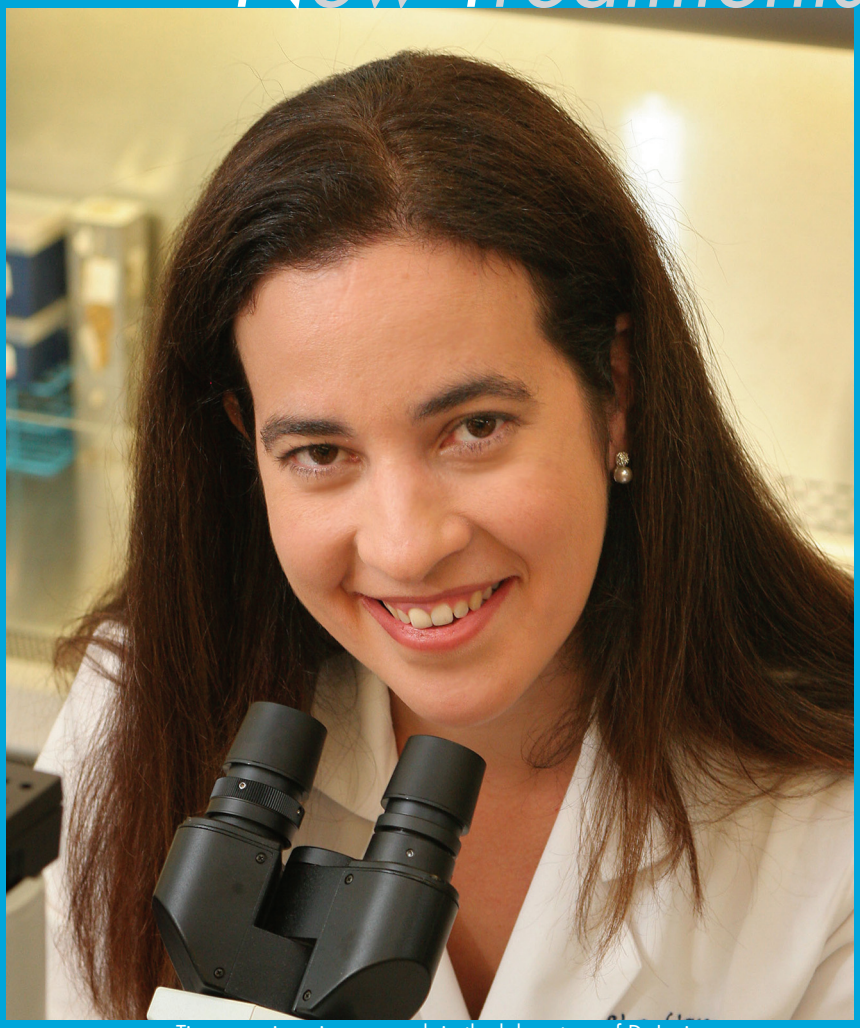
CLARK Urological Center
newsletter

Summer 2005 Vol. 17, No. 2

Engineering New Treatments



Tissue engineering research in the laboratory of Dr Larissa Rodríguez has yielded promising results.

Could patients' own stem cells hold the key to the first effective minimally invasive treatment for stress urinary incontinence – a huge quality of life issue for millions of Americans, particularly women? Could such cells be used for bladder reconstruction in patients with conditions ranging from spina bifida to bladder cancer, or to construct vaginal tissue for women with vaginal prolapse? While there is more work to be done before going to human clinical trials, results thus far from pioneering tissue engineering research in the laboratory of Larissa Rodríguez, MD, assistant professor of urology, indicate that such applications may indeed be feasible.

