

# CDMRP

## III. Prostate Cancer Research Program

## IMPACT



**Vision** To conquer prostate cancer.

**Mission** Support research that will eliminate prostate cancer.

The Prostate Cancer Research Program (PCRP) has managed \$810 million (M) in congressional appropriations and remains the second largest funder of extramural prostate cancer research in the United States. The PCRP fills important gaps not addressed by other funding agencies in support of prostate cancer research. To accomplish this goal, the PCRP has focused on bringing new discoveries to patients through clinical research and trials, eliminating the disparate burden of prostate cancer on the African American community and other affected populations, funding high-risk and high-gain research of exciting new ideas, inspiring and training prostate cancer researchers during their early career stages, and fostering collaborations to accelerate finding a cure for prostate cancer. The PCRP is making an impact on research focused on conquering prostate cancer.



**PCRP Making Headlines**

- ❖ **UI Researchers Studying Novel Therapy for Prostate Cancer**  
University of Iowa News Release, October 13, 2006
- ❖ **Breakthrough Study at the BC Cancer Agency Halts Growth of Prostate Cancer in the Lab**  
BC Cancer Agency News Release, January 31, 2007
- ❖ **Inflammation May Play a Role in Metastasis of Prostate Cancer**  
University of California, San Diego News Release, March 19, 2007
- ❖ **Veterinary Scientists Explore Poultry Virus Approach to Human Prostate Cancer**  
Virginia Tech News Release, April 9, 2007

## The Disease

- ❖ Prostate cancer is the most commonly diagnosed cancer in men.
- ❖ Prostate cancer is second only to lung cancer as a leading cause of cancer deaths in men.
- ❖ In 2007, approximately 218,890 men in the United States will be diagnosed with prostate cancer, and an estimated 27,050 will die from the disease.
- ❖ Prostate cancer incidence rates remain significantly higher in African American men compared to Caucasian men, and the death rate for African American men remains more than twice that of Caucasian men.<sup>1</sup>
- ❖ Currently, there is no cure for locally advanced or metastatic prostate cancer.

## Signs and Symptoms

Signs and symptoms do not typically accompany early cases of prostate cancer. However, some indicators of more advanced prostate cancer include:

- ❖ Frequent urination, especially at night
- ❖ Weak or interrupted urine flow
- ❖ Inability to urinate or difficulty starting or stopping the urine flow
- ❖ Painful or burning sensation when urinating
- ❖ Blood in the urine
- ❖ Continual pain in the lower back, pelvis, or upper thighs

Many of these symptoms are nonspecific and are not always related to a serious condition.<sup>1</sup>



<sup>1</sup> American Cancer Society, *Cancer Facts and Figures*, 2007.

## Program Background: 10 Years of Excellence

The Department of Defense (DOD) PCRCP was established in fiscal year 1997 (FY97) by Appropriations Conference Committee Report No. 104-863, which provided \$45M for research in prostate cancer. Today, the PCRCP is celebrating 10 years of excellence in support of its vision of conquering prostate cancer, as described later in this section under “Making an Impact: The First