50-100 times the expression levels of the original system in laboratory tests while retaining sufficient specificity – the extent to which the gene continues to target PSA-producing cells. "In the laboratory, we are getting the level of activity that current clinical trials are achieving, but with greater specificity," Dr Wu says. "That's extremely exciting, since the ultimate goal is to make more potent therapies while decreasing their side effects."



Mouse with a human prostate tumor is injected with a specially equipped virus, enabling the prostate cancer cells to be tracked through optical imaging. Twelve days after administration, the signal is observed in the animal's lung (left panel); this signal is then correlated with the presence of metastatic human cancer cells in the lung (right panel).

Her current research effort exploits the strength and efficiency of the system to detect androgen-independent and metastatic lesions in living mice, and then convert the engineered virus into a tool that, once it identifies the hidden prostate cancer cells, will also destroy them. Dr Wu's group is following multiple paths in attempting to execute this strategy. One study uses the system to generate a virus that would replicate only in prostate cancer cells, essentially bursting the cells through regeneration of multiple copies of the virus. Another delivers genes that would kill the cancer cells directly, while a third inhibits the blood vessel growth that enables the tumor to thrive.

Dr Wu suspects her team's molecular biology approach is at least two years away from being ready for testing in humans. But results in the lab continue to fuel the hope that the day will come when urologists will be able to offer a much more targeted approach to metastatic prostate cancer diagnosis and treatment.



Mai Johnson (with Dr Lily Wu) preparing a mouse injection for an imaging study.

Friends of UCLA Urology Tour New Surgical Center

Friends of UCLA Urology, a special group initiated in 1998 by Dr Jean B. deKernion, professor and chairman of the Department of Urology, to recognize the department's most valued donors, were given the opportunity to tour the technologically impressive Center for Advanced Surgical and Interventional Technology (CASIT) in May.

CASIT, co-directed by Drs Peter Schulam, associate professor of urology, and Carlos Gracia, associate professor of surgery, includes an 800-square foot "operating room of the future" to be used for simulating new procedures, as well as for telesurgery and teleconferencing. The Friends were treated to a demonstration of how a surgeon can control robotic arms that perform minimally invasive surgery with greater range of motion and more precise movements than a surgeon would normally have.

An annual gift of $1,000 or more secures membership in Friends of UCLA Urology and supports the department's continuing efforts to find innovative approaches to preventing and treating urologic diseases and disorders. Members are invited to attend luncheons, lectures, tours, and other activities that will highlight research and programs in the Department of Urology.

State-of-the-Art Urology Conference Set for March

The 19th annual UCLA State-of-the-Art Urology Conference will be held March 12-14 at the Ritz-Carlton Hotel in Marina del Rey, Calif. The conference, offered by the Department of Urology in conjunction with the Continuing Medical Education office of the David Geffen School of Medicine at UCLA, provides continuing medical education credits and is specifically designed for practicing urologists and the challenges they face in patient management.

Along with departmental speakers, several prestigious visiting lecturers have been invited. Those experts speaking about prostate cancer are Drs Anthony D'Amico from Brigham and Women's Hospital, Nicholas Vogelzang from the University of Chicago Cancer Research Center and Patrick Walsh from The James Buchanan Brady Urological Institute at Johns Hopkins University. In addition, Drs Culley C. Carson, from the University of North Carolina will speak on the topic of impotence; Victor Nitti from NYU School of Medicine will discuss female urology; Joseph W. Segura of the Mayo Clinic will give a talk on endourology/kidney stones; and Michael L. Blute of the Mayo Clinic will discuss both bladder and kidney cancers.

To inquire about the final program and registration information, please contact Ms Rain Burch at 310-794-2159.

Kudos

Dr Lily Wu, assistant professor of urology, recently received three grants totaling over $1.2 million to further her research in prostate cancer. She received a $562,867 award from the U.S. Army/Department of Defense to develop improved diagnostic and tumor-killing approaches for advanced prostate cancer. She was also awarded $475,000 over three years from the California Research Program for her research entitled "Targeted Gene Transfer to Detect and Treat Metastatic Prostate Cancer." In addition, she received a grant of $178,000 for "Gene-Based Imaging and Therapy to Target Metastatic Prostate Cancer," supported by the NIH/National Cancer Institute.

