

The new UCSF KURe Scholars group discuss current research.



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The Power of Collaboration

“No man is an island,” according to the saying, and neither are premier academic research centers. As UCSF’s urology program has grown, faculty increasingly reach out to colleagues at other institutions. UCSF leads or participates in many research studies that, performed in collaboration with other centers, increase the numbers of participants and the power of study findings.

These collaborations are proving particularly useful in prostate cancer, providing answers to questions ranging from who is most likely to develop the disease to how aggressively an individual patient should be treated. UCSF collaborations with Northern California Kaiser Permanente are allowing UCSF researchers access to this health system’s incomparable primary care data

collection for projects ranging from urinary tract infections in infants to lower urinary tract symptoms in men with HIV. Other multi-institutional studies are examining the role of chemicals used in plastics that may affect infant genital development and the utility of the common fruit fly as a model for urinary stones. [U](#)

The Power of Collaboration

The Harvard Connection

In the past 10 years, UCSF researchers have regularly collaborated with colleagues at Harvard University, exploring in tandem possible associations between prostate disease and specific behaviors. Investigators have worked with two cohorts in these studies: a subset of the Harvard School of Public,

Health Professionals Follow-up Study (HPFS), for which UCSF epidemiologist June Chan, ScD, who trained at Harvard, still serves as a co-investigator, and the UCSF Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database. These investigations have fostered the careers

of several young faculty members, who have completed portions of their doctoral and postdoctoral work at each institution.

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Letter from the Chair

Peter Carroll, MD, MPH

Over the last decade and a half, I have witnessed the extraordinary growth of the Department of Urology. It has expanded in number of staff, sites of service, and laboratory facilities. Paralleling such growth has been its impact on the core missions of the department – innovative, expert and compassionate care, educating the future leaders in the field and discovery, whether it be the laboratory, the hospital or the field that improves the lives of those with or at risk of suffering from a variety of urological diseases. The Department of Urology has had a very positive impact locally, regionally and internationally as witnessed by its consistent ranking as one of the best Urology programs as assessed by US News and World Report, but also in the amount of grant support it receives from the National Institutes of Health (#5). The latter would be higher as the ranking excluded several major department grants submitted through NCIRE, the research administrator for the San Francisco Veterans Affairs Medical Center.

Given the Department's size and breadth, it is simply not possible to capture all the incredible things being done in a single newsletter so we have to highlight just a few. In this newsletter we highlight the very positive impact of collaboration, the promise and peril of personalized medicine, the impact of robotic technology on urological surgery, and fascinating research methods and findings in such varied fields as genetics, stone disease and childhood development. I also want to highlight the department's emerging role at UCSF's new campus at Mission Bay where the Helen Diller Family Cancer Research Building has become a thriving home for much of the Department's cancer research and where the clinical programs in cancer care and pediatrics will move commensurate with the opening of our new hospital in 2015. This site provides us with much needed and well - designed space and the proximity to many of our research colleagues, both essential to our program's expansion.

I also want to acknowledge the Department's sadness in losing two of its most familiar figures – Frank Hinman, Jr. and Eugene Cattolica. The Hinman family, Frank Hinman Jr. and Sr., had a profound, positive and long – lasting impact on this department. Their vision and leadership shaped, to a very large extent, what we aspire to be. Eugene Cattolica, the Chief of Urology at Kaiser Permanente Hospital in Oakland for many years, trained and mentored countless UCSF graduates, including me. Both will be missed by many.

Lastly, I fully recognize that our achievements as a department are the product of a group of people who share a common passion, energy, and enthusiasm for what we do. I am grateful to the trainees, staff, faculty surgeons, and scientists who allow us to be the best we can be.



Sincerely,

Peter R. Carroll, MD, MPH

Professor and Chair of Urology

Ken and Donna Derr-Chevron Distinguished Professor

Exploring Genetic Differences in Prostate Cancer

Statistical genetic epidemiologist John Witte, PhD, professor of Epidemiology, Biostatistics and Urology, is undertaking exciting research examining the entire genomes of men with advanced prostate cancer. His studies are using next-generation sequencing to look for genomic differences between men's tumor and normal blood cells. These include chromosomal rearrangements, such as deletions, that may reflect the biology underlying a tumor's potential for aggressive growth.

This work has only recently become possible because of the plummeting cost of sequencing genomes. What previously cost millions of dollars and took years to complete, now costs a few thousand and is done in a matter of weeks, said Witte.

Scientists have previously identified many genetic markers associated with prostate cancer development and aggressiveness, but most of these have had limited clinical relevance. In contrast, full-genome sequencing "provides the whole map," said Witte, showing specifically which genes and chromosomal regions are altered in tumor cells.

