



RESEARCHERS IDENTIFY "MISSING LINK" CONNECTING INFLAMMATION AND CANCER

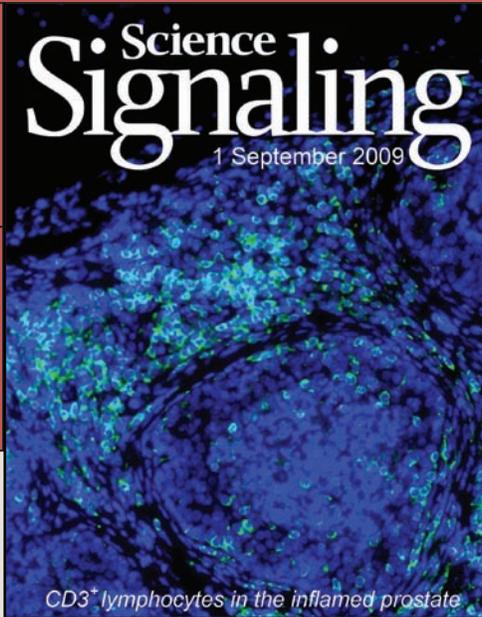


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Science
Signaling
1 September 2009



CD3⁺ lymphocytes in the inflamed prostate

Clinicians and scientists have recognized the association of chronic inflammation and development of cancer for over a century. More recently, chronic inflammation in the prostate has been identified as the likely etiologic mechanism for human prostate cancer and there is considerable interest in understanding the source of inflammation and the potential for interventions to prevent tumor development.

Inflammation is known to stimulate proliferation of epithelial cells and it is this expansion of growing cells that is thought to set the stage for mutation and malignant transformation. However, it has never been clear how inflammation induces epithelial proliferation. Dr. Travis Jerde, a postdoctoral fellow in Dr. Bushman's laboratory, has found one important link. He showed

that interleukins, inflammatory cytokines associated with conditions such as chronic inflammation in the adult human prostate, are important growth regulators during normal development. When inflammation occurs in the adult prostate, it elicits the expression of interleukins from the prostate tissue and from leukocytes that populate the inflammatory lesions. These interleukins reactivate developmental growth pathways and trigger epithelial proliferation. The work was published in the September issue of the prestigious journal *Science Signaling* and featured as the journal's cover story.

In commenting on the work the editor wrote: "Both embryonic development and response to inflammation and injury are characterized by the proliferation of epithelial and progenitor cells and remodeling of the tissue stroma. Moreover, signaling pathways involved in development are reactivated during wound healing. Jerde and Bushman investigated the reverse scenario and found that the inflammatory cytokine interleukin-1 (IL-1) stimulated epithelial cell growth in the developing prostate. Their data suggest that IL-1 family cytokines produced by epithelial cells act on stromal cells to stimulate insulin-like growth factor production, which in turn acts on epithelial cells to stimulate their proliferation. Noting that both inflammation and reactivation of developmental signaling pathways are associated with adenocarcinomas—another condition associated with epithelial and progenitor cell proliferation and stromal remodeling—the authors speculate that inflammatory mediators may play a conservative role in promoting epithelial proliferation in all of these conditions."

The work was supported by the NIDDK and the Robert and Dolores Schnoes Chair in Urologic Research. **WU**

>> A MESSAGE FROM THE CHAIR



STEPHEN Y. NAKADA, MD

As our nation's health care system evolves, we are faced with numerous challenges. The delivery of care and services will be scrutinized at every level. Here at UW, we are very fortunate to still be patient-focused; this is true from both a clinical and academic standpoint. This approach will keep us rock solid in the coming years.

I am delighted to announce two new faculty arrivals, Dr. Tracy Downs and Dr. Jason Abel. Dr. Downs joined our faculty in early April from the University of California, San Diego. Dr. Downs trained at Harvard and completed a urologic oncology fellowship at the University of California, San Francisco. He brings great expertise in urologic oncology, bladder cancer, and robotic procedures. Dr. Abel will join us in July. Dr. Abel trained at the University of Utah and completed his urologic oncology fellowship at M.D. Anderson Cancer Center. His interests are in all aspects of cancer and his expertise will deepen the breadth of our oncologic services, specifically kidney and prostate cancer. We welcome both outstanding surgeons to Madison!