Dr Robert Reiter, associate professor of urology and director of urologic research, received a three-year, $571,858 award from the U.S. Army/Medical Research Acquisition Activity for his work entitled "A PSCA Promoter based Avian Retroviral (TVA) Transgenic Model for the Study of Normal and Malignant Prostate Disease." This project studies prostate stem cell antigen (PSCA), a cell surface marker or protein found in both normal and cancerous prostates, to see if it plays a role in the development of prostate cancer. Preliminary data from Reiter's lab suggests that PSCA is a marker of an intermediate, incompletely differentiated cell population, where prostate cancer may begin.

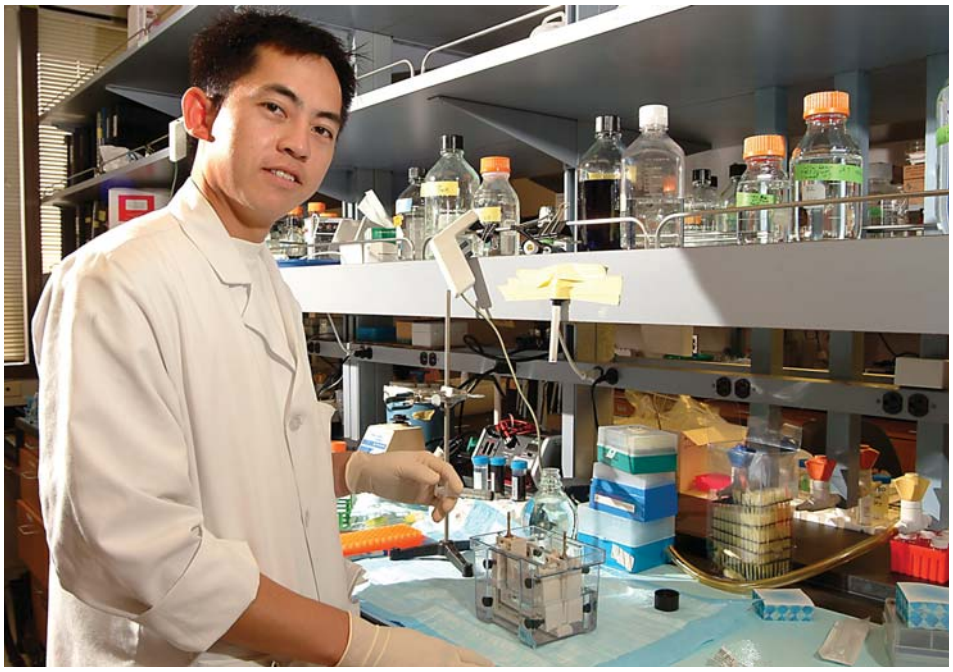
Dr William Aronson, associate clinical professor of urology, has been awarded a two-year grant from the California Cancer Research Program in the amount of $265,625 to study the effect of a low-fat, high-fiber diet on growth factors in the blood that may play a role in prostate cancer growth and development.

Graduation Dinner

This year's graduation dinner was held on June 13 at the Bel-Air Bay Club. The department's three former chief residents, Drs Stephen J. Freedland, Joseph Chihping Liao and Ganesh S. Palapattu, received their diplomas, as presented by Dr Andrew C. Novick, the Joseph J. Kaufman Visiting Professor, who is a professor of urology at the Cleveland Clinic Foundation. Dr Palapattu was honored with the Willard E. Goodwin Resident Teaching Award for his outstanding teaching efforts throughout his residency, and in particular during his sixth and final year as chief resident. This year's Clinical Faculty Member of the Year award was given to Dr James Mollenkamp, a community urologist in Torrance who has been a clinical instructor at UCLA since 1989.