Witte's laboratory plans to study the full genomes of dozens of men in the next six months. The first five tumor-normal pairs were sequenced from African American men with very advanced

disease, and another 20 are presently underway. African Americans are of particular interest to researchers because they have the highest incidence and mortality of prostate cancer in the world.

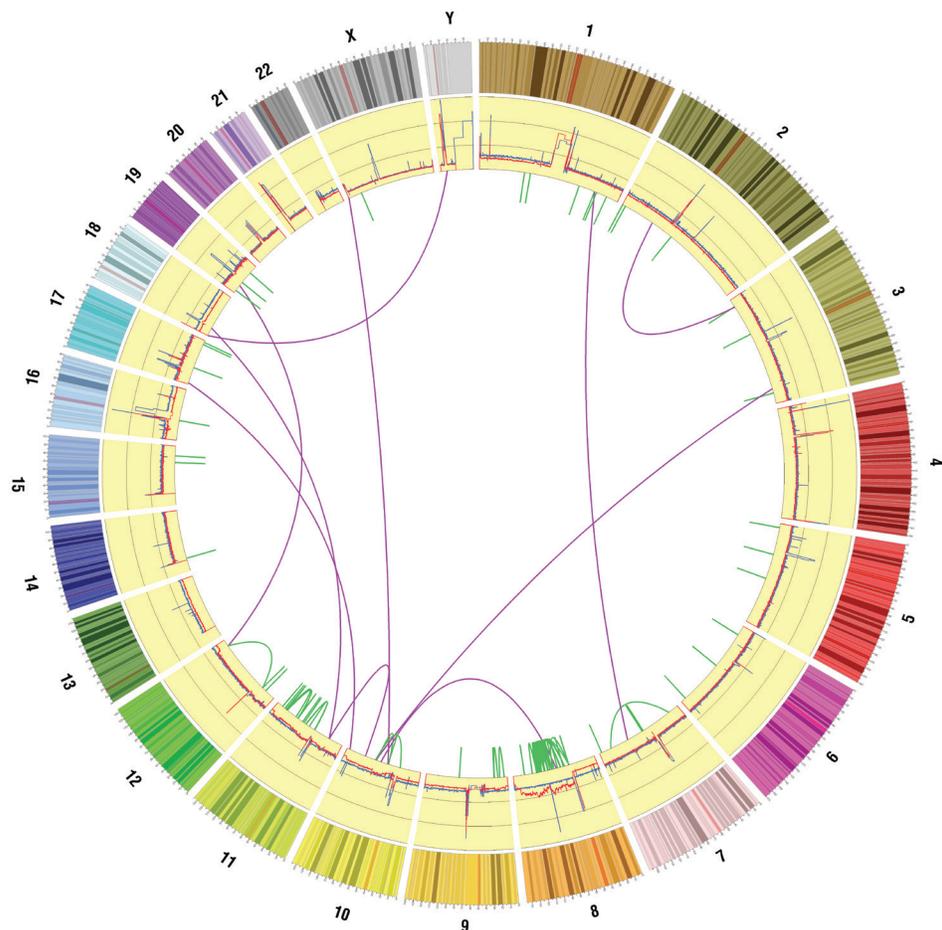
A second set of tumor genomes is being sequenced from men diagnosed with more advanced disease who had very low PSA levels at diagnosis. The sequencing is being undertaken by Complete Genomics, a company located in Silicon Valley, which sends the data to Witte's laboratory for statistical analysis.

"With this work we're moving toward being able to guide treatment decisions based on a man's genetic profile," said Witte. A number of Urology faculty members are collaborating on this project, including Drs. Carroll, Chan, Febbo, Paris, and Simko. [U](#)



John Witte, PhD, MS

Next-generation sequencing results for a metastatic prostate tumor. Chromosomes are arranged sequentially around the circle, and DNA rearrangements are shown with lines inside the circle.





Robotics

The advent of robot-assisted surgery over the past 10 years has been the subject of significant ongoing controversy, particularly in the field of urologic surgery.

In fact, a recent report by the Institute of Medicine on national priorities for future comparative effectiveness research highlighted robot-assisted surgery as among the top 100 areas for future investigation, with specific reference to robot-assisted versus open prostatectomy.

Radical prostatectomy involves removal of the prostate gland and surrounding tissue. It is the most common treatment for prostate cancer and ten years ago, most of these surgeries were performed with an open retropubic approach. But since then, an increasing number of prostatectomies are being performed laparoscopically with robotic assistance. The robot allows the surgeon to sit at a console and direct a camera and two to three laparoscopic arms, performing the operation with high magnification and three-dimensional visualization.