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In This Issue

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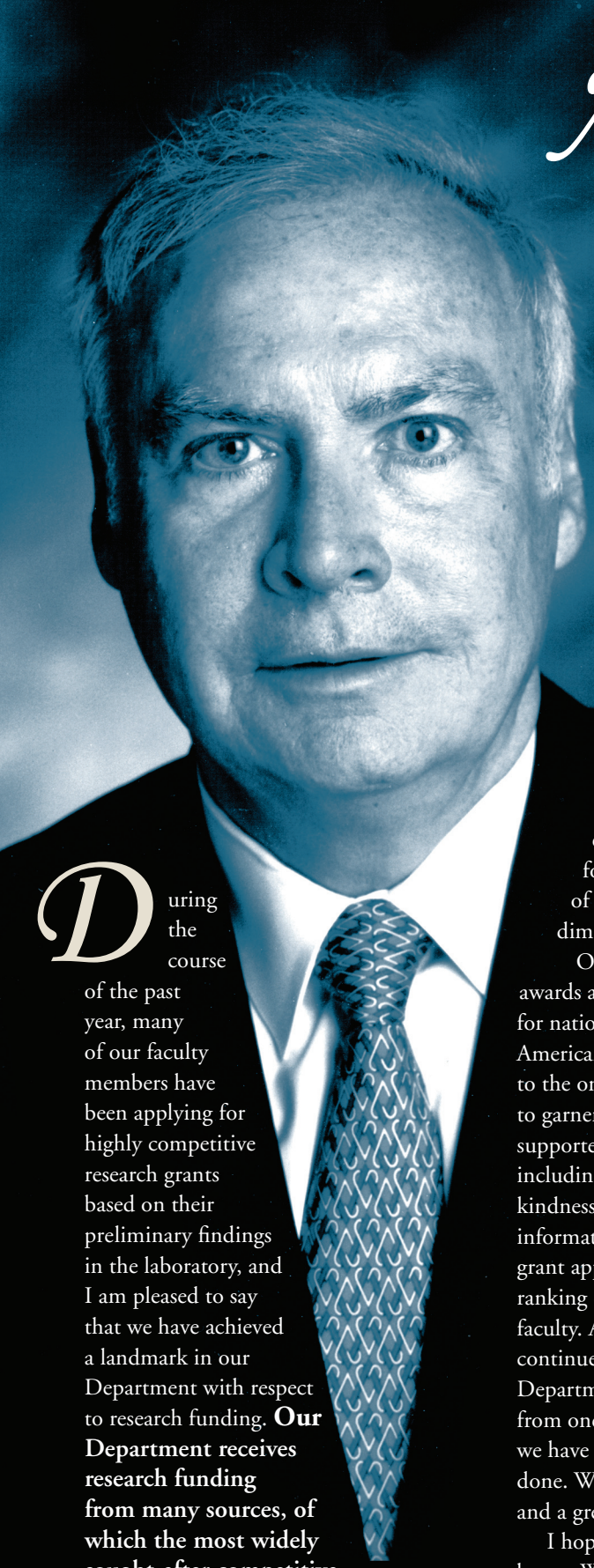
A Letter from the Chairman



During the course of the past year, many of our faculty members have been applying for highly competitive research grants based on their preliminary findings in the laboratory, and I am pleased to say that we have achieved a landmark in our Department with respect to research funding. **Our Department receives research funding from many sources, of which the most widely sought-after competitive grants are awarded by the National Institutes of Health (NIH). The NIH recently published its ranking of research for various medical disciplines, and the UCLA Department of Urology was number one in the nation in NIH funding, significantly above other major institutions. The addition of sources of funding other than the NIH would result in nearly double the amount of funding. We are all extremely gratified and proud of this achievement, which is a reflection of the talent and hard work of our faculty and staff.**

This summer's newsletter particularly focuses on the work of Dr Larissa Rodríguez's program on stem cell research. While embryonic stem cell research has been controversial, the use of stem cells from a patient's own fat cells is certainly an excellent alternative, and is an innovative approach to rebuilding a patient's own tissues. While still in its early stages, it is clear that this research has enormous potential for human application in the foreseeable future. This is one of the few programs of its type in the country, and brings an entirely new dimension of research to our Department.

