

# CLARK UROLOGICAL CENTER

N E W S L E T T E R

## PAVING NEW GROUND – IN THE CLINIC AND IN THE LAB

*Dr Larissa Rodríguez Hopes Her Group's Research on Common Female Urology Conditions Will Lead to a Better Quality of Life for the Patients She Treats*

**U**rinary incontinence affects 13 million people in the United States, the vast majority of them women, whose risk of developing the condition increases with age. The annual cost of incontinence in this country has been estimated at more than \$26 billion – only a small portion of which is spent on treatment. “Most of the cost is for protective devices, such as diapers and pads,” says Larissa Rodríguez, MD, assistant professor of urology at UCLA. “Many women think that as they get older they're *supposed* to have incontinence, and so they don't see a doctor about it.”

The impact of living with the problem on these individuals' quality of life is severe. In addition to the fear of embarrassment that keeps many women from going out socially or being active sexually, there is increased risk of urinary tract infection. The elderly become more likely to enter a nursing home as they develop incontinence, and are at increased risk for falls. “A lot of things are associated with incontinence, and yet we're not really treating it,” says Dr Rodríguez.

Currently, the only curative treatment for stress urinary incontinence – the most common form of incontinence, in which a loss of anatomic support of the urethra results in uncontrolled urination during activities in which abdominal pressure is increased, such as coughing, laughing, and sneezing – is major surgery. But Dr Rodríguez, who, in addition to seeing patients as co-director of the Division of Female Urology, Reconstructive Surgery and Urodynamics, heads a research team focused on female urology, is conducting pioneering tissue engineering studies that



**Dr Larissa Rodríguez (front row, center), assistant professor of urology, heads a research group that includes (back row, left to right): Shiqing Zhang, MD; Fernando de Almeida, MD; Samuel Olson; (front row, left to right) Zeni Alfonso, PhD; and medical student Gustavo Casillas.**

could one day make the optimal treatment far less invasive. She is also among the only investigators focusing on vaginal prolapse, another common urological problem affecting women, through research on the physiology of the vagina and bladder that she is undertaking in collaboration with Dr Louis Ignarro, 1998 Nobel Laureate.

Paving new ground is nothing new for Dr Rodríguez, who is one of a small number of female urologists in the United States and among the few Latinas practicing in the specialty. Born and raised in Puerto Rico, she has wanted to be a scientist for as long as she can remember. As an undergraduate at MIT, she majored in math. But she found that science alone wasn't

enough. “I always wanted to help people and have an impact on their lives,” she says. “Academic medicine, in which I could integrate discovery with patient care – seeing patients and conducting research on their problems – seemed like the ideal mix.”

It was as a urology resident at Stanford – where she also attended medical school – that Dr Rodríguez decided to sub-specialize in female urology, because of the impact of incontinence on women's health. “It's extremely underreported and undertreated, and as a woman in the field I felt that focusing in that area was the right thing to do,” she says. So, following residency, Dr Rodríguez did a fellowship in female urology

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and reconstructive surgery with one of the world's leading experts in the area, Dr Shlomo Raz, professor of urology at UCLA.

In 2001 she joined the UCLA Department of Urology faculty as Dr Raz's associate. Among the conditions Drs Raz and Rodríguez treat are female and male urinary incontinence, neurologic conditions affecting the function of the lower urinary tract, pelvic floor disorders including vaginal prolapse and chronic pelvic pain, and benign prostatic hyperplasia (BPH) in men, along with the voiding dysfunction usually caused by BPH.

In the laboratory, her research group has been driven by the need to understand more about the causes of female stress incontinence, vaginal prolapse, and voiding dysfunction – and, in the case of stress incontinence, to develop innovative approaches that would make optimal treatment less invasive. “As women age and their hormonal milieu changes after menopause, the smooth musculature of the urethra atrophies and the urethra begins to lose its ability to close,” Dr Rodríguez explains. “We want to see if, rather than performing major reconstructive surgery, we can rebuild this tissue back to its normal state.”