There is no question that robot-assisted prostatectomy is associated with less blood loss, a shorter hospital stay and a slightly more rapid convalescence than the open procedure. Short-term complications appear to be less common with the robot-assisted approach, and in terms of cancer cure, the preponderance of evidence suggests that the two approaches are equivalent. However, the relative impact of robot-assisted versus open surgery on long-term health-related quality of life issues such as urinary and sexual function is less clear. Surgeons and institutions that perform high volumes of robot-assisted prostatectomies report success in maintaining continence and potency that is unequalled in the open surgery literature. On the other hand, reports based on analyses from large administrative data sets and cohorts have been unable to verify these results. In fact, some reports have suggested inferior

outcomes with robotic assistance, though there are significant methodologic limitations associated with these studies.

The skill and experience of the provider and hospital, as well as the technology used, play an important role in patient outcomes. A large body of literature has shown that positive outcomes are correlated with the volume of procedures performed by a surgeon and facility. It is important to consider that there is a learning curve for both open and robot-assisted surgeries, and that outcomes may well relate to mastery of a particular technique.

At this point in time, based on experience at UCSF, it appears that robotic surgery results in equivalent cancer control rates compared to the open technique and may well be associated with a more rapid recovery and improved quality of life in key areas.

UCSF has always been at the forefront of surgical innovation, and has focused on new technologies that add substantial value—not just novelty—to patient care. Our department was one of the early adopters and promoters of laparoscopy in urology, and robot-assisted surgery has played a growing role in our management of urologic malignancies since the early part of the last decade. We now are one of the busiest centers for robot-assisted urologic surgery in Northern California and one of the busiest center for such surgery nationally. All patients managed for prostate cancer at our center complete validated quality-of-life questionnaires before and after treatment, which has allowed us to track our outcomes with a high degree of honesty and rigor. We believe that our outcomes with robot-assisted prostatectomy are better now than they were with the open procedure. Nonetheless, we are continuously seeking to improve our techniques and outcomes. [U](#)

Drs Cooperberg, Carroll, Deng, Greene and Meng in front of the working elements of the daVinci™ Robot. Robotic surgery is used routinely to manage a wide variety of both benign and malignant urologic diseases at UCSF.

UCSF also has a growing program in robot-assisted partial nephrectomy (removal of part of the kidney) to treat kidney cancer and related problems. This is an extension of our experience in laparoscopic partial nephrectomy, which allows for a much faster recovery and substantially less pain than the open approach. The robot allows us to treat lesions whose size and location make them especially challenging, and lets us do so with shorter interruption of blood flow to the kidney than would be possible with standard laparoscopy. We now perform roughly half of our partial nephrectomy procedures with robotic assistance. We also have a growing program in robot-assisted radical cystectomy for bladder cancer. The robot is also being used in reconstructive urology—including procedures such as pyeloplasty for kidney obstruction and sacrocolpopexy for pelvic prolapse.

The Promise and Perils of Targeted Cancer Therapy

At UCSF basic scientists and clinicians work in tandem to apply new knowledge as quickly as possible to the treatment of cancer patients. The process requires a constant back and forth as new ideas or hypotheses are generated, tested, revised, and retested.

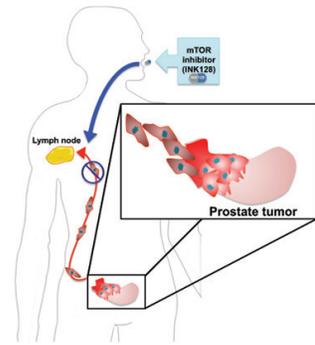
One example is the recent work by UCSF faculty members on a signaling pathway that is active in 90 percent of cancers, including prostate cancer. The work focuses on mammalian target of rapamycin (mTOR), a protein involved in cellular metabolic processes such as protein synthesis regulation and growth control that is activated by a pathway referred to as the PI-3 kinase pathway. Researchers have known for many years that PI-3 kinase was activated by the loss of a tumor suppressor gene or "PTEN" in many prostate cancers. It was only within the last decade that scientists realized how they might deactivate the pathway through its link to mTOR, says newly recruited medical oncologist Phillip Febbo, MD, Director of the Prostate Cancer Research Program of the Helen Diller Family Comprehensive Cancer Center at UCSF. Febbo, then at Harvard, worked with a team of scientists who found that treating mice with an inhibitor of mTOR returned precancerous prostate tissue displaying PI-3 kinase pathway activation to a normal state. This led to clinical trials of rapamycin and similar drugs in men with localized and metastatic prostate cancer. However, the drugs were found to be ineffective.