Our faculty has recently received a number of awards and recognition, including successfully competing for national research and clinical awards given by the American Urological Association. Of important note to the ongoing successes of our faculty in their ability to garner research funding are the contributions of our supporters. As I have said many times, medical research, including research in our Department, is fueled by the kindness of our citizens. Without that help, the basic information needed for an effective and competitive grant application cannot be generated. Our number-one ranking can be attributed as much to our donors as to our faculty. All of those who have helped us over the years and continue to support us should feel that they are part of our Department's success. We feature in this issue a major gift from one of our friends, which is just one example of why we have had a measure of success. Much more must be done. We now have more opportunities than ever before, and a greater need for dedicated supporters.

I hope this good news makes your summer even better. We will report further on our progress in the next newsletter.

Jean B. deKernion, MD
Chairman

Comings and Goings

The close of the academic year in June marked the end of urology residencies for three physicians and the start of two new urology careers. The three outgoing chief residents were honored at the June 10 graduation, where Dr Donald S. Coffey, the Joseph J. Kaufman Visiting Professor for 2005 gave the evening's keynote addess on the topic of "Frontiers in Cancer Research." Dr Coffey is a professor of urology, oncology, pathology and pharmacology and molecular sciences at the Johns Hopkins University School of Medicine.

Graduating Residents

N. Janzen, MD

Dr Nicolette Janzen, the recipient of the Willard E. Goodwin Resident Teaching Award, will be moving to Houston for a one-year pediatric fellowship at Texas Children's Hospital.

I. Garraway, MD

Dr Isla Garraway will be continuing her academic career within the UCLA Department of Urology, with a focus on basic research. She will be joining the laboratory of Dr Robert Reiter, professor of urology, and expanding her research interests in the area of animal models for bladder and prostate cancer.

B. Kristo, MD

Dr Blaine Kristo has accepted a faculty appointment in urology at the University of Hawaii. He will be doing laparoscopy at Kaiser Moana Lua Medical Center in Honolulu.

Incoming Residents

J. Bergman, MD

Dr Jonathan Bergman is a graduate of the David Geffen School of Medicine. He would like to focus his research on pediatric urology, oncology or health services research. Clinically, he is interested in either pediatric urology or oncology.

R. Konijeti, MD

Dr Ramdev Konijeti joins the department's residency program from the University of Missouri, Kansas City School of Medicine. His research interests include basic and translational research in developmental and cancer biology.

Graduating Postdoctoral Fellows

T. Krupski, MD

Dr Tracey Krupski, who has completed a two-year fellowship with Dr Mark Litwin in urological health services research and a one-year fellowship in urologic oncology with Dr Jean deKernion, has accepted a position at Duke University as an assistant professor in the Department of Urology.

S. Vemulapalli, MD

Dr Sreenivas Vemulapalli completed a one-year urologic oncology fellowship with Drs Jean deKernion, Arie Belldegrun and Robert Reiter, and will return to the University of Oklahoma Health Sciences Center as an assistant professor of urology.

M. Bui, MD

Dr Matthew Bui, a former UCLA Department of Urology resident, has just finished his one-year fellowship in endourology with Dr Peter Schulam and has accepted a position as an assistant professor in urology at the Mayo Clinic in Scottsdale, AZ.

C. Johnson, MD

Dr Crista Johnson completed a one-year clinical fellowship in female sexual medicine, and has been accepted as part of the Robert Wood Johnson Clinical Scholars Program at the University of Michigan.

D. Deng, MD

Drs Donna Deng and Matthew Rutman both completed one-year fellowships in urodynamics with Drs Shlomo Raz and Larissa Rodríguez. Dr Deng will join UCSF's Department of Urology as an assistant professor, while Dr Rutman heads east to assume the position of assistant professor of urology at Columbia University.