Her group has focused on inducing fat-derived stem cells to become functional smooth muscle; the ultimate goal is to be able to take stem cells derived from patients'

own fatty tissues and re-inject the cells into the urethra, under local anesthesia, to rebuild the faulty tissue. “We have successfully turned the fat cells into functioning smooth muscle, which is in itself a triumph,” Dr Rodríguez says. She and her colleagues are now testing the approach in an animal model for stress incontinence. If successful, clinical trials in human patients could follow.

Current minimally invasive approaches to treating stress urinary incontinence typically seek to add bulk to the urethra, increasing resistance so it doesn't leak. But these approaches have not been as effective as hoped at producing long-term cures, Dr Rodríguez says. Rather than injecting materials to build up the system, as these treatments do, she is interested in injecting cells to rebuild the patient's urethra. While the research is focused on the problem of stress urinary incontinence, Dr Rodríguez notes that the same approach could be applied to other problems caused by the dysfunctional smooth muscle, including vaginal prolapse – a disease of postmenopausal women in which the vagina loses its supportive ability, causing symptoms that can include pressure, discomfort, and urinary obstruction.

Although prolapse is known to be associated with women who have had vaginal deliveries – though symptoms usually do not occur until after menopause – little



**In the lab, Dr Rodríguez focuses on stress incontinence and vaginal prolapse.**

is known about why it occurs, or how it can be prevented. Dr Rodríguez is investigating both questions. In collaboration with Dr Ignarro, she is studying the normal and abnormal physiology and function of the bladder, urethra and vaginal tissues – in particular, how the genitourinary tract changes with age. The researchers are testing their hypothesis that reduced estrogen levels in postmenopausal vaginal tissue lead to increased levels of nitric oxide, resulting in smooth muscle atrophy and decreased collagen deposition. In human tissue studies, they are seeking to determine whether these changes are what lead to loss of support of vaginal structures, stress urinary incontinence, and loss of normal vaginal physiology.

“A better understanding of the cause of these changes could enable us to prevent them from occurring,” Dr Rodríguez explains. In a separate study with Eric Vilain, MD, PhD, assistant professor of urology, human genetics and pediatrics at UCLA, Dr Rodríguez is exploring genetic factors that predispose certain women to vaginal prolapse.

“These conditions that we're studying and treating patients for have a major impact on their quality of life,” Dr Rodríguez says. “People need to know that this isn't just something that ‘happens’ – that incontinence and prolapse are conditions that can be treated. We hope in the future to offer even better treatments and to work toward prevention.”



**Dr Rodríguez divides her time between the laboratory and the clinic, where she sees patients such as Carmen Davenport (left). She joined the UCLA Department of Urology faculty in 2001.**

# LABORATORY FINDINGS LEAD TO TRIAL OF IMMUNOSUPPRESSANT

## *Drug Approved for Kidney Transplant Recipients May Prove Beneficial for Some Prostate Cancer Patients*

**I**mportant findings made by a member of UCLA's Department of Urology on the potentially positive impact in certain prostate cancer patients of an immunosuppressant drug used for kidney transplant recipients will move from the laboratory to the clinic in a trial scheduled to begin this summer.

The trial of CCI-779 is part of the Specialized Program of Research Excellence (SPORE), a designation conferred on UCLA's Prostate Cancer Research Program by the National Cancer Institute. The distinction, given to only a handful of centers in the country, provides \$11.5 million in funding aimed, in part, at facilitating the translation of promising laboratory observations into effective clinical treatments that target the molecular errors leading to the disease.