"We went from enthusiasm in the animal model to disappointment in the clinical trial," said Febbo. Tumor biopsies demonstrated that rapamycin-like drugs could inhibit at least part of mTOR activity, but that partial inhibition did not result in a meaningful clinical response.

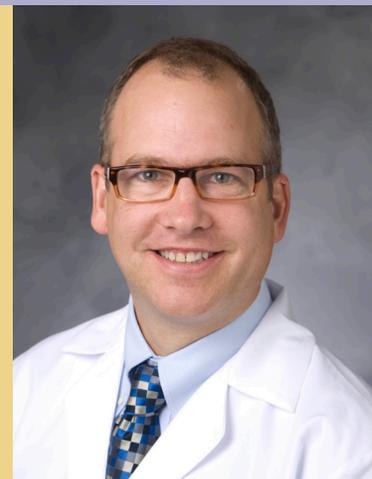
Davide Ruggero, PhD, a basic scientist at UCSF and co-director of the Prostate Cancer Developmental Research Program, set to work to learn why rapamycin and related drugs were not working in prostate cancer. Ruggero's expertise lies in exploring the mechanisms by which genetic mutations lead to cancer. He examines these mutations in mice to determine how they disrupt cells and promote cancer growth. If a finding looks promising in mice and is confirmed in human tissue, his laboratory then identifies and tests compounds that can interfere with whatever mechanism is spurring cancer growth.

When he examined the effect of rapamycin and rapamycin-like drugs in prostate cancer cells, Ruggero and his team found that these drugs do not fully block mTOR activity. In addition, both the Ruggero and Febbo laboratories have found that an oncogene called MYC, which is frequently expressed at high levels in prostate cancer, can limit inhibition of mTOR and prostate cancer's sensitivity to rapamycin.

Working with Kevan Shokat, PhD, chair of cellular and molecular pharmacology at UCSF, Ruggero employed a new compound, known as PP242, which was able to completely block mTOR and abnormal protein synthesis in cancer. This discovery was featured as a cover story in the journal *Cancer Cell* (March 2010). Most recently, the Ruggero lab used this molecule and its clinical analogue, INK128, as well as a new technology to find out how mTOR controls the expression of specific proteins that turn human prostate cancer cells metastatic. The striking results from this research were recently published in *Nature* (Feb. 2012). Ruggero and his colleagues identified the genetic players that instruct or execute decisions



A group of proteins that lead to prostate cancer metastasis can be targeted.



Phillip Febbo, MD



Davide Ruggero, PhD

Remembering Frank Hinman, Jr. 1915 - 2011



A renowned genitourinary surgeon, educator, and illustrator, Frank Hinman, Jr. died on May 22, 2011 in San Francisco, the city of his birth and career.

The son of the first chair of the UCSF Division of Urology, Dr. Hinman completed his undergraduate work at Stanford University and medical school at Johns Hopkins, graduating in 1941. Following a two-year surgical residency in Cincinnati, he served in the Navy with the Seabees during WWII and also on the carrier *Intrepid*. On his return he completed a urology residency at UCSF and joined his father in private practice in 1946. Thus began many decades of interest in urological research and education. In 1951 Hinman was one of eight founders of the Society for Pediatric Urology. He became chief of Urology at San Francisco General Hospital in 1958 and a clinical professor at UCSF in 1962. His research interest in bladder defense mechanisms received 17 years of NIH support and led to better clinical approaches to the treatment of infection. He also described a form of bladder dysfunction known to this day as the "Hinman syndrome". The author of more than 250 scientific articles covering many aspects of urology, Hinman also edited several books, including the *Atlas of Pediatric Urologic Surgery*, the *Atlas of Urologic Surgery*, and *UroSurgical Anatomy*. His many professional honors included the Pediatric Urology Medal of the American Academy of Pediatrics, Barringer Medal of the American Association of Genitourinary Surgeons, Valentine Medal of the New York Academy of Medicine, Distinguished Medical Alumnus Award from Johns Hopkins, and honorary membership to the Gold-Headed Cane Society at UCSF. The American Urological Association honored him with the Hugh Young Award, the Ramon Guiteras Medal, and the William P. Didusch Award for contributions to medical art. Hinman retired from clinical practice in 1985 but continued to be active in teaching and national meetings.

During his lifetime, Hinman was honored with the establishment of the Frank Hinman, Jr., Urological Research Laboratory at UCSF.

Appointments Honors & Awards

Benjamin Breyer, MD, MAS was appointed Assistant Professor of Urology on July 1, 2011. Dr. Breyer completed his residency and clinical fellowship training at UCSF. Dr. Breyer specializes in Trauma and Reconstructive Surgery. His research interests include examining the effect of sexually transmitted infections in the pathogenesis of lower urinary tract symptoms. Dr. Breyer is a scholar on the UCSF KURe - a multidisciplinary career development award sponsored by the National Institutes of Health.