UROLOGY RESIDENTS PROBE KEY ISSUES IN RESEARCH YEAR

Topics Under Investigation Include Potential New Prostate Cancer Marker, Vaccine for Metastatic Kidney Cancer, Development of Electronic Medical Record



Dr Jonathan Chin, a fourth-year resident in the Department of Urology, is working in the laboratory of Dr Robert Reiter on a study of Reg IV, a potential new marker for prostate cancer that appears to be overexpressed in hormone-refractory metastatic disease.

In UCLA's Department of Urology, residency isn't only about seeing patients. Residents spend their fourth year conducting research on important urology issues. The pursuits of three fourth-year residents are featured here.

Dr Jonathan Chin

Having seen prostate cancer patients during the first three years of his residency, Dr Jonathan Chin is going back to basics in his fourth year, seeking to gain a better understanding about the course of the disease in order to improve the care provided to these patients in the future.

Dr Chin is working in the laboratory of Robert Reiter, MD, associate professor of urology at UCLA, on a study of a potential new marker for prostate cancer – a protein known as Reg IV. The hope is that the protein, which appears to be overexpressed in hormone-refractory metastatic prostate cancer, might eventually serve as a prognostic marker for the disease.

"Prostate cancer usually has a slow-growing course, but in some patients it's much more aggressive," Dr Chin notes. "If we can do a better job of predicting whether the cancer is going to behave aggressively, it might help us to make decisions on which patients need more aggressive treatment or closer surveillance." If it is specifically expressed in cancer cells, Dr Chin notes, Reg IV could possibly become a therapeutic target.

The fourth year of the UCLA Department of Urology's six-year residency program is a time when trainees such as Dr Chin step away from patient-care duties and gain valuable experience working with the department's clinical and basic scientists on a wide variety of research projects. "It's very exciting to be at the forefront of new developments that might eventually affect the treatment of prostate cancer," says Dr Chin.

Dr Oleg Shvarts

Dr Oleg Shvarts met Arie Belldegrun, MD, professor of urology at UCLA, as a second-year medical student and assisted Dr Belldegrun in the launch of the Kidney Cancer Database, which includes all patients treated surgically for kidney cancer at UCLA since the early 1990s – well over 1,000 patients. He continued to devote whatever time he could to conducting kidney cancer research with Dr Belldegrun, and is pleased to be able to devote his fourth year as a urology resident to full-time research in his mentor's lab.

Dr Shvarts is part of a group seeking to create a vaccine that would equip the immune systems of patients with metastatic kidney cancer to be able to attack the cancer cells. Kidney cancer has not been amenable to chemotherapy or radiation therapy, the mainstays of treatment for most tumors. Boosting the immune system to fight the disease with agents such as Interleukin-2 and Interferon has proved effective in some patients, but no more than 20 percent. "The main problem has been a

lack of sensitivity," says Dr Shvarts. "These drugs are gearing an army to fight an enemy without a face, because there's no specific target."