M. Rutman, MD

Incoming and Continuing Postdoctoral Fellows

The department also provides further specialized training in specific areas of urology through one- and two-year fellowships. The following six physicians are filling 2005-2006 postdoctoral training slots:

M. Maher, MD

A. Mourtzinos, MD

J. Veale, MD

Dr John Lam begins the third year of his three-year fellowship in urologic oncology, working with Drs Arie Belldegrun, Jean deKernion and Robert Reiter. Dr Joseph Liao begins his final year of a three-year pediatrics/endourology fellowship with Drs Bernard Churchill and Peter Schulam. Dr Jennifer Tash-Anger is continuing her two-year fellowship with Dr Mark Litwin in urological health services research. Both Drs Mary Gray Maher and Arthur Mourtzinos will join Drs Shlomo Raz and Larissa Rodríguez for one-year fellowships in urodynamics from Yale University School of Medicine and Lahey Clinic Medical Center in Burlington, MA, respectively. Dr Jeffrey Veale joins Dr H. Albin Gritsch and the transplantation team following his residency at University of Manitoba, Canada.

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The most advanced of Dr Rodríguez's tissue engineering applications is for stress urinary incontinence (SUI), a common condition in which a loss of anatomic support of the urethra results in urinary leakage during activities in which abdominal pressure is increased, such as coughing, sneezing, and laughing. Of note in a society with a fast-growing elderly population (the number of U.S. residents 65 and older is expected to double over the next 25 years) is that the incidence of SUI increases with age – one-third of women older than 65 have some degree of incontinence. The annual cost of incontinence in the United States has been estimated at more than $26 billion – only a small portion of which is going to treatments of the underlying problem. "Most of the cost is for protective devices, such as diapers and pads, or the results of incontinence – treatment of urinary tract infections, or people falling because they're rushing to make it to the bathroom," explains Dr Rodríguez.

Dr Larissa Rodríguez with Xiaoyong Zeng, MD, PhD

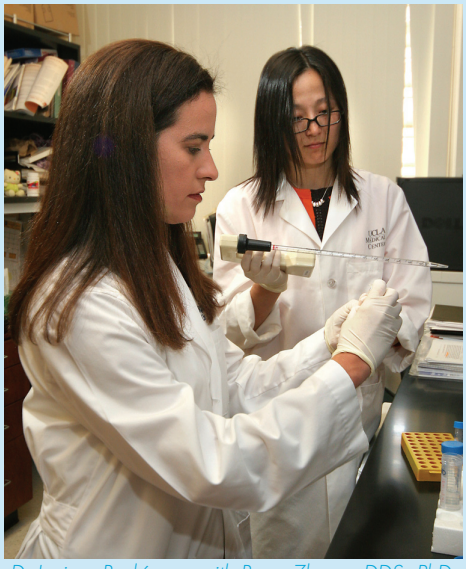
That's partly because the only curative SUI treatment is major surgery. Minimally invasive approaches, which involve injecting inert materials to increase the resistance of the urethra, in the best cases offer only short-term cures, often after several procedures. "Because these are the options, a lot of people don't seek treatment; they just live with the problem," Dr Rodríguez notes.

In her tissue engineering research, Dr Rodríguez aims to reconstruct the urethra by injecting cells taken from the patient's own fat tissue. The urethra is composed mostly of smooth muscle; this musculature, believed to play a key role in the continence mechanism, tends to atrophy following the trauma of vaginal delivery, and then again during the hormonal changes after menopause.

> "With all of these applications there is a lot of work to be done before we can use them in humans," Dr Rodríguez notes. "But we're very encouraged by our progress so far."

Dr Rodríguez and colleagues began by successfully showing that they could take fat-derived stem cells – cells harvested from human liposuction specimens – and, in the laboratory, transform these cells into tissues essential for the continence mechanism, in particular the smooth musculature. Next, they studied the viability of these cells – first, to see if they could be successfully delivered, via injection, into the urethra; and second, to determine whether they could survive in the lower urinary tract, becoming functioning smooth muscle cells. After developing animal models for incontinence, Dr Rodríguez's team showed that the cells could, in fact, be delivered and remain viable in animals. Now, Dr Rodríguez's group is testing the impact of the treatment in the animal models, the important last step before possible clinical trials in human patients.