Our department has an invigorating educational program in store this year. The 2010 Schnoes lecturer is Dr. Robert Flanigan of Loyola University. In October, Dr. William Steers from Virginia will be our 2010 Uehling Lecturer.

This year our entire team is deserving of many kudos but a few accomplishments merit highlighting. Dr. Bruce Slaughenhoupt will be

promoted to Associate Professor at the start of the 2010-2011 academic year in July. Bruce has been a wonderful addition to our faculty and I am very pleased about his promotion. Also worthy of note, the residency program received full accreditation this year! Congratulations to Dr. John Kryger, Nancy Hawkins, and all of our residents. John is also to be congratulated on becoming this year's President of the Wisconsin Urological Society, which will hold its spring meeting at the Fluno Center in Madison.

As always, we hope to see you all at the AUA meeting and, more specifically, at the Annual Wisconsin Alumni Reception. Have a wonderful spring and see you soon! **WU**

STEPHEN Y. NAKADA, MD
CHAIRMAN AND THE UEHLING
PROFESSOR OF UROLOGY

>> UPCOMING UW UROLOGY EVENTS TRICIA MAIER

• DEPARTMENT PICNIC

The Department of Urology will hold its annual Summer Picnic on Sunday, June 13, 2010 from 1:00-4:00 PM at Warner Park.

• SAVE THE DATE!

Please mark your calendars for these yearly events!

2010 Robert F. Schnoes Lecture Series
June 17, 2010



ROBERT C. FLANIGAN, MD

The department will hold its annual Robert F. Schnoes Lecture Series this June at UW Health Sciences Learning Center. We have invited Robert C. Flanigan, MD from Loyola University Medical Center. Dr. Flanigan is Professor and Chairperson of the Department of Urology, and the first Albert J. Speh, Jr. and Claire R.

Speh Professor of Urology at Loyola. Dr. Flanigan is a renowned expert in urologic oncology, renal transplantation, and urologic reconstructive surgery. His research interests include renal, prostate, and bladder cancer including clinical trials in urologic oncology and chemoprevention. Dr. Flanigan is currently Secretary of the American Urological Association. He has also served as President of the American Board of Urology, the Society of Urologic Oncology, and the North Central Section of the AUA.

2010 Uehling Lecture
October 29, 2010



WILLIAM D. STEERS, MD

The 2010 Uehling Lecture will take place Friday, October 29, 2010 at the Fluno Center in Madison. We have invited

Williams D. Steers, MD, Hovey Dabney Professor of Urology and Chair of the Department of Urology at the University of Virginia School of Medicine to be our 2010 Uehling Lecturer. Dr. Steers' clinical interests include voiding and sexual dysfunction, prostate disease, and robotic surgery. Program information will be forthcoming in the summer issue of *Wisconsin Urology*.

Future Uehling Lectures:

2011 Uehling Lecture

Eric A. Klein, MD from Cleveland Clinic Lerner College of Medicine is our 2011 Uehling Lecturer. Dr. Klein is Professor and Chairman of the Glickman Urological and Kidney Institute and Head of the Section of Urologic Oncology in the Department of Urology at Cleveland Clinic. Dr. Klein's clinical interests cover all aspects of urologic oncology including cancers of the prostate, bladder, testes, and kidney. Dr. Klein is also the editor of the journal *Urology*. **WU**

NEW CLINICAL INITIATIVES: Developments in Stone Prevention

KRISTINA PENNISTON, PHD, RD - ASSISTANT SCIENTIST



Surgical modalities for the removal of urinary tract stones are constantly developing, and our urologic surgeons are experts at the most effective and minimally-invasive techniques.