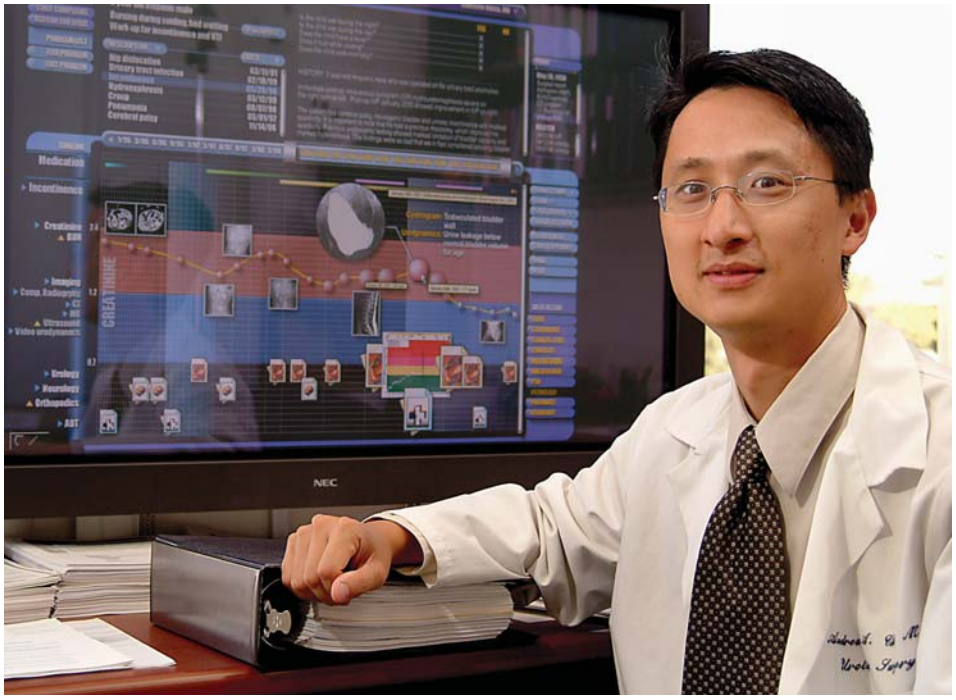
But researchers have identified an antigen, CA9, that is found in approximately 80 percent of kidney tumors and not in normal kidney tissue. "This is an excellent marker for kidney cancer," says Dr Shvarts. With that target, he is helping to create genetically engineered dendritic cells. Dendritic cells recognize foreign substances and present them to other cells that can kill them; the dendritic cells employed by Dr Shvarts will express CA9 as foreign. "The idea is to rev up the immune system – but directly against this antigen present in kidney cancer cells," Dr Shvarts explains. In kidney cancer models in mice, his group will test the theory that injecting these genetically engineered dendritic cells can slow the tumor's growth.

"If we're going to conquer this disease, it is going to have to be through the manipulation of the immune system with strategies such as this one," says Dr Shvarts.

Dr Oleg Shvarts (left) is part of a group seeking to create a vaccine that would equip kidney cancer patients' immune systems to be able to attack the cancer cells.

Dr Andrew A. Chen

For Dr Andrew A. Chen, a fourth-year resident with a background in engineering and computing and a specific interest in pediatric urology, an important project at the Clark-Morrison Children's Urological Center offered the perfect fit. Dr Chen is working with UCLA's medical informatics group and Dr Bernard Churchill, head of the Division of Pediatric Urology, on an effort to create an electronic medical record for both physicians and patients.



Dr Andrew A. Chen is putting his engineering and computing background to use, working with UCLA's medical informatics group and Dr Bernard Churchill on an effort to create an electronic medical record for both physicians and patients.

"Our health information systems are becoming increasingly sophisticated, but there's still a great need for the huge amounts of information that we require from patients regarding their laboratories, imaging studies, and clinical visits to be accessible at one point and in an intuitive way, so that a physician is not missing information when making a medical decision," Dr Chen explains. The task is easier said than done. "The medical record is this pool of strings and characters and numbers that a computer can't really understand unless you design smart algorithms for pulling out the important content," he says.

In addition, Dr Chen notes, patients want to know not only about their diseases, but also about their own medical records. So Dr Chen is part of a group devising a method in which patients could tap into an educational software program that will interact with their electronic medical record to inform them about their diagnosis, treatment options and prognosis. "The idea is for the patient to be educated about their problem so that they can communicate with their physicians and understand what needs to be done," he says.

The researchers intend to test the new system on patients with spina bifida. "These children need to be doing self-catheterization at home, but they tend not to," Dr Chen says. "We would like to use this software program to provide patients and their families with feedback on how compliance relates to their overall outcomes, including preservation of kidney and bladder function and reduction in incontinence, infections, and hospitalizations. We believe that by connecting patients' medical records with their state of health, we can improve their compliance and their overall outcomes."