Robert Blleloch, MD, PhD earned the 2011 International Society of Stem Cell Research Outstanding Young Investigator Award for his exceptional achievements as an early-career stem cell researcher. Since joining the Department of Urology in 2006, Dr. Blleloch has distinguished himself as a leader in small RNA and stem cell research as recognized by this internationally recognized achievement.

Maurice Garcia, MD, MAS was awarded a Mentored Scientist Training Award from the National Institutes of Health. Dr. Garcia also earned first place for the American Urologic Association Physician's Essay Contest.

Matthew Cooperberg, MD, MPH was awarded the Prostate Cancer Foundation Young Investigator Award. This highly competitive award is focused on eliminating death and suffering from prostate cancer. Dr. Cooperberg aims to capture prostate cancer treatment trends and analyze comparative effectiveness of treatments during a period of unprecedented change in the treatment field. He will analyze the comparative effectiveness of these treatment in terms of clinical and patient-reported quality of life outcomes, and will further analyze costs of care and other resource utilization.

Stacey A. Kenfield, ScD will be a new Assistant Professor in the Department of Urology. She is an epidemiologist focused on cancer prevention, and in particular, examines modifiable risk factors for prostate cancer development, progression, and death; and quality of life among men living with the disease. She trained at the Harvard School of Public Health.

Tom Lue, MD was named an honorary member to the Chinese Urological Association.

Jack McAninch, MD, FACS, FRCS(Hon) was awarded the Ferdinand C. Valentine Medal by the New York Academy of Medicine for his contributions to the art and science of Urology. Dr. McAninch was also recognized with a Distinguished Career Award by the Societe Internationale d'Urologie.

Laurence Baskin, MD was elected President of the Society of Pediatric Urology. He will receive 2010 AUA Foundation John W. Duckett, MD Pediatric Urology Research Excellence Award.

Meet the new class of Urology Residents 2017

Jonathan Brajtbord, MD; graduate of Mount Sinai School of Medicine of New York University

Helena Chang, MD; graduate of University of Wisconsin School of Medicine and Public Health

Matthew Truesdale, MD; graduate of Columbia University College of Physicians and Surgeons

Meet the class of Urology Residents 2018

David Bayne, MD; graduate of Harvard Medical School

Selma Masic, MD; graduate of Keck School of Medicine, University of Southern California

Samuel Washington, MD; graduate of University of California, San Francisco School of Medicine



June Chan, ScD

The Role of Diet and Lifestyle

Harvard and UCSF researchers Chan, Erin Richman, ScD, Stacey Kenfield, ScD, and Peter Carroll, MD, MPH have worked on several studies examining how lifestyle factors such as diet and smoking tobacco affect prostate cancer incidence, progression and recurrence.

- Researchers examined the effects of diet in approximately 1,300 men from the UCSF CaPSURE study. After two years of follow-up, researchers found that processed or unprocessed red meat, fish or skinless poultry was not associated with prostate cancer recurrence or progression, but consumption of eggs and poultry with skin may increase the risk.
- A study of physical activity in a group of approximately 1,300 men in the CaPSURE cohort found that brisk walking after diagnosis may inhibit or delay prostate cancer progression in men with localized prostate cancer.
- In examining the impact of vegetable and fruit intake on the risk of prostate cancer progression., UCSF investigators found that increased intake of cruciferous vegetables (broccoli, cabbage, etc.) after diagnosis may reduce the risk of prostate cancer progression.
- Smoking at the time of prostate cancer diagnosis was associated with increased overall mortality, including death from cardiovascular disease *and* prostate cancer, as well as prostate cancer recurrence. Men who have stopped smoking for at least 10 years have risks for death from prostate cancer similar to those who have never smoked.
- Chan and a team at UCSF and the Harvard-affiliated Dana-Farber Cancer Institute looked at levels of selenium in the blood of men diagnosed with prostate cancer and found that variations in selenium metabolism and transport-related genes may affect the risk of having aggressive prostate cancer. Prior observational studies, including studies that had measured selenium levels in the body, suggested that selenium might protect against prostate cancer. However, the large, national Selenium and Vitamin E Cancer Prevention Trial (SELECT) reported that supplemental selenium vs. placebo was *not* associated with risk of prostate cancer. Dr. Chan and colleagues from UCSF, the Harvard School of Public Health, and the Dana-Farber Cancer Institute are now collaborating with the Southwestern Oncology Group and investigators from SELECT to examine whether genetics might modify the effects of supplemental selenium and vitamin E on the risk of developing prostate cancer. [U](#)

Prostate Cancer - Collaborative Studies Expand Our Knowledge

Pooling information gathered in large, observational studies helps scientists tease out the secrets of prostate cancer. Which ethnic groups are most susceptible and why? Which tumors are more likely to progress? Who can be safely managed with active surveillance? What roles do lifestyle and diet play in prostate cancer? Only by looking at large numbers of men can investigators provide definitive answers to these questions. UCSF is a recognized leader in such efforts and has productively partnered with others.