CCI-779 is a variant of rapamycin, a drug approved by the Food and Drug Administration to prevent organ rejection in kidney transplant patients. In mouse models, Charles Sawyers, MD, professor of medicine and urology and the Bing Professor of Urologic Research at UCLA, found that the drug also has anti-cancer properties – specifically in prostate cancer tumor cells lacking PTEN, a so-called tumor suppressor gene that acts like a switch regulating access to a cell-signaling pathway. When a mutation causes PTEN's function to be lost, other genes normally regulated by PTEN are turned on. Among these are MTOR, the gene that produces the protein blocked by rapamycin. In their laboratory experiments, Dr Sawyers and colleagues found that MTOR activity was high in tumors with no PTEN, and that when the potent form of rapamycin was used in these tumors, blocking such activity, the tumors' growth was halted.

Other research groups have confirmed that lacking the PTEN gene leads to greater sensitivity to the effects of rapamycin, leading a UCLA team headed by Dr Sawyers



**Drs Robert Reiter (left) and Charles Sawyers**

and Robert Reiter, MD, associate professor of urology and co-principal investigator of the SPORE, to initiate the clinical trial. They will test the impact of CCI-779 in men with newly diagnosed prostate cancer who are considered to be at high risk for recurrence following radical prostatectomy. Adopting a test developed by Dr Sawyers's lab, the researchers will take a biopsy of the patients' tumors after diagnosis to determine whether PTEN is present, then administer CCI-779 – an oral drug with very few side effects – for seven weeks prior to their surgery. Upon removal, the prostates will be examined to determine whether the predicted targets of the therapy were affected. "Our thought is that perhaps only those prostate cancers caused by the PTEN abnormality are going to be the ones that respond to CCI-779," says Dr Sawyers.

The study exemplifies the SPORE's ability to turn the latest basic discoveries into potential clinical advances, adds Dr Reiter. "This is truly translational work," he says. "We're taking laboratory observations made at UCLA and bringing them into the clinic; then we'll take observations we make in the clinic and move them back into the lab to further refine the treatment."

## UROLOGY BRIEFS

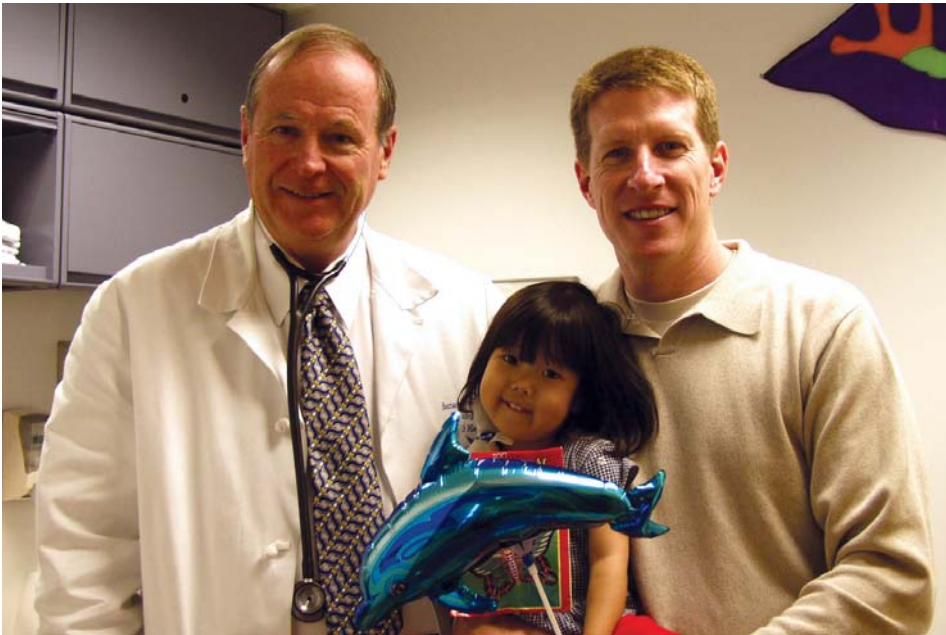
The second annual Women's Sexual Health, State-of-the-Art Conference was held this spring at the Fairmont Miramar Hotel in Santa Monica. The conference addressed key factors in a mind/body approach to the evaluation, diagnosis and treatment of female sexual function and presented methods for incorporating female sexual medicine into an existing urological or gynecological practice. Dr Jennifer Berman, director of the Female Sexual Medicine Center at UCLA, and her sister Dr Laura Berman, director of the Berman Center in Chicago, chaired the two-day conference. Faculty experts in female medicine from around the globe discussed a wide range of topics affecting women's health.