APPLYING SUCCESSFUL MELANOMA STRATEGY, RESEARCH TEAM LOOKS TO DEVELOP TARGETED KIDNEY CANCER VACCINE

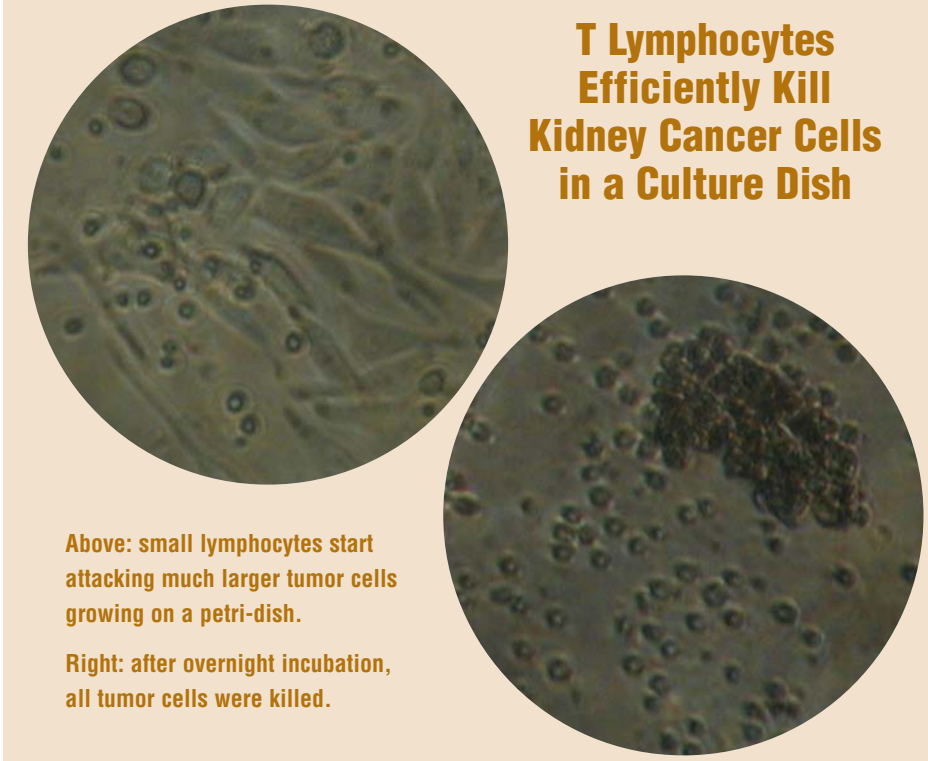
Dr Gang Zeng Brings Technology Honed in NCI Laboratory

The prognosis has been poor for most of the approximately 32,000 people in the United States diagnosed with kidney cancer each year. Nephrectomy (surgical removal of the diseased kidney) can cure patients whose cancer is confined to the organ, but roughly half of kidney cancer patients who have surgery eventually relapse. For these patients and the one in three who already have metastatic disease at the time of diagnosis, the conventional treatment approach holds no benefit. Less than 5 percent of patients with metastatic renal cell carcinoma – the most common form of kidney cancer – survive more than three years.

"The problem is that kidney cancer is resistant to both chemotherapy and radiation therapy," says Gang Zeng, PhD, assistant professor of urology and research director of the UCLA Kidney Cancer Program. "We need to come up with new therapies to attack this disease."

One approach has proved effective in a small percentage of metastatic kidney cancer patients. Interleukin-2 (IL-2), approved by the U.S. Food and Drug Administration on the heels of pioneering research at the National Cancer Institute and UCLA in the 1990s, stimulates the patient's immune system to fight the cancer. Approximately 10 percent of patients can have long-term disease-free survival with the drug. "The problem is, that's not enough," says Dr Zeng. In addition, he notes, IL-2 is highly toxic, causing severe side effects and an inability for some patients to tolerate the drug at all. "It's like a weapon of mass destruction, because it doesn't recognize any specific target – it just goes after all cells, so we try to come up with a 'guided missile' approach," says Dr Zeng.