In the United States, 50,000 people are diagnosed with bladder cancer each year, most of whom require



Dr Larissa Rodríguez with Rong Zhang, DDS, PhD

bladder reconstruction. Children born with congenital anomalies affecting the bladder can also be candidates. One in 1,000 newborns have spina bifida; many of them have neurogenic bladders, a condition in which interference with the normal nerve pathways associated with urination causes a dysfunction. Currently, though, the only feasible source of replacement tissue for the bladder is from the bowel, a procedure that is wrought with complications and difficulties.

Since the bladder, like other parts of the urinary tract, consists mostly of smooth muscle and nerves, Dr Rodríguez began applying her tissue engineering efforts to bladder reconstruction. Working closely with biomedical engineers on the UCLA campus, Dr Rodríguez and colleagues have used fat-derived stem cells to generate healthy smooth muscle, and have engineered a "scaffold" out of nontoxic, biodegradable materials to temporarily hold together the bladder wall while the cells are differentiating into the necessary tissues. They are currently testing the approach in an animal model.

"With all of these applications there is a lot of work to be done before we can use them in humans," Dr Rodríguez notes. "But we're very encouraged by our progress so far."

A Special Gift

Howard and Nancy Marks have made a $1 million gift to support the research of Arie Belldegrun, MD, within the Urologic Oncology program at UCLA.

The gift was made in memory of Nancy's mother, who was treated in the Department of Urology for kidney cancer.

"Dr Belldegrun operated on my mom, and gave her amazing care," says Nancy. "We wanted to make a donation in her memory, and in support of his work. We hope that it helps to make inroads into the cure for kidney cancer, and for other urologic diseases that Dr Belldegrun studies."

The couple hope that their donation to support the work of Dr Belldegrun, who also happens to be a close friend, will serve as an example that others will follow. "We also wanted to support UCLA Medical Center and the Department of Urology in general, because they have been great," says Howard.

"Aside from the treatment, there was such love and support from the department," Nancy adds. "My mother was very thankful for that."

Scott Quintard/ASUCLA

An Artist's Appreciation

LaVerne McDonnell was so pleased with the care her husband received at the Clark Urological Center that she decided she wanted to give something back. In her case, it was two "somethings" – a pair of 32" x 40," framed watercolor paintings that now hang at the UCLA Tiverton House, where the award-winning Cambria, Calif., artist and her husband Bob stayed at times during his treatment for prostate cancer.

Bob McDonnell was originally diagnosed with prostate cancer near the McDonnells' coastal community. Rather than accept that physician's advice to follow a course of "watchful waiting," he and his wife journeyed to UCLA for a second opinion. At the Clark Urological Center, Robert B. Smith, MD, professor of urology, recommended going forward with a radical prostatectomy that the McDonnells believe saved Bob's life.

LaVerne donated two watercolor paintings to the UCLA Tiverton House, which was established to meet the needs of patients being treated at UCLA Medical Center and their families, making it possible for families to be nearby when support and closeness are most needed.

"Art can be healing," says LaVerne, in explaining the motivation behind her gift. "My hope is that future patients will be able to enjoy these paintings and see the beauty of our Earth in just a little different way to help them through a cancer or other medical trauma."

Briefs:

Two recent UCLA Department of Urology studies for prostate cancer patients attracted wide coverage. A study by lead author Dr John Gore, fourth-year urology resident, and Dr Mark S. Litwin, professor of urology and public health, showed that married and partnered men fare better than single men after prostate cancer treatment. The resulting paper, "Partnership Status Influences Quality of Life in Low Income, Uninsured Men with Prostate Cancer," was published online May 23 and in the July 1 print issue of the journal *Cancer*. Drs Gore and Litwin showed that men with prostate cancer who are in a relationship report significantly better psychosocial and physical well-being and fewer disease-specific and general cancer-related adverse effects. Their study reported that partnered men were better able to tolerate symptoms related to their disease and treatment. "Quantity of life with prostate cancer can be extensive, and so we continue to search for factors associated with improved quality of life," explains Dr Gore.

