



# Duke Prostate Center News

Clinical and research updates from one of the nation's leading prostate cancer centers

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## From the lab to the clinic

Translational research at the Duke Prostate Center

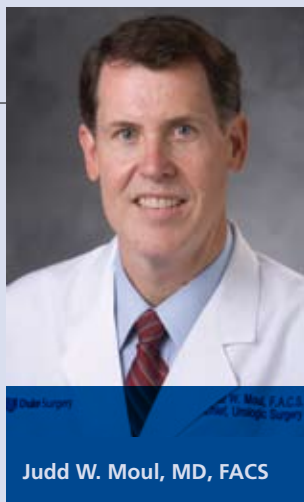
**T**ranslational research at Duke takes important findings from the laboratory to the clinic and back to the laboratory, with the ultimate goal of improving care.

Duke Prostate Center translational teams—researchers and physicians—are committed to discovering and improving upon therapies and outcomes for men with prostate cancer. These teams are responsible for advancing knowledge that is put to use through dietary interventions, exercise and lifestyle modifications, and novel therapies (vaccines, drugs, hormonal therapies, experimental agents). They are also conducting biomarker research and making basic discoveries about how cancer cells grow,

spread, and develop resistance to current therapies.

As a member of the Department of Defense Prostate Cancer Clinical Trial Consortium, one of only 13 centers of prostate cancer research excellence in the United States, the Duke Prostate Center is able to bring these novel treatments directly to our patients. This issue of *Duke Prostate Center News* highlights some of these recent findings.

In addition, please refer to past issues of the Duke Prostate Center News where other projects, still ongoing, are described. These are available online at [dukehealth.org/services/prostatecancer](http://dukehealth.org/services/prostatecancer).



FROM THE DIRECTOR

## My take on screening controversies and other issues in the news

Dear Patients, Colleagues, and Friends,

There has been much news and excitement in the field and at Duke Prostate Center recently.

The big news this past spring was the publication of two major randomized clinical trials related to prostate cancer screening using the PSA test. Early results of the National Cancer Institute's large-scale Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial showed no survival benefit to prostate cancer screening. However, more than half of the participants in the control group also had at least one PSA test during the course of the study, so many experts feel the study is too flawed to rely on for current guidance.

The other trial, the European Randomized Study of Screening for Prostate Cancer, showed a 20 percent survival benefit for the men in the PSA screening group compared to control-group men who were not tested. However, the controversy here is that some experts feel that too many men had to be screened to save lives, and that many cases of prostate cancer detected are very early stage and may not have harmed the men even if the cancer had been left undiscovered.

Duke Prostate Center continues to monitor the field and at this time favors the recommendation of the National Comprehensive Cancer Network and the American Urological Association: that men consider getting a baseline PSA test at age 40 and then to work with their doctor to determine their individual risk for prostate cancer and how often to be screened.

In other news, there are many promising new medications and treatments in the pipeline for prostate cancer. Degarelix, a new hormonal medication for advanced prostate cancer, was approved by the FDA in December 2008 and is now available at Duke. The sipuleucel-T (Provenge) vaccine for advanced prostate cancer continues to demonstrate improved survivals and is under consideration now by the FDA. Other agents in phase 3 trials include ZD 4054, abiraterone, dasatinib, and MDV3100. Duke Prostate Center is contributing knowledge about all these agents through our participation in national clinical trials. Other treatments being studied here include high-intensity focused ultrasound and focal cryotherapy.

Finally, we are in the midst of a broad discussion in this country regarding comprehensive health care reform. Duke physicians and leaders are at the forefront of this debate, and our cutting-edge outcomes research may help policy-makers with some of the future decisions and initiatives.

As always, we at the Duke Prostate Center continue to offer state-of-the-art care and clinical trials for men touched by prostate cancer. I remain grateful and blessed to lead a world-class team of urologists, medical oncologists, radiation oncologists, researchers, and dedicated staff. Thanks for your support.