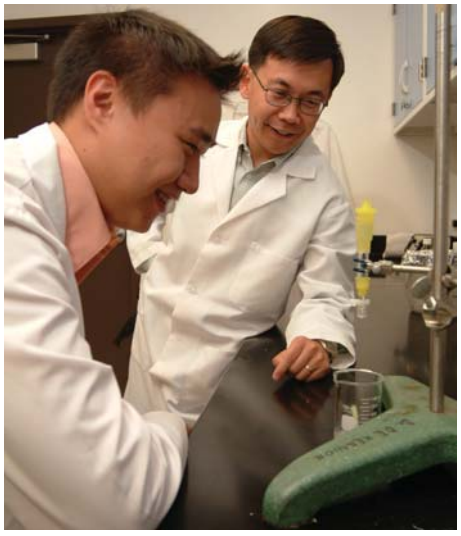
Since joining the program last year, Dr Zeng and members of his and Dr Arie Belldegrun's laboratory have focused on identifying targets in the form of antigens – the genes that are expressed on kidney cancer and recognized by the killer cells of the immune system. The hope is that this will facilitate a shift from an approach such as IL-2, which broadly stimulates the immune system, to new therapies that vaccinate patients against their cancer by taking direct aim at the kidney cancer cells, reducing the toxicity and increasing the percentage of patients who benefit.



T Lymphocytes Efficiently Kill Kidney Cancer Cells in a Culture Dish

Above: small lymphocytes start attacking much larger tumor cells growing on a petri-dish.

Right: after overnight incubation, all tumor cells were killed.



Dr Gang Zeng (r.) with lab assistant Allen Wang

The strategy being followed by Dr Zeng's group is to isolate those T cells – the "killer" immune system cells boosted by IL-2 – that specifically recognize kidney cancer cells. "We have identified promising antigens that can recognize the tumor and kill it in laboratory experiments," Dr Zeng explains. "Now we are in the process of fishing out the genes responsible for producing these T cells."

This strategy, though new to kidney cancer, has been used with more success in melanoma research – most notably at Dr Steven Rosenberg's laboratory at the National Cancer Institute, where Dr Zeng was trained as a postdoctoral fellow from 1997-2002 before bringing his expertise in the technology to the kidney cancer research effort at UCLA.

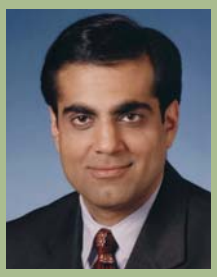
Born and raised in China, where he attended the prestigious Beijing University

as an undergraduate biology student, Dr Zeng came to the United States to study biochemistry at Virginia Tech, where he earned his PhD. From there he went to the National Cancer Institute, helping to identify tumor antigens for use in melanoma vaccines. His mentor, Dr Rosenberg, was the first to develop IL-2 as a cancer drug in the laboratory and use IL-2 in the clinic, treating melanoma patients. Given that kidney cancer has also responded to immunotherapy, Dr Zeng notes, it was a natural next step to come to UCLA, where the Kidney Cancer Program, under the leadership of Drs Arie Belldegrun and Robert Figlin, is world renowned. Dr Zeng's responsibility in the program is to conduct basic laboratory research in conjunction with Dr Belldegrun, the surgical director who takes on kidney cancer with nephrectomy; and Dr Figlin, the medical director who focuses on IL-2 based immunotherapy against kidney cancer. "We work well together," says Dr Zeng. "This is such a complicated problem that it would be impossible for one person to do it all."

Many hurdles remain to be cleared. For one thing, the kidney cancer research field is small, and public funding for the effort is limited. In addition, Dr Zeng says, "we still have a lack of defined tumor antigens – fewer than 10 are currently available, and these tend to be unsuitable for most patients. And we need to continue to develop a better understanding of how to boost the patients' immune systems specifically against their kidney cancer. We can boost them a little bit, but not enough to eradicate the cancer completely. The reason the cancer continues to progress is that this marginal number of T cells and antibodies that we can produce is not enough."

But Dr Zeng is optimistic that the approach, once it is refined, could help many patients – even, perhaps, those with other cancers. "Melanoma and kidney cancer are considered the most immunogenic cancers," he says. "But more and more molecular evidence has shown that patients with prostate cancer and lung cancer are also able to generate T cells and antibodies against their tumor. Cancer immunology and vaccine development is now seen as a very promising field that has become increasingly active."