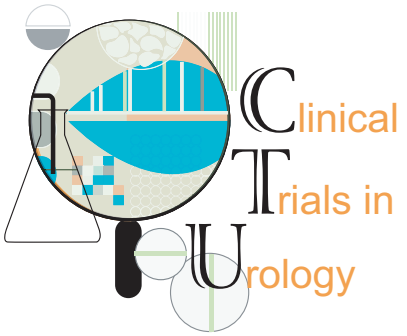
A study led by Dr Allan Pantuck, assistant professor of urology, focusing on the use of pomegranate juice in fighting prostate cancer was presented at the 2005 American Urological Association's annual meeting held in San Antonio, TX. The findings indicate that pomegranate juice may help prevent the recurrence of prostate cancer after surgery or radiation treatment, but further studies must be done since this was the first trial of its kind. "In 48 patients, we found that the treatment was safe, well tolerated and was associated with significant changes in patients' PSA levels," says Dr Pantuck. "We are quite excited about the positive and significant beneficial effects on PSA parameters achieved, which we hope to confirm with further testing."

Kudos:

The UCLA Department of Urology carried the essay competition for the 81st Annual Meeting of the Western Section of the American Urological Association, held July 31 - August 4, 2005 in Vancouver, BC, Canada, where two residents and one faculty member were chosen to collect four awards. For the Miley B. Wesson Resident Essay Competition, fourth-year resident Dr Greg Jack earned the second-prize honor for his work entitled "Processed Lipoaspirate Cells for Tissue Engineering of the Lower Urinary Tract: Implications for the Treatment of Stress Urinary Incontinence and Bladder Reconstruction." Dr John Leppert, also a fourth-year resident, won third prize in the same competition for his essay "Expression of Vascular Endothelial Growth Factor Receptors Predicts Hematogenous and Lymphatic Metastases in Clear Cell Renal Cell Carcinoma." In the Joseph F. McCarthy Physician Essay Contest, Assistant Professor Dr Larissa Rodríguez was selected for both the first- and third- place prizes for the following two essays, respectively: "New Objective Measures to Quantify Stress Urinary Incontinence in a Novel Durable Animal Model of Intrinsic Sphincter Deficiency" and "Long Term Durability of the Distal Urethral Polypropylene Sling (DUPS) Procedure for Stress Urinary Incontinence: Minimum 5-year Follow Up of Surgical Outcome and Satisfaction Determined by Patient Record Questionnaires."

Two members of the laboratory of Dr Robert Reiter, professor of urology, have been awarded grants. Dr Hideyo Miyaki, a postdoctoral fellow, has been awarded a one-year $30,000 seed grant from the Jonsson Cancer Center Foundation for his research on epithelial-mesenchymal transition (EMT) and the effects and clinical impact of N-Cadherin on prostate cancer. In addition, Aram Lee, a medical student, received a Research Training Fellowship for Medical Students from the Howard Hughes Medical Institute (HHMI). This HHMI fellowship supports a year of full-time biomedical research training for medical and dental students by providing a stipend, an allowance and research support.

Dr Larissa Rodríguez received the Fishbein Award from the Interstitial Cystitis Association: Fishbein Family IC Research Foundation & ICA Pilot Research Program. This $30,000, one-year grant was for her proposal "Traditional Chinese Medicine and Acupuncture in the Treatment of IC: Relationship of Outcome to Modulation of the Stress Response System." Interstitial cystitis (IC) is a bladder syndrome characterized by chronic urinary urgency, frequency, and pelvic or bladder pain, and affects more than 500,000 American women.



The Department of Urology is committed to ongoing research in a quest to develop new treatments and cures for all urologic conditions. It is our goal to focus on basic and population-based research with the hopes that we can rapidly translate the findings into clinical trials and community applications. Currently, 14 clinical trials are open for enrollment and available to patients. Below is a list of our newest trials. For additional program information, please contact the Clinical Trials Office at (310) 825-5538.