As the recurrence rate for renal stones is quite high, we are committed to identifying and applying evidence-based strategies to prevent stones. We know that urolithiasis can be a debilitating disease with multiple physical, emotional, and

Through our epidemiologic and observational studies, we have:

- Found that gastric band placement for obesity is a safer procedure than gastric bypass (also known as the Roux-En-Y Bypass) with respect to its risk for kidney stones
- Identified that topiramate, a medication commonly prescribed for migraine headaches, increases urinary stone risk
- Identified specific characteristics in patients' diets that contribute to stone risk

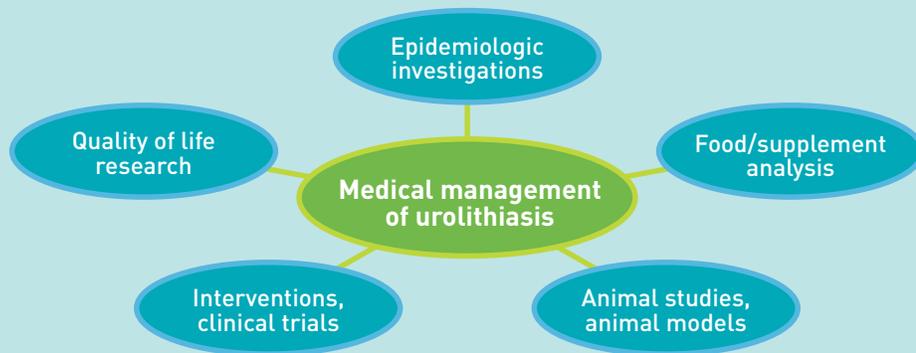
Through interventions and clinical studies, we have:

- Confirmed that specific dietary changes can reduce urinary oxalate excretion and calcium oxalate supersaturation
- Documented that beverages rich in citric acid can help reduce risk for stones by increasing urinary citrate excretion and urine volume
- Found that vitamin D repletion does not increase urinary calcium excretion in healthy post-menopausal women
- Identified key barriers to patients' compliance with medical management

Through our quality of life research, we have:

- Documented the consequences of kidney stones on patients' health-related quality of life and identified symptoms and issues specific and of most importance to kidney stone formers
- Confirmed that patients have favorable attitudes toward medical management of stone disease

In research currently underway or planned, we are evaluating the effect of over-the-counter dietary supplements on urinary oxalate excretion, examining the safety of vitamin D repletion or supplementation in individuals with calcium stone disease, comparing the effectiveness of dietary changes on the risk for stone disease, testing whether certain nutrition or pharmacologic strategies can ameliorate the effects of topiramate on stone risk, and developing a disease-specific instrument to measure the health-related quality of life of patients with recurrent kidney stones. **WU**



social consequences for patients. We know that patients want prevention. We have developed a multi-faceted research program (see diagram) and have garnered funding from multiple sources, including the American Urological Association Foundation, the UW Medical School Research Committee, the Department of Surgery, UW Health, UW Hospital and Clinics, and the Department of Urology. We have built collaborations with various researchers in and outside of the UW-Madison, including Wake Forest University School of Medicine, the UW-Madison Swine Research and Teaching Center, and with epidemiologists of the Marshfield Epidemiologic Study Area at Marshfield Clinic.

- Found evidence of increased kidney stones incidence in women in a defined area of northern Wisconsin

Through food/supplement analysis, we have:

- Identified commonly used over-the-counter dietary supplements with high oxalate concentrations
- Assessed the citric acid content of various commercially-available fruit juice products

In our animal research, we have:

- Conducted preliminary studies toward development of a porcine model for calcium oxalate urolithiasis

>> UW UROLOGY AT THE AUA

TRICIA MAIER

• Annual Alumni Reception

The Wisconsin Alumni Reception will take place on Sunday, May 30, 2010 from 5:00-7:00 PM. The reception will be held in Union Square 13 at the San Francisco Hilton. Be sure to join us for this annual event. We enjoy seeing and catching up with everyone! Please call Nancy Hawkins at (608) 263-1358 for further details.

• UW Faculty at the AUA

Dr. Stephen Nakada is Course Director for "Urolithiasis: Surgical Management: Percutaneous, Shock Wave Lithotripsy and Uteroscopy." This course offers the practicing urologist a comprehensive, case-based review of the surgical management of urolithiasis and will pay special attention to the prevention of complications.

Dr. Nakada's course will take place on Tuesday, June 1, 2010 from 6:00-8:00 AM.

Dr. Reginald Bruskwitz will participate as a speaker in the course "AUA BPH/LUTS Clinical Guidelines" on Tuesday, June 1, 2010 from 1:00-3:00 PM. This course will provide a systematic review and synthesis on the clinical literature of current and emerging therapies for the treatment of BPH.

Dr. Stephen Nakada will give a lecture on the topic of ureteroscopy to the Confederacion Americana de Urologia (CAU), the Spanish specialty society of the American Urological Association, on Saturday, May 29, 2010.