A May United Press International article featured new UCLA prostate cancer research led by Dr Mark Litwin, professor of urology and researcher at UCLA's Jonsson Cancer Center. The study addressed quality-of-care measurements for patients with early-stage prostate cancer and concluded that choosing the provider for care might be just as important as choosing the type of treatment for early-stage prostate cancer. Dr Litwin and his colleagues at the RAND Health Science Program – Benjamin Spencer, Michael Steinberg, Jennifer Malin, and John Adams – identified 49 quality-of-care indicators that would assist patients and their physicians in medical decision-making. The study appears in the May issue of *Journal of Clinical Oncology*. Please contact Ms Linda Mattingly at [lmatingly@mednet.ucla.edu](mailto:lmatingly@mednet.ucla.edu) if you would like a copy mailed or e-mailed.

Physician members of the American Urological Association (AUA) have created an online patient information resource: [www.urologyhealth.org](http://www.urologyhealth.org). The user-friendly site provides reliable urological information along with detailed medical illustrations.

# DELICATE SURGERY COMPLETES TURNAROUND FOR PATIENT WHO WAS ONCE GRAVELY ILL

*Three-Year-Old Julia Welch Was Brought by Her Adoptive Parents from China for a Rare Procedure That Dramatically Improves Her Quality of Life*



**Left: Three-year-old patient Julia Welch with her father, Michael (right), and Dr Bernard Churchill, head of pediatric urology at the UCLA Clark-Morrison Urological Center. Above: After the surgery, a healthy, happy Julia in May with her four siblings (l. to r.): Jonathan, Annelise, Karissa and Bradley.**

**F**ew children are born into circumstances as devastating as those encountered by Julia Welch. But the 3-year-old's fortunes have taken a remarkable turn for the better recently, thanks to the parents who adopted her and the team at the UCLA Clark-Morrison Children's Urological Center that performed a rare surgery to correct her debilitating bladder condition.

Born in China with a host of severe medical problems including a form of spina bifida, Julia was abandoned as an infant and was being raised in an orphanage when Michael and Victoria Welch, who live and work in China and are from the Los Angeles area, came by for a visit. The couple soon became attached to the girl, whose health was deteriorating rapidly. She was extremely gaunt – to the point of being unable to raise her head. Her cheeks were sunken; her face emotionless. The orphanage doctor explained that there was little that could be done, and that the girl would soon die. Still, the couple wanted to help. They convinced the orphanage director to release the girl to

*“It really is profound that physicians like Dr Churchill have spent their lives developing solutions for children like Julia. Already, when people meet Julia they never guess the horrible start she had in life.”*

**Michael Welch**

them, so she could at least spend her last days in a loving home.

She did not die – in fact, today she is a normal, happy child, having been adopted by the Welch family, which brought her to UCLA for surgery that dramatically improved her quality of life.

As with many children born with congenital spinal cord problems, Julia could not completely empty her bladder. This necessitates use of a catheter, but also leads to problems with urinary leakage,

potentially resulting in infections and damage to the kidneys. Dr Bernard Churchill, head of pediatric urology at the Clark-Morrison center, performed a delicate surgery to prevent the leakage and increase the size of Julia's bladder, giving it a greater storage capacity. The complicated procedure, which involves resection of part of the intestines and is particularly difficult in young children because of their size, is done by only a small number of pediatric urology subspecialists. Its success ensures that Julia can live a normal life, needing only to catheterize herself every 4-6 hours as opposed to growing up wearing diapers, enduring infections and putting her kidneys at risk.