Kidney Cancer:

A Randomized Double Blind Phase III Study to Evaluate Adjuvant cG250 Treatment Versus Placebo in Patients with Clear Cell RCC and High Risk of Recurrence (PI: Arie Belldegrun, MD/ Co-PI: Robert A. Figlin, MD)

This is a multi-center study to evaluate the efficacy and safety of a new form of therapy called cG250 for the treatment of kidney cancer patients who have a high risk of cancer recurrence after surgery. cG250 is an experimental antibody that selectively targets the CAIX protein that is on the surface of the majority of kidney cancer tumors. This is a form of immunotherapy that will try to stimulate the patient's own immune system to fight his or her cancer. CAIX has previously been shown to be an important protein for kidney cancer. The treatment involves 24 weekly intravenous infusions.

A Phase III, Randomized Study of SU011248 Versus Interferon-a as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma (PI: Robert A. Figlin, MD/Co-PI: Arie Belldegrun, MD)

Prostate Cancer:

A Study to Determine the Effect of Fish Oil in Newly Diagnosed, High-Risk Patients Undergoing Radical Prostatectomy (PI: William Aronson, MD)

Survivor Health-Related Quality of Life and Spouse Satisfaction After Prostate Cancer Therapy (PI: Christopher Saigal, MD/Co-PI: Mark Litwin, MD, MPH)

Chemotherapy Combination for Patients Who Have Stopped Responding to Hormone Treatment (PI: Allan J. Pantuck, MD/Co-PI: Arie Belldegrun, MD)

Vaccine Treatment for Patients with Prostate Cancer Who Stopped Responding to the Hormone and Their Disease Spread to Bones and/or Other Organs (PI: Allan Pantuck. MD/Co-PI: Arie Belldegrun, MD)

High Grade PIN For Patients with High Risk Prostate Tumors (PI: Mark Litwin, MD, MPH)

Bladder Cancer:

Phase III Clinical Trial of Green Tea Extract and Tarceva to Prevent Clinical Bladder Cancer Recurrence in Former Smokers at High Risk (PI: Allan J. Pantuck, MD/Co-PIs: Arie Belldegrun, MD, Robert A. Figlin, MD)

Pelvic Medicine, Incontinence and Reconstructive Surgery:

Evaluation of Family History and Genetic Predisposition for Development of Vaginal Prolapse (PI: Larissa Rodrìguez, MD/Co-PI: Eric Vilain, MD)

Alumni Spotlight

When he was delivering patient care as a UCLA Urology resident, Dr Stephen J. Freedland decided he wanted to learn more about why certain individuals fared much better or much worse than others with the same condition, often defying predictions. "When that happens, you wonder whether it's because there is an important piece of information that we don't understand," Dr Freedland explains.

So Dr Freedland, working with UCLA Department of Urology mentors Drs William Aronson and Arie Belldegrun, began gathering data on patients in an effort to glean new information on variables that correlate with their outcomes. "It started from the standpoint of trying to give patients a better idea of what to expect," Dr Freedland explains. "Then, as we saw patterns emerge suggesting factors related to poor outcomes, we became interested in pursuing the biology that might be contributing to these patterns."

Although he initially saw himself as a basic scientist, Dr Freedland came to realize that outcomes and epidemiology research could provide valuable insight into associations that would otherwise go unnoticed. "You make observations looking at data from thousands of patients, and then you go into the lab and learn why such associations exist," he says. "These are valuable and underutilized tools to help us understand biological mechanisms."

Stephen J. Freedland, MD, joins the faculty at Duke University School of Medicine in November.

Through this type of approach, working with Dr Aronson, Dr Freedland first identified that obese men undergoing radical prostatectomy are at higher risk for later prostate cancer progression than non-obese men. In addition, during his residency he spent a year in the laboratory with Dr Belldegrun, pursuing the fundamental mechanisms underlying more aggressive prostate cancer in general.