Very respectfully,

Judd W. Moul, MD, FACS  
Director, Duke Prostate Center  
Chief, Division of Urologic Surgery  
James H. Semans, MD, Professor of Surgery

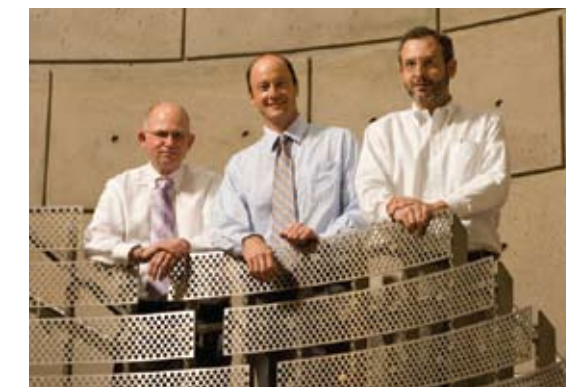
## Duke Prostate Center investigators study circulating tumor cell biology

Researchers led by Andrew Armstrong, MD, ScM, in collaboration with the laboratory of Mariano Garcia-Blanco, MD, PhD, have begun to study the process of how prostate cancer cells spread (metastasize) through the bloodstream into the bone and other locations. Through a mixture of preclinical models and the collection of circulating tumor cells from men with prostate cancer, these investigators are evaluating changes that occur in these cells that may make them more aggressive. In addition, these potentially lethal cells are being characterized at the molecular level for evidence of coordinated programs that drive their behavior, with the hope of finding targets for future therapies.

“By isolating and characterizing these cells directly and at a detailed molecular level, we hope to identify potential therapeutic strategies that may help prevent or delay cancer spread,” says Armstrong. “This is a true translational project, in which we are studying model systems of prostate cancer metastasis and applying these findings directly into the clinic, with clinical findings then informing further laboratory experiments.”

Several groups have recently recognized this work with grant funding and support, including the Prostate Cancer Foundation, the Duke Comprehensive Cancer Center (pilot grant and K12 program), the NIH (R01), and the American Cancer Society.

Duke Prostate Center researchers plan to publish initial findings within the coming year.



Translational team members: Mark Dewhirst, DVM, PhD, Andrew Armstrong, MD, ScM, and Mariano Garcia-Blanco, MD, PhD

## Diet and exercise are critical elements of prostate cancer survivorship

Lee Jones, PhD, and Stephen Freedland, MD, are taking a unique approach to treating men diagnosed with prostate cancer. Instead of testing the effects of a new drug or device, they test the effects of good old-fashioned lifestyle interventions, stressing the importance of exercise and diet as cornerstones of prostate cancer survivorship.

Jones is an exercise physiologist with expertise in investigating better ways to evaluate the physiological and functional impact of prostate cancer and the role of exercise to mitigate these effects. Freedland is a urologist with expertise in investigating the effects of different dietary combinations on prostate cancer growth and progression.

“We’ve known for at least 70 years that having a high fitness level and exercising regularly is protective against diseases of the heart and blood vessels,” says Jones. “What we don’t know is how exercise, either alone or in combination with other strategies such as dietary interventions, impacts cancer progression following a prostate cancer diagnosis.” Indeed, Jones and Freedland, in collaboration with Andrew Armstrong, MD, and Susan Halabi are planning to investigate whether objec-

tive measures of physical fitness can more accurately predict long-term survival in men with advanced recurrent prostate cancer than currently used subjective measures of physical functioning. “This is an important study,” says Armstrong. “More accurate markers of clinical outcome can help clinicians individualize treatment more effectively, which leads to better overall patient care.”

It’s a similar story for diet, says Freedland. “A proper diet is a key component of overall health. To what degree one diet can slow tumor growth relative to another diet remains to be determined.”

Over the past three years, Jones and Freedland have initiated several studies to examine the effects of exercise and diet in mice implanted with human prostate cancers. Preliminary results from these experiments suggest that exercise and diet can not only influence how fast a prostate tumor grows, but also what is happening in the tumor itself in terms of its biology. “We are finding some fascinating and completely unexpected findings—every day we learn something new,” says Jones.



Lee Jones, PhD

Stephen Freedland, MD

Jones and Freedland are continuing their animal studies but are also about to launch some of the first human trials. They just received a large NIH grant to study the effects of exercise on erectile dysfunction in men following a radical prostatectomy, as well as a grant from the Atkins Foundation to study the effects of the Atkins diet on side effects from hormonal therapy.

Antonelli J, Freedland SJ, Jones LW. Exercise therapy across the prostate cancer continuum. *Prostate Cancer and Prostatic Diseases* 12(2):110-15, 2009.