“When Julia was first examined in China, no one in the doctor's office knew whether she would make it, or what her quality of life would be,” says Michael Welch. “It really is profound that physicians like Dr Churchill have spent their lives developing solutions for children like Julia. Already, when people meet Julia they never guess the horrible start she had in life.”

# RESEARCHER PROBES GENETIC FACTORS DETERMINING SEX; FINDINGS KEY TO BETTER UNDERSTANDING OF INTERSEX

*One in 4,000 Babies Is Born with Atypical Genitalia and Unclear Gender*

**W**hat determines whether a person is male or female? One in 4,000 babies is born with atypical genitalia and unclear gender. These “intersex” births, more frequent than commonly believed, are rarely discussed, notes Eric Vilain, MD, PhD, assistant professor of urology, human genetics and pediatrics. “There has been a lot of scientific progress in the last decade that has helped us to understand, and therefore more quickly diagnose, intersex,” Dr Vilain says. “The challenge now is to understand the mechanisms of gender identity and how it is determined, helping us to make better choices about gender assignment at birth.”

The discovery in 1959 that sex is determined by the Y chromosome – those who have it are male; those who don’t are female – ushered in the modern era of gender assignment, but it left unanswered many questions that continue to be the focus for researchers such as Dr Vilain, who has homed in on the answers by studying the genes responsible for sex determination. Intersex is caused either by a hormonal disorder – the most common being congenital adrenal hyperplasia, in which an enzyme deficiency causes an accumulation of testosterone that masculinizes XX fetuses – or a genetic mutation. In 1990, based on patients identified by Dr Vilain’s research team, the first gene associated with sex determination was cloned. Dr Vilain’s group studied males who had two X chromosomes but no apparent Y chromosome and found, using molecular probes, that these individuals carried very small fragments of the Y chromosome on one of their X chromosomes. These fragments contained a gene called SRY. Moreover, Dr Vilain found that just one mutation of the SRY gene in an XY fetus changed the fate of that individual from male to female. “That was powerful genetic evidence of the role of this gene,” he says.

At the time, it appeared that SRY explained everything about sex determina-



**Dr Eric Vilain, assistant professor of urology, human genetics and pediatrics at UCLA, contributed to the discovery of the first human gene associated with sex determination. Dr Vilain, who also sees intersex patients with the pediatric urologists at UCLA’s Clark-Morrison Children’s Urological Center, has followed up that 1990 discovery with the identification of other genes that are factors in sex determination. These findings are facilitating more rapid diagnoses.**

tion: if completely mutated, it was thought, SRY rendered an XY female; if it moved to one of the X chromosomes, an XX male; if partially mutated, an intersex individual. As it turns out, though, SRY plays a smaller role – for example, only about 15 percent of XY females can be explained by SRY mutations. What of the remaining cases? Several other genes have been identified that explain either complete sex reversal – XX males or XY females – or, when they are partially mutated, intersex. The most recent of these is WNT-4. Dr Vilain’s team found that having a duplicate copy of this gene can feminize an XY, often resulting in ambiguous genitalia.

These genetic findings have immediate clinical value, notes Dr Vilain, who, in addition to his laboratory work, sees intersex patients with the pediatric urologists at UCLA’s Clark-Morrison Children’s Urological Center. “The genetics has revolutionized the way we diagnose babies born intersex,” he explains. “With molecular

testing, we are able to more quickly and accurately make a diagnosis related to sex, which helps parents and the medical team make the best possible decisions about gender assignment.” Among the options discussed with the parents is whether or not to perform surgery on the genitals. Dr Vilain notes that this is a difficult decision given the lack of data on the quality-of-life impact of such surgery.

As Dr Vilain and other researchers continue to hunt for other genes responsible for sex determination, they also face a more profound challenge, which is to understand the biological factors in gender identity – an issue that goes beyond anatomy. Part of Dr Vilain’s laboratory now studies sexual differentiation in the brain. “I’m convinced that there are environmental factors that influence gender identity, but there must also be biological determinants,” he says. “There are subtle yet real differences between the male and female brain, and those differences may play a role.”