Dr. Stephen Nakada has again been asked to host a table at Lunch with the Experts, speaking on endourology and laparoscopy on Sunday, May 30, 2010. These sessions allow attendees to ask questions and gain new perspectives in an invigorating and informal setting with some of the best-known leaders in the urological community.

Dr. Stephen Nakada is moderating the Panel Discussion, "Who Determines Competence for Robotic Surgery? Industry or Residency Programs?" at The Society of Urology Chairpersons and Program Directors (SUCPD) meeting on Friday, May 28, 2010.

Dr. David Jarrard is the co-organizer of the 2010 Joint Society of Urologic Oncology/Society of Basic Research meeting to be held in conjunction with the AUA this year.

Dr. Sean Hedican and **Dr. Stephen Nakada** will co-chair the 25th Annual Engineering and Urology Society meeting at the upcoming AUA.

• AUA Abstract Podium and Poster Presentations

This year UW Urology faculty, staff and residents have 10 accepted abstracts for either podium or poster presentation. The abstract titles and authors are listed below:

Educating oncologists about male infertility increases sperm cryopreservation rates prior to cancer treatment. Lauren Wagner, Charles Bormann, Sana Salih, Dan Lebovic, Julianne Zweifel and Daniel Williams, IV.

Rising prevalence and incidence of urolithiasis among women in Northern Wisconsin. Ian McLaren, Kristina Penniston and Stephen Nakada.

Differences in the reported oxalate content of foods: Implications for designing research studies and for counseling calcium oxalate stone formers. Kristina Penniston and Stephen Nakada.

Differences in pediatric urinary metabolite concentrations based on age and gender. Bruce Slaughenhaupt, Sharon Bartosh, John Asplin and Charles Durkee.

Superoxide Dismutase 1 knockdown induces oxidative stress and loss of DNA methylation in the prostate. Sachin Bhusari, Joe Dobosy, Vivian Fu, Nima Almassi, Terry Oberley and David Jarrard.

Senescence as cytostatic therapy: Drug-induced senescence in prostate cancer cells requires Skp2-regulated p27Kip1 expression. Jonathan Ewald, Josh Desotelle, F. Michael Hoffmann and David Jarrard.

Defining the field defect associated with prostate cancer development using unbiased methylation profiling. Bing Yang, Jessica Kueck, Sachin Bhusari, Wei Huang and David Jarrard.

Bone morphogenetic protein (BMP) signaling sustains phosphatase homologue of tensin analogue (PTEN) protein expression in the prostate epithelial cell lines. Travis Jerde, Zhong Wu, Daniel Theodorescu and Wade Bushman.

Insulin-like growth factor-1 signaling drives acute inflammatory reactive hyperplasia in the mouse prostate. Travis Jerde, Eliza McFarland and Wade Bushman.

IFG-signaling mediates growth effects of both androgen and inflammatory signaling during prostate development, castration-regrowth, and hyperplasia. Christopher Loftus, Wade Bushman, Adam Kaye and Travis Jerde. **WU**

>> NOTABLE AND NEWSWORTHY

• Kudos to **Bruce Slaughenhaupt, MD**, for being promoted to Associate Professor, effective July 1, 2010!

• **Dr. Kristina Penniston** received funding from the UW-Madison Women in Science & Engineering Leadership Institute (WISELI) for her study "SPARKS: Strategies to Prevent and Reduce Kidney Stones."

• The 2nd edition of "Essential Urologic Laparoscopy: The Complete Clinical Guide" co-edited by **Dr. Sean Hedican** and **Dr. Stephen Nakada** has recently been published.

• **Dr. David Jarrard** has been elected to serve a two-year term on the American Urological Association Education Council.

• Congratulations to **Walt Hopkins, PhD**, who will be receiving an NIH grant to study the role of specific E. coli virulence factors in the etiology of chronic prostatitis.

• **Dr. Wade Bushman** has been appointed to the AUA International Academic Fellowship Committee.

• **Dr. Daniel Williams** has been named Editor of the *Society for Male Reproduction and Urology (SMRU) Newsletter*.

• **Dr. Bruce Slaughenhaupt** was selected for a Surgical Education Research Fellowship sponsored by the American College of Surgeons. This is a 1 to 2 year fellowship designed to help foster academic research concerning surgical education.