## Targeting hypoxic cells may make therapy more effective

A team of Duke investigators led by Mark Dewhirst, DVM, PhD, collaborated with scientists at the Catholic University of Louvain (Belgium) and found a unique metabolic relationship that appears to exist in many cancers, including prostate. Features of this symbiotic relationship are potentially targetable, which may lead to a novel means to sensitize cancers to radiation therapy and perhaps chemotherapy as well.

Many forms of cancer, including prostate cancer, contain regions that are starved for oxygen—the term for this is “hypoxia.” Hypoxic cells are very resistant to treatment by radiation and drugs, and they are also very malignant (they have an increased propensity to spread through the body). “There have been many attempts over the past 60-plus years to eliminate hypoxic cells,” says Dewhirst, “but nothing so far has been uniformly successful and there is no established standard of care that specifically targets hypoxic cells.”

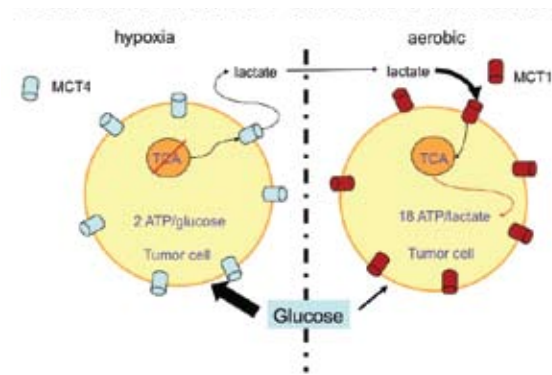
The only method that hypoxic cells have to produce energy is by using anaerobic metabolism, which produces lactate as a byproduct, much like exercising muscle. The research team

discovered that tumor cells that have adequate amounts of oxygen (aerobic cells) take up lactate that is produced by hypoxic cells and break it down for energy, which tumor cells require to grow. When aerobic tumor cells use lactate, they use less sugar, thereby permitting the sugar to reach the hypoxic tumor cells. The team showed that when they prevented aerobic cells from using lactate for energy, their sugar consumption increased. The result was that the hypoxic cells no longer had an adequate amount of sugar for energy, and as a result, they starved to death.

“This method for killing hypoxic cells is completely unique and not likely to cause damage to normal tissues,” says Dewhirst. “It opens for the first time the possibility of selectively killing these cells, which are likely to be responsible for many treatment failures in prostate and other cancers.”

Hypoxia is a prominent feature of prostate cancer and there are several therapeutic approaches to killing hypoxic cells that are being explored

Function of lactate transporters in prostate cancer cells



within the genitourinary oncology program at Duke. For example, Andrew Armstrong, MD, and colleagues are conducting a trial in patients with advanced cancer that uses chemotherapy with a drug that is selectively activated to be toxic to tumor cells under hypoxic conditions.

Sonveaux P, Vegran F, Schroeder T, Wergin MC, Verrax J, Rabbani ZN, et al. Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice. *The Journal of Clinical Investigation*. 2008 Dec;118(12):3930-42.

## Another reason to forgo the doughnuts?

New data from the Duke Prostate Center suggest that certain diets may be better than others at slowing tumor growth—at least in mice.

A team lead by urologist Stephen Freedland, MD, tested three different diets for their ability to slow prostate cancer growth when implanted into

mice: a very low-fat diet (12 percent calories from fat), a very low-carbohydrate diet (zero percent calories from carbohydrates), and a Western diet (40 percent calories from fat). The mice were fed to maintain equal body weights in all groups, as slight differences in body weights could make the tumors grow faster or slower.

The team found that mice on either the very low-fat diet or very low-carbohydrate diet lived longer than mice on the Western diet. Interestingly, in a prior Duke study, the team found that only the low-carbohydrate diet slowed tumor growth. Thus, when combined with results from the earlier study it appears that a low-carbohydrate diet can prolong survival of mice with cancer.

Freedland just launched the world’s first clinical trial of a low-carbohydrate diet for men with prostate cancer funded jointly by the National Institutes of Health, the Prostate Cancer Foundation, and the Robert Atkins Foundation. The goal is to minimize the side effects of hormonal therapy—a treatment for advanced, aggressive prostate cancer. If that is successful, future studies will examine whether this diet can actually slow tumor growth in humans.