ALUMNI SPOTLIGHT



Samir S. Taneja, MD
Assistant Professor of Urology and
Director of Urologic Oncology
New York University School of Medicine

It's been only seven years since Samir S. Taneja, MD, completed his residency at UCLA's Department of Urology. But in that relatively short period, Dr Taneja has taken great strides in the laboratory with intriguing observations about the function of the androgen receptor and its role in prostate cancer growth – findings with great relevance to the fight against the second-leading cancer killer in U.S. men, given that advanced prostate cancer treatment eventually fails when patients become hormone-refractory.

"Dr. Taneja came to UCLA to prepare himself for a career in academic urology," says Dr Jean B. deKernion, chairman of the UCLA Department of Urology. "During his training and his subsequent tenure at NYU, he has demonstrated abilities as a clinician, teacher, and investigator. He is a model young academic urologist with a very promising career in our specialty."

After leaving UCLA in 1996, Dr Taneja did a two-year American Foundation for Urologic Disease research scholarship in the NYU laboratory of Dr Michael Garabedian, a steroid receptor biologist. Though the laboratory's research was not related to the prostate, Dr Taneja began to use similar methods to study the influence of androgen receptor stimulation on the cell cycle. On the faculty at NYU, he and his colleagues began an ambitious search for specific proteins involved in regulating the androgen receptor's function – which they referred to as Androgen Receptor Trapped (ART) proteins. Dr Taneja's group has recently focused on characterizing two proteins in particular: ART-27 and ART-5.

Identifying ART-27 and ART-5 was important in and of itself, since few proteins that interact with the androgen receptor had previously been discovered. But upon closer examination, Dr Taneja's team began to see that one of them, ART-27, appears to have a significant association with prostate cancer growth, and may also serve as a checkpoint of sorts, through which cells pass before becoming malignant. Dr Taneja's group has demonstrated that placing the ART-27 protein into a cell with the androgen receptor can enhance the receptor's activity, increasing its function over time, and that ART-27's expression is greatly diminished – or even lost – in prostate cancer cells.

"This work is still quite preliminary, but if ART-27 is a protein that slows down the growth of prostate cancer or even stops it, it might be a great therapeutic," Dr Taneja notes. "And if we can understand how it's regulated, it could help us with strategies to prevent prostate cancer formation by making sure that its expression continues in the prostate."

Dr Taneja credits the role models he had as a resident in UCLA's Department of Urology with setting him on the right career course. "As a faculty member in a residency program now, I realize the importance of role models for residents," he says. "The importance of academics was stressed throughout our training at UCLA, which is very unique. Certainly, being in the lab sparked my interest in prostate cancer molecular biology and in experimental therapeutics, but it was really the mentors and role models at UCLA who have shaped my career."

Department of Urology Faculty

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Specialty: *Urologic Oncology*

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Specialty: *Urologic Oncology, Biologic Therapy*

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Specialty: *Male Infertility*

Jennifer R. Berman, MD
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Bernard M. Churchill, MD
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Specialty: *Pediatric Urology*

Robert A. Figlin, MD
Professor of Clinical Urology and Medicine
Specialty: *Oncology*

Stuart Fisher, MD
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Specialty: *General Urology*

Nestor Gonzalez-Cadavid, PhD
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Lily Wu, MD, PhD
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Specialty: *Molecular Biology, Gene Research*

Gang Zeng, PhD
Assistant Professor of Urology
Specialty: *Tumor Immunology, Cancer Vaccine*

Giving Opportunities

The Department of Urology welcomes your contributions throughout the year. To send a contribution or to become a member of Friends of UCLA Urology, please make your check payable to "Regents of UC" and mail it to Ms Rain Burch at the Department of Urology, Box 951738, Los Angeles, CA 90095-1738. For donations by credit card, please call Ms Burch at 310-794-2159.

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