• **Dale Bjorling, DVM, MS**, has been invited to join the Editorial Review Board of *Frontiers in Autonomic Neuroscience*, a specialty section of *Frontiers in Neurology*.

• **Dr. David Jarrard** received funding from the Department of Defense for a grant titled "Epigenetic Alterations Associated with CCCTC-binding factor Deregulation in Prostate Cancer."

• Congrats to **Dr. Wade Bushman** who received a supplemental grant from the NIH for his Shi-Gli Pathway research. **WU**

>> CLINICAL TRIALS IN WISCONSIN



KATHLEEN ZAREMBA
RESEARCH PROGRAM MANAGER

Research Updates

The University of Wisconsin-Madison Institute for Clinical Translational Research (ICTR) was established in the fall of 2007 to connect and guide researchers from multiple academic units including Medicine and Public Health, Nursing, Pharmacy, Veterinary Medicine, the College of Engineering and the Marshfield Clinic Research Foundation. The overall goal of ICTR is to facilitate the translation of basic laboratory research forward through clinical trials and into community health care practices.

Through the ICTR initiative, Drs. Stephen Nakada and David Jarrard in the Department of Urology have established collaborative research relationships with the Marshfield Clinic Research Foundation. The Marshfield Epidemiologic Study Area (MESA) health care system includes 23 mostly rural regional primary care centers over an area of 24 postal codes across central and northern Wisconsin. The regional health centers have been collecting detailed health care records for greater than 86,000 residents for more than 30 years. The creation of this database was made possible through the participation of over 60% of the residents from this Wisconsin population. Two Department of Urology collaborative research studies are currently underway to examine health information collected from the MESA database.

Dr. Nakada, principal investigator for the research team, Dr. Kristina Penniston and medical student Ian McLaren are conducting an epidemiological study in collaboration with Dr. Robert Greenlee, MESA Database Lead Scientist. The initial study will examine the changes in incidence and prevalence of kidney stones in the MESA population for the past 20 years and the trends over time in this Wisconsin population. Future research with this database information will be conducted to study kidney stone disease in association with other medical conditions.

Dr. Jarrard has been studying the outcomes of radical prostatectomy and radiation treatment regimens and watchful waiting follow-up for prostate cancer patients who have received their care at the University of Wisconsin Urology, Oncology and Radiation Clinics. Outcomes are compared between patients receiving the different treatment regimens based on clinical presentation, pathological staging, questionnaires in follow-up clinic and American Urological Association (AUA) symptoms scores. Dr. Jarrard is collaborating with Deanna Cross, PhD, Project Scientist at the Marshfield Clinic Research Foundation to examine the prostate cancer outcomes from the patient population included in the MESA database. Andrew Livermore, a Shapiro Summer Research Program medical student, will be working with Dr. Jarrard on this project.

Upcoming Clinical Research Studies

Dr. Tracy Downs is preparing to initiate a clinical phase II optical coherence tomography (OCT) device study through the UW Department of Urology in collaboration with principal investigator Dr. Seth P. Lerner, MD, of Baylor College of Medicine, and co-investigators at Cleveland Clinic.

Previous studies have demonstrated that OCT is able to distinguish normal and abnormal bladder tissue. The primary objective for this study will be to assess the accuracy and positive predictive value for the Niris fiber optic light-based OCT imaging device for diagnosing and staging bladder tumors during the cystoscopic procedure, as compared to histopathic stage and grade evaluation.

Dr. Daniel Williams will be participating in a Reproductive Medicine Network NICHD multi-center randomized clinical trial to examine the outcome of microsurgical varicocelectomy procedures in infertile couples in which the male partner has a palpable varicocele and an abnormal semen analysis. The study will measure the change in the live birth rate in infertile couples in which the male has undergone the microsurgical procedure compared to those who have not undergone the procedure. Dr. Williams will be collaborating with researchers from the University of Michigan, the University of Colorado, the University of Pennsylvania, Yale University, and Vanderbilt University on this study. **WU**

>> PROGRAM NEWS

2010 RESIDENCY MATCH RESULTS

JOHN McGETRICK, MD
University of Chicago

INGE TAMM-DANIELS, MD
University of Alabama

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