Mavropoulos et al, *Cancer Prevention Research*, June 2009

Freedland et al, *Prostate*, January 2008

### PRE-OPERATIVE TRIALS

- Radiation.** Bridget Koontz, MD, is investigating the use of radiation prior to surgery in order to eliminate prostate cancer cells that may be outside the prostate prior to undergoing radical prostatectomy.
- Novel agents.** DPC researchers are investigating the use of several drugs and compounds intended to interfere with the normal growth of prostate cancer (sunitinib, pomegranate supplements, chemotherapy) for men with prostate cancer prior to undergoing radical prostatectomy.
- Careful observation.** For men with low-risk prostate cancer who are not sure that any therapy is needed for their prostate cancer at this time, Duke is participating in an active surveillance clinical trial prior to definitive therapy.

### SURGICAL TRIALS AND FOCAL THERAPIES

- Cryotherapy.** Tom Polascik, MD, is investigating the use of focal prostate cancer therapy (cryotherapy) to treat prostate cancer without removal of the entire prostate, both with and without radiation therapy.
- HIFU.** Cary Robertson, MD, is investigating the use of high intensity focal ultrasound (HIFU) to focally destroy prostate cancer without removal of the entire prostate.
- Soy protein.** David Albala, MD, is investigating whether soy protein extracts can reduce the chances that prostate cancer will recur after surgery.

### RADIATION TREATMENT

- Chemotherapy following radiation.** For men at high risk for recurrence after radiation and hormonal therapy, Duke is participating in a multicenter trial of chemotherapy given after completion of radiation.
- Shorter courses of radiation.** Robert Lee, MD, and colleagues are investigating the use of shorter but more intense time periods (5 1/2 weeks vs. 8 weeks) of radiation treatment for men with low-risk disease in this multicenter trial. A second trial is investigating the safety and efficacy of one week of focal stereotactic radiation in this setting.

### RISING PSA AFTER SURGERY

- Multimodality therapy.** This phase 2 study is investigating the use of a combination of salvage radiation therapy and aggressive systemic chemotherapy and anti-angiogenic therapy for men who have experienced a PSA recurrence within 3 years of radical prostatectomy.

- Dietary changes.** Researchers led by Stephen Freedland, MD, are investigating the role of a low carbohydrate diet in improving blood sugar control for men starting on hormonal therapies.
- Chemotherapy.** Docetaxel is the standard of care for men with metastatic disease, but does it work better if used earlier? This study is investigating that question for men who have a rising PSA after surgery.
- Vaccines.** Researchers are investigating the use of the Provenge vaccine in men with advanced, metastatic prostate cancer through an open-label expanded access protocol.

### PREVENTION OF FRACTURES

- Zoledronic acid.** Duke is participating in a multicenter trial of an intravenous medication to prevent or delay the risk of bone fractures in men with metastatic prostate cancer.

### NOVEL AGENTS

- Chemotherapy plus novel agents.** Researchers are investigating the use of several novel agents alone or in combination with standard-of-care chemotherapy treatments for men with recurrent and metastatic prostate cancer. These treatments include inhibitors of tumor blood vessel growth (vascular endothelial growth factor inhibitors, hypoxia-activated drugs), inhibitors of prostate cancer cell growth and function (insulin-like growth factor inhibitors), bone-targeted agents (src kinase and endothelin inhibitors), novel hormonal therapies (abiraterone acetate, MDV3100), and epigenetic agents that work at the level of changing broad patterns of gene expression.
- Genomic predictors.** Duke has led efforts to develop genomic predictors of response to chemotherapy, hormonal therapy, and novel agents and continues to pursue strategies to individually tailor therapy based on a man’s prostate cancer genomic profile.
- Circulating tumor cells.** Duke researchers are studying the biology of prostate cancer cells in the bloodstream and how novel agents reduce and alter the behavior of these cells.
- mTOR inhibitors.** A multidisciplinary team of investigators are looking at ways to prevent prostate cancer cells from spreading and growing, using a new class of medications called mTOR inhibitors. One of these agents was FDA approved in 2007 for kidney cancer treatment and investigators at the Duke Prostate Center are researching the use of these medications for men with prostate cancer.

More on clinical trials: [cancer.duke.edu](http://cancer.duke.edu)

WELCOME NEW DPC FACULTY

**Deborah Bradley, MD**

Medical Oncology

Training: MD, University of Cincinnati College of Medicine (Ohio), 2002; Residency, University of Cincinnati College of Medicine, 2002; Fellowship, University of Michigan, 2002-2008.