“As our departmental resources have become richer data sources, we are having more opportunities for collaborative work,” says UCSF urologic cancer specialist Matt Cooperberg, MD, MPH. Some of these efforts are highlighted below.

The UCSF Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) constitutes one of the nation’s largest databases on prostate cancer. Since it began in 1995 under principal investigator Peter Carroll, MD, MPH, this longitudinal, observational study of 14,000 men with all stages of biopsy-proven prostate cancer has enrolled patients at 40 community urology practices, academic medical centers, and VA hospitals throughout the United States. CaPSURE research findings have expanded knowledge of prostate cancer risk prediction, diagnostic trends, treatment patterns, outcomes and quality of life. Investigators have published more than 125 articles in peer-reviewed journals and presented over 200 papers at professional conferences. Residents, medical students and fellows have authored many of the publications under the direction of senior investigators. The experience gained by these junior investigators has helped to shape and accomplish career goals.

Physicians participating in CaPSURE provide clinical data on patients who have consented to be in the study, including methods of screening, PSA values at diagnosis and at every patient visit, diagnostic and pathologic Gleason grade and stage, surgical pathology, and information on all treatments the patient undergoes. Patients contribute data before and at regular intervals after treatment, including information on urinary, bowel, and sexual function, general health, other conditions and medications, any lifestyle modifications they have made after diagnosis or treatment of prostate cancer, and their satisfaction with medical care.

The Prostate Active Surveillance Study (PASS) is designed to identify and validate biomarkers that predict aggressive prostate cancer so that men can be safely followed through active surveillance. Peter Carroll, MD, serves as principal investigator for UCSF, with funding from the Canary Foundation. PASS includes nine academic medical centers, with UCSF and the University of Washington serving as lead sites. The study is unique in that serum, urine and tissue are prospectively banked for analysis. UCSF has received funding from the Department of Defense to use these samples to identify and validate biomarkers that predict aggressive prostate cancer. These biomarkers will help refine the decision process for men who choose active surveillance in lieu of standard surgery or radiation.

The Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) study group includes a number of academic centers and focuses on comparing the effectiveness of surgery and radiation for localized prostate cancer. Funding is provided by the federal Agency for Healthcare Research and Quality (AHRQ). The



Matthew Cooperberg, MD, MPH



Hillary Copp, MD



Benjamin Breyer, MD, MAS



Stephen Van Den Eden, PhD

The Power of Collaboration

Kaiser Collaborations

As an academic medical center, UCSF specializes in the care of complex medical conditions, many of them uncommon. To look at urological health in a more general population, UCSF researchers have worked with Kaiser Permanente epidemiologist and professor of Urology Stephen Van Den Eden, PhD, to evaluate data collected by this large health maintenance organization. Analyses have recently provided insight into two common health problems.

Urinary tract dilation, which may indicate an obstruction of the flow of urine from the kidneys to the bladder, appears on prenatal ultrasounds in from 1.5 to 8% of fetuses, and may persist in about 1 in 200 births. The condition often resolves on its own, and watchful waiting is usually recommended rather than immediate surgery.

In some cases, physicians prescribe antibiotic prophylaxis during this waiting period to prevent urinary tract infections (UTIs). Studies have suggested that there is a similar infection rate whether or not a child is receiving antibiotics (ranging from 0-36%) and there is also evidence that resistant infections are more common in children on antibiotic prophylaxis.

The Prenatally-detected Urinary Tract Dilation (PNUT) study, which UCSF urologist Hillary Copp, MD, MS, developed in collaboration with Van Den Eden, will look at the risks and benefits of antibiotic use in these children. It will analyze information in a mother and child electronic medical record database from the Northern California Kaiser Permanente Medical Care Program. With 30,000 births each year in the study group, an average of 300 patients with urinary tract dilation should be diagnosed annually. The study will provide clues as to which children are more likely to develop UTIs, whether antibiotic prophylaxis is helpful, and whether it is associated with treatment-

resistant bacterial strains. Dr. Copp has organized this study as a scholar in the K12 Urologic Research (KURe) Career Development Program, which provides mentoring and research funding to young scientists investigating benign urologic diseases.