## UCLA Prominently Featured at AUA Annual Meeting

The UCLA Department of Urology was well represented at the American Urological Association's 98th Annual Meeting held in Chicago in April. Department faculty, fellows and residents presented podium and poster sessions, chaired courses, and served on panel discussions at the meeting, which is attended by more than 9,000 urologists from the United States and approximately 75 other countries each year.

Two faculty from the department presented state-of-the-art lectures: Bernard M. Churchill, MD, professor and chair of pediatric urology, addressed "Transplant in Children: Concern for Lower Urinary Tract Abnormalities," and Robert Figlin, MD, professor of medicine and urology and the Henry Alvin and Carrie L. Meinhardt Chair for Kidney Cancer Research, discussed "Advanced Renal Cancer – Who and How to Treat?"

In addition, Mark S. Litwin, MD, professor of urology and health services, distilled the weeklong meeting's proceedings to report take-home messages involving urological outcomes and health services research. And Drs Shlomo Raz, professor of urology and director of the Division of Female Urology, Pelvic Medicine, and Reconstructive Surgery, and Larissa Rodríguez, assistant professor of urology, offered a one-day state-of-the-art urology course to their urology colleagues from Spain and Latin America. The lectures, given by distinguished specialists from around the United States, were simultaneously translated from English to Spanish.

## COMINGS AND GOINGS



Freedland

Liao

Palapattu

Chin

Davé

Gulati

The close of the academic year in June marks the end of urology residencies for three physicians and the start of three new urology careers.

This year's graduates were **Drs Stephen J. Freedland, Joseph Chihping Liao, and Ganesh S. Palapattu**. Drs Freedland and Palapattu will move to Baltimore to begin fellowships at Johns Hopkins: Dr Freedland with Dr William Isaacs in urological oncology; Dr Palapattu with Dr William Nelson to study prostate cancer chemoprevention. Dr Liao will undertake a dual fellowship at the UCLA Department of Urology with Dr Bernard Churchill in pediatric urology and Dr Peter Schulam in endourology.

On July 1, three new physicians began their six-year residencies in UCLA's Department of Urology: **Drs Arnold I. Chin, Dhiren S. Davé, and Mittul (Mitch) Gulati**. Dr Chin received his BA in chemistry from Princeton University and his MD from UCLA. After his second year in medical school, he took a four-year leave of absence to earn a PhD in molecular biology from the Molecular Biology Institute, also at UCLA.

Dr Davé's BS in biomedical engineering was granted by Johns Hopkins University; his MD by Vanderbilt University School of Medicine in Nashville. He interrupted his medical education for one year to pursue an NIH-funded research fellowship program through Vanderbilt's Medical Scholars Program.

Dr Gulati graduated magna cum laude from Harvard College with a BA in history and science. He received his MD from UC San Francisco, also extending his education by one year to accept a Howard Hughes Medical Institute research fellowship.

The department also provides further specialized training in specific areas of urology through one- and two-year fellowships.

**Drs Raviender Bukkapatnam and Sovrin M. Shah** hold female urology fellowships under the supervision of Dr Shlomo Raz. Dr Bukkapatnam earned his MD from the University of Alabama and did his residency at the University of South Florida College of Medicine. Dr Shah's medical degree is from the State University of New York at Stony Brook, followed by residency training at the State University of New York's Downstate Medical Center in Brooklyn.

**Dr John Lam** holds a two-year oncology fellowship, the first year with Dr Arie Belldegrun and the second with Dr Jean deKernion. Dr Lam earned his MD at Wayne State University in Detroit (with two extra middle years as a research scholar at the National Cancer Institute in Bethesda, Maryland). He completed his residency at Columbia Presbyterian Medical Center in New York.