Clinical Interests: Investigation of novel therapies for treatment of bladder, kidney, prostate cancer; care of patients with advanced bladder, kidney, prostate, and testicular cancer



**Brant Inman, MD**

Urology

Training: MD, University of Alberta Faculty of Medicine and Dentistry (Canada), 2000; Residency, Laval University (Canada), 2005; Fellowship, Mayo Clinic (Minnesota), 2008; Fellow, Royal College of Surgeons, Canada

Clinical Interests: Urologic oncology, robotic surgery, bladder cancer, penile cancer, testicular cancer, surgical management of advanced genitourinary tumors



TRANSLATIONAL TEAMS

**Androgen Receptor Signaling**

Donald McDonnell and Phillip Febbo

**Metastasis and Survival in Prostate Cancer**

Mariano Garcia-Blanco, Andrew Armstrong, Phil Febbo, and Mark Dewhirst

**Aptamer Technology**

Daniel George and Bruce Sullenger

**Lifestyle, Diet, Metabolism, and Fitness**

Steve Freedland, Lee Jones, Judd Moul, and David Albala

**Focal Therapies**

Cary Robertson, Tom Polascik, W. Robert Lee, Bridget Koontz, Daniel George, and John Madden

**Angiogenesis and Prostate Cancer**

Daniel George, Andrew Armstrong, Susan Halabi, Phil Febbo, Mark Dewhirst, and John Madden

**Targeted Molecular Therapies**

Andrew Armstrong, Daniel George, Phil Febbo, Steve Freedland, Judd Moul, Deborah Bradley, and John Madden

AWARDS AND HONORS

**Clinical Excellence Award**

Judd Moul, MD, director of the Duke Prostate Center, received the National Physician of the Year Award from Castle Connolly Medical Ltd. The award recognizes physicians who exemplify excellence in clinical medical practice. Moul is also chair of the Public/Patient Education Council of the American Urological Association Foundation; a member of the localized prostate cancer guidelines committee of the American Urological Association; and physician advisor for *Men's Health* magazine.

**Prostate Cancer Foundation YIA Award**

Medical oncologist Andrew Armstrong, MD, received the 2008 Prostate Cancer Foundation Young Investigator Award. Armstrong's research focuses on discovering biomarkers that will identify patients with prostate cancer who are at higher risk for a more aggressive clinical progression of the disease. Molecular markers to predict metastasis will be studied on circulating tumor cells—the small proportion of prostate cancer cells that break away from the primary cancer and enter blood circulation. Patients presenting these markers might be treated aggressively at an earlier stage of disease.

Identification and validation of novel therapeutic targets for the treatment of prostate cancer

The treatment of advanced prostate cancer usually consists of surgical/chemical castration with or without antiandrogen treatment. Although androgen ablation therapy is effective, hormone-independent disease invariably emerges and is uniformly fatal. Recent studies suggest that although these tumors are referred to as androgen-independent, they still require a functionally active androgen receptor (AR).

Thus, novel therapies targeting AR may have clinical utility for the treatment of advanced prostate cancer. In this regard, Donald McDonnell, PhD, and colleagues have undertaken a multi-faceted research program whose goals are to 1) define the mechanism(s) by which resistance to androgen ablation arises, 2) develop novel approaches to inhibit the activity of the androgen receptor in prostate cancer, 3)

develop small molecules (drugs) that can be used to reduce prostate cancer risk, and 4) define and interfere with the cellular processes that enable androgens to stimulate growth and spread of prostate cancer cells.

From these studies, two new therapeutic strategies have emerged that we believe have clinical utility. The first is the development of a new class of antiandrogens called coactivator binding inhibitors (CBIs). These molecules function by



Donald McDonnell, PhD

directly blocking the interaction of AR with cellular proteins required for its transcriptional activity. It is envisaged that molecules of this class would be used in combination with conventional antiandrogens to effect a complete inhibition of receptor transcriptional activity.

A second line of investigation has led to the development of a drug that inhibits the activity of serum glucocorticoid kinase (SGK-1), an enzyme that is required for androgen-dependent growth of prostate cancer cells. Our goals are to evaluate the clinical utility of these new therapeutic approaches and to continue to dissect the androgen signaling pathway with a goal of identifying additional therapeutic targets.