After completing his residency in 2003, he began a two-year fellowship in urological oncology at Johns Hopkins University School of Medicine, where Dr Freedland has pursued models for predicting prostate cancer outcomes and has continued to pursue the association between obesity and aggressive prostate cancers. Dr Freedland has been conducting large studies of genes activated within the cancers of obese and non-obese men; his group has identified 132 genes that are significantly different in the cancers of these two patient populations. Dr Freedland hopes that this approach will help determine the genetic culprits causing the more aggressive cancers in the obese men. He and his colleagues are also conducting dietary studies, with the aim of altering activity of these genes in a favorable manner to help slow prostate cancer growth.

With his fellowship coming to an end, Dr Freedland has accepted a faculty position in the Department of Surgery, Division of Urology at Duke University School of Medicine, where he will continue to pursue this line of research. "I'm very excited to be going to a phenomenal institution with world-class collaborators," he says, noting that he will continue to draw on his UCLA Department of Urology training.

Department of Urology Faculty

Jean B. deKernion, MD
Professor and Chairman of Urology
Specialty: Urologic Oncology

William Aronson, MD
Associate Clinical Professor of Urology
Specialty: Urologic Oncology

Arie Belldegrun, MD
Professor of Urology
Specialty: Urologic Oncology, Biologic Therapy

Carol Bennett, MD
Associate Professor of Urology
Specialty: Male Infertility

Bernard M. Churchill, MD
Professor of Urology
Specialty: Pediatric Urology

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

Isla P. Garraway, MD
Visiting Assistant Professor of Urology
Specialty: Urologic Research

Nestor Gonzalez-Cadavid, PhD
Adjunct Professor of Urology
Specialty: Biochemistry, Andrology Research

H. Albin Gritsch, MD
Associate Professor of Urology
Specialty: Renal Transplantation

Christina Jamieson, PhD
Assistant Professor of Urology and Human Genetics
Specialty: Urologic Research

David A. Leff, MD
Assistant Clinical Professor of Urology
Specialty: BPH, Sexual Dysfunction, General Urology

Steven E. Lerman, MD
Assistant Professor of Urology
Specialty: Pediatric Urology

Gerald S. Lipshutz, MD
Assistant Professor in Residence
Specialty: Renal Transplantation

Mark S. Litwin, MD, MPH
Professor of Urology and Public Health
Specialty: Urologic Oncology, Prostate Diseases

James R. Orecklin, MD, MPH
Associate Clinical Professor of Urology
Specialty: BPH, Urinary Stones,General Urology

Allan J. Pantuck, MD
Assistant Professor of Urology
Specialty: Urologic Oncology

Jacob Rajfer, MD
Professor of Urology
Specialty: Male Infertility, Sexual Dysfunction

Shlomo Raz, MD
Professor of Urology
Specialty: Urodynamics, Female Urology

Robert E. Reiter, MD
Professor of Urology
Specialty: Urologic Oncology, Prostate Diseases

Larissa V. Rodríguez, MD
Assistant Professor of Urology
Specialty: Urodynamics, Female Urology

J. Thomas Rosenthal, MD
Professor of Urology
Specialty: Renal Transplantation

Christopher Saigal, MD, MPH
Assistant Professor of Urology
Specialty: Health Services Research

Charles L. Sawyers, MD
Professor of Urology and Medicine
Specialty: Prostate Cancer

Peter G. Schulam, MD, PhD
Associate Professor of Urology
Specialty: Urinary Stones, Endoscopic Procedures

Jennifer S. Singer, MD
Assistant Professor of Urology
Specialty: Renal Transplantation, Pediatric Urology

Robert B. Smith, MD
Professor of Urology
Specialty: Urologic Oncology, General Urologic Surgery

Eric Vilain, MD, PhD
Assistant Professor of Urology,
Human Genetics and Pediatrics,
Director, Laboratory of Female Urology
and Sexual Medicine
Specialty: Sexual and Gender-based Medicine Research

Lily Wu, MD, PhD
Associate Professor of Urology
Specialty: Molecular Biology, Gene Research

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

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