Lower urinary tract symptoms (LUTS), such as having to urinate frequently or urgently, become more common with age, and can negatively impact a person's quality of life. LUTS has been associated with depression, falls and fractures, and increased mortality. Billions of dollars are spent annually in the United States to treat the condition.

UCSF urologist and KURe scholar Benjamin N. Breyer, MD, MAS, is exploring the association between LUTS and human immunodeficiency virus (HIV), a virus carried by more than 1 million Americans. Breyer conducted the first population-based study examining the association of HIV/AIDS and LUTS in men who have sex with men. His study included over 3,000 men who were reached by using novel social media techniques.

Breyer is now teaming with Van Den Eden to examine HIV/AIDS and LUTS in men enrolled in Kaiser Permanente, California. Preliminary results from over 50,000 participants show that after adjusting for age, race/ethnicity, diabetes, smoking, and hypertension, being HIV-positive nearly doubled the odds that a man would report LUTS. How HIV might increase the risk of LUTS is not clear. It may be that the virus directly affects the central or peripheral nervous system, or that symptoms arise from side effects of HIV treatment, opportunistic infections, or inflammation. By exploring disease epidemiology, the researchers aim to improve providers' awareness and treatment of this important quality of life issue. [U](#)

The Power of Collaboration

Study Examines Impact of Phthalates on Infant Genital Development

Phthalates, chemicals that soften plastics, are widely used in food packaging, medical devices and personal care products. Scientists are concerned that phthalates may pose a health risk because they can disrupt the function of androgen and other sex hormones and have been linked to urogenital abnormalities in animal studies.

UCSF is collaborating with four other sites on a National Institutes of Health-funded study to determine whether phthalates affect urogenital development in human infants. The Infant Development and Environmental Study (TIDES) will attempt to correlate maternal phthalate levels with the development of reproductive organs in infant boys and girls. The study will follow participating women through three trimesters of pregnancy and record information about the urogenital development of their newborns shortly after birth, says Sarah Janssen, MD, PhD, MPH, director of TIDES at UCSF. Janssen holds academic appointments in Urology and Occupational and Environmental Medicine at UCSF. She and UCSF Pediatric Urology Chief Laurence Baskin, MD, are working closely on this study.

Approximately 1,200 infants will be included in TIDES, once data are gathered from UCSF and the other study sites: the University of Rochester

School of Medicine, New York; Seattle Children's Hospital and University of Washington School of Medicine; and the University of Minnesota. The study is being coordinated through the Mt. Sinai School of Medicine under principal investigator Shanna Swan, PhD. Recruitment at UCSF ended in August and enrolled infants will be followed for one year.

As part of the study, researchers hope to establish a simple, reliable method of measuring anogenital distance (AGD) and determine the average length of this measurement in male and female infants. AGD is a standard measure used in toxicology to detect anti-androgen activity. In animal studies, the male AGD is twice the length of the female AGD, said Janssen, but the average length for human males and females has never been established. Rat models show that AGD is shorter in the male offspring of pregnant animals exposed to bis(2-ethylhexyl) phthalate (DEHP) and dibutyl phthalate (DBP), the two phthalates that will be measured in this study. [U](#)



Laurence Baskin, MD



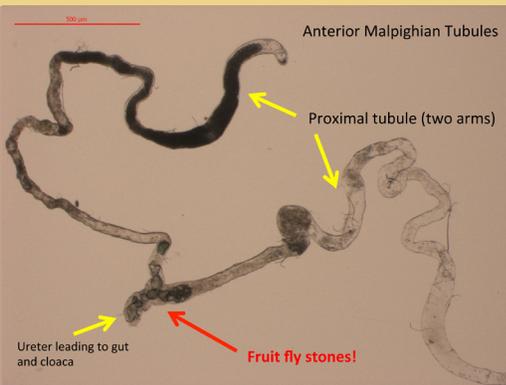
Sarah Janssen, MD, PhD, MPH



Marshall Stoller, MD



Tom Chi, MD



Dissected tubules contain stones.

The Power of Collaboration

Buck Institute and UCSF Collaborate on Animal Model for Kidney Stones

Kidney stones are a significant source of morbidity in the United States and mortality in the developing world. They affect up to 12% of Americans, almost half of whom will require surgery for treatment. To improve understanding of the underlying mechanisms of stone formation, scientists have sought an animal model that would allow them to explore how stones form and how they can best be prevented or treated medically. In collaboration with researchers at the Buck Foundation, UCSF urologist Marshall Stoller, MD, is demonstrating that the common fruit fly, *Drosophila melanogaster*, is a novel and promising model for stone disease.