Personalizing care for men with advanced, castration-resistant prostate cancer

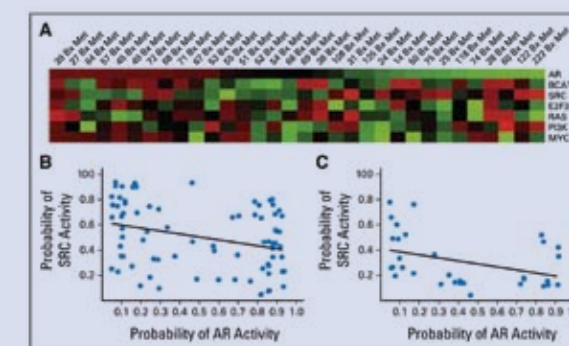
While there is growing knowledge regarding the molecular state of advanced prostate cancer, therapeutic decisions for men with metastatic disease are not based upon the molecular characteristics of their individual tumor.

The Duke Prostate Center has recently developed an androgen receptor (AR) signature that uses the expression of 300 genes to accurately detect relative AR activity in prostate cancer tumors (Mendiratta et al, JCO 2009). We are now using our AR signature to guide therapy for men with castration-resistant prostate cancer.

For the first time ever in the United States and abroad, men at Duke enrolled in our trial are having treatment personalized based upon a molecular characteristic of their tumor. In this trial, we perform radiologically guided biopsies, laser capture microdissection, RNA isolation and amplification, and microarray analysis. We then apply our AR signature to the individual's sample and if they are found to have relatively high levels of AR activity, the man receives nilutamide (Nilandron), an anti-androgen that binds directly to AR. If the

man's tumor has relatively low levels of AR activity, they receive dasatinib (Sprycel, BMS), a drug that targets the SRC family of tyrosine kinases. We chose to target SRC after discovering that as AR activity decreases, SRC activity increases. If men progress on single agent therapy, they start combination therapy with both agents.

This trial represents a true team approach with co-investigators from the departments of radiology, medicine, and statistics all playing critical roles. There is great interest in our trial nationally, and the Fred Hutchinson Cancer Center in Seattle, Washington, Oregon Health and Sciences University in Portland, Oregon, the Dana Farber Cancer Institute in Boston, Massachusetts, and MD Anderson Cancer Center in Houston, Texas, are all in the process of opening our trial and participating in this first-of-a-kind trial developed at Duke.



Androgen receptor (AR) and pathway signatures in metastatic prostate cancer. (A) Clustering of pathways across metastatic, castration-resistant prostate cancer. Samples (n = 32) are ordered according to AR activity and pathways are ordered based on complete correlation. Expression values were logged, median centered, and row normalized; red high probability of activity, green low probability of activity. (B) Plot of predicted SRC activity (y-axis) versus predicted AR activity (x-axis) in localized prostate cancer samples (n = 79). (C) Plot of predicted SRC activity (y-axis) versus predicted AR activity (x-axis) in metastatic castration-resistant tumors (n = 32).

# Duke Prostate Center News

DUKE UNIVERSITY MEDICAL CENTER

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## What is the Duke Prostate Center?

The DPC is a multidisciplinary collection of physicians, research scientists, and health care providers at Duke University Medical Center who seek to prevent prostate cancer and improve the care of men living with prostate cancer. We aim to achieve this through a team approach—by providing information and consultation at the time of diagnosis, providing state-of-the-art treatment options in urology, radiation oncology, and medical oncology, and in developing new treatments based on basic, translational, and clinical research. We are

located on the second floor of Duke Clinic in 2L, a new space dedicated to our multidisciplinary center.

Our research staff is dedicated to understanding the underlying causes of prostate cancer and how it progresses, and developing therapies based on these findings, including new surgical and radiation techniques, active surveillance, and novel drugs targeted at prostate cancer. Our goal is to allow men to continue living free of prostate cancer and the symptoms associated with this illness and its treatments.

## Duke Prostate Center

To make an appointment in the Duke Prostate Center, please contact Terry Witting at **919-668-8108**.

For other appointments or information on prostate cancer services at Duke, call the Duke Consultation and Referral Center at **1-800-MED-DUKE** (physicians) or **1-888-ASK-DUKE** (patients). Representatives are available Monday through Friday, 7:30 a.m. to 6:00 p.m.

To discuss giving opportunities, contact Thomas Kosempa at **919-667-2602** or [thomas.kosempa@duke.edu](mailto:thomas.kosempa@duke.edu).