**Dr Debra S. Wickman** will join Dr Jennifer Berman at the Female Sexual Medicine Center. Dr Wickman holds bachelor's and master's degrees in nursing and was the director of pediatric nursing at Loma Linda Community Hospital before pursuing her medical degree at the University of Washington in Seattle, where she also completed her OB/Gyn residency.



## CAN POMEGRANATE JUICE HELP IN PROSTATE CANCER PREVENTION?

### *UCLA Clinical Trial Provides First Major Test*

**T**hroughout history the pomegranate has been an evocative fruit, whether it was being extolled in literature by no less than Shakespeare, Chaucer and Homer, held up as an aphrodisiac by certain cultures and a blessed fruit in certain religions, or used as a tool for temptation in Greek mythology.

For just as long, certain societies have seen medicinal value in the pomegranate, and recent scientific findings suggest they've been onto something. Pomegranate juice has been found to contain as much as three times the antioxidant level of green tea or red wine, and studies have found it can reduce harmful LDL cholesterol and blood pressure. A large randomized controlled trial under way at UC San Francisco is studying the benefits of pomegranate juice for cardiovascular health. And now researchers at UCLA have begun the first clinical trial seeking to determine whether the juice has a role to play in prostate cancer prevention.

"Studies from laboratories here at UCLA have shown that in both cell cultures and mouse models for prostate cancer, pomegranate juice can slow the growth of prostate cancer tumors and prolong life," says Allan J. Pantuck, MD, assistant professor of urology, who heads the clinical trial with Arie Belldgrun, MD. "This is a promising, non-toxic nutritional strategy that we were interested in bringing from the laboratory to the clinic."

Their Phase II trial is evaluating the effect of pomegranate juice in 40 patients whose prostate-specific antigen (PSA) levels are found to be rising – though still relatively low – following treatment with radical prostatectomy or radiation therapy. The study will examine whether pomegranate juice taken daily over an 18-month period slows the rise of PSA, or even decreases it. "Rising PSA is a sign that the cancer may be returning, but it can often take as long as 10 years before the recurrent tumor actually shows up on the x-ray," notes Dr Pantuck. "That's a fairly large window of opportunity to try something non-toxic." Standard treatments for recurrent prostate cancer – radiation and hormone therapy – are ineffective in about one in three patients, who eventually develop distant metastases.

With dozens of active chemicals, pinpointing the specific agent in the pomegranate – or in any nutritional strategy, for that matter – is difficult, and will be one of the goals of the UCLA researchers. What *is* clear is the growing evidence of the role of diet in prostate cancer. "Disparities in prostate cancer levels in different parts of the world are very striking," Dr Pantuck notes. "In Asia, prostate cancer occurs at a lower rate than in North America – but second- or third-generation Asian Americans rise to similar levels as native North Americans. That suggests an environmental component, and diet is a big part of our environment."

For more information, or to inquire about participating in this study, contact Nazy Zomorodian, the study coordinator, at 310-825-4415 or by e-mail at [nzomorodian@mednet.ucla.edu](mailto:nzomorodian@mednet.ucla.edu).

## KUDOS



Krupski



Bui



Zomorodian

**D**r Ganesh Palapattu, graduating chief resident, received The Willard E. Goodwin Resident Teaching Award from the faculty of the UCLA Department of Urology.

**D**r Tracey Krupski, clinical instructor in urologic oncology, and Drs Joseph Liao and Ganesh Palapattu, graduating chief residents (see Comings and Goings), received prestigious research fellowships from the American Foundation for Urologic Diseases (AFUD). The foundation awarded only 30 of these grants throughout the country.

**D**r Matthew H. T. Bui, incoming chief resident, has been awarded the 2003 Pfizer Scholars in Urology Award. The Department of Urology receives a \$2,000 grant in his name.

**N**azy Zomorodian, RN, MSN, NP, CCRC, and now CUNP, successfully completed the Urologic Advanced Practice Certification Examination and achieved the highly regarded designation of Certified Urology Advanced Practice (CUNP). Ms Zomorodian is director of the Clark Urological Center's Clinical Trials Program.

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