Stoller is an internationally recognized expert in the field of kidney stones and has had a longstanding interest in understanding mechanisms of stone formation. He demonstrated that in humans, kidney stones may originate from Randall plaques, areas of early calcification in the kidney.

Stoller became intrigued with the possibility of using the fruit fly as an animal model for stone disease. Scientists had observed that fruit flies form something that resembles stones in their Malpighian tubules, the fly equivalent of the human kidney. The fruit fly has been used to study many other disease processes, and its genome is well documented. Flies can be genetically bred to increase or decrease stone formation, and their short lifespan of 30-45 days lets scientists observe the entire disease course.

In searching for an expert in *Drosophila* research, Stoller was introduced to Pankaj Kapahi, PhD, of the Buck

Institute for Research on Aging.

Kapahi's laboratory has focused on the effect of nutrients on the aging process. He discovered that flies fed with low-protein diets can live up to 40% longer than flies on a high-protein diet. His laboratory was also the first to show that the conserved nutrient-sensing target of rapamycin (TOR) pathway mediates the effects of dietary restriction within cells.

Under Dr. Stoller's mentorship, UCSF urology residents Thomas Chi, MD, and Lawrence Flechner, MD, in conjunction with Dr. Kapahi and Arnold Kahn, PhD, from the Buck Institute, demonstrated that in the fly, protein-rich diets worsen stone formation and shorten lifespan. Analysis of the fly stones showed them to be very similar to human stones.

These findings have sparked continued interest both at the Buck Institute and UCSF in establishing *Drosophila* as an animal model that may yield new insights into the mechanisms of stone formation.

"The combination of basic science and *Drosophila* research at the Buck Institute and clinical expertise in kidney stone disease at UCSF has provided a broad range of perspectives for the development of this project," said Stoller. "Our goal is to use this model to discover new ways for medically managing and even preventing kidney stones." [U](#)

Translational Medicine...

CONTINUED FROM PAGE 5

made by mTOR, and they discovered how mTOR deregulates one of the last stages of gene expression—when ribosomes translate genes into proteins.

The research team used a method called ribosome profiling, which allows researchers to collect millions of ribosomes from inside cells and determine which genes they are turning into proteins. In their research, Ruggero found that mTOR increases the production of specific proteins that make prostate cancer cells become metastatic. Importantly, Ruggero and his colleagues showed that a mouse model of human prostate cancer treated with INK128 did not metastasize. They also showed

that INK128 has a strong therapeutic effect on human prostate cancer cells as well as on metastatic cells derived from ovarian, breast and kidney tumors. Thus, the results from these experiments are widely applicable to many cancers.

The Ruggero lab also found that INK128 is more effective than other mTOR inhibitors, such as rapamycin, in restraining abnormal protein synthesis driven by mTOR. Deregulations in protein synthesis are a hallmark of cancer, and therefore targeting the aberrant protein synthesis apparatus in many cancers is an exciting new avenue for therapeutic intervention. The INK128 compound is

currently being tested in Phase I/Phase II clinical trials, where it appears to be well tolerated, and will likely be further tested in men with metastatic prostate cancer, said Ruggero.

The combined work of Drs. Febbo, Shokat and Ruggero represents an important “learning loop,” where data are brought from the laboratory to the clinic and back to the laboratory. This integration of laboratory and clinical efforts is only possible within a multidisciplinary program such as the UCSF Prostate Cancer Developmental Research Program—one that includes clinical, translational, and basic investigators. [U](#)

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Prostate Cancer...

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study is designed to measure a variety of outcomes, including cancer control, costs and the side effects of treatment. Such information will be critical to a deeper understanding of which prostate cancer treatments may be most appropriate for certain patients. David F. Penson, MD, MPH, at Vanderbilt is principal investigator for this study, and participating centers include Cancer Institute of New Jersey, Emory University, Louisiana State University Health Sciences Center, New Orleans, University of California Irvine, University

of Southern California and MD Anderson Cancer Center, in addition to UCSF.

In a study group similar to CEASAR, UCSF investigators have partnered with a consortium of academic centers led by Martin Sanda, MD, at Dana Farber/Harvard (Beth Israel Deaconess Medical Center), to look at the comparative effectiveness of robotic v. open surgery for prostate cancer. Robotic surgery is an expensive technology that has been heavily marketed and widely adopted in the last decade. As many as 80% of

prostatectomies are performed with robotic assistance, but high-quality prospective multicenter studies have not been conducted to date. Indeed the Institute of Medicine has listed open v. robotic prostate surgery as a top priority for comparative effectiveness research. This study seeks to provide data on many outcomes, including urinary continence and sexual function following open and robotic surgery. [U](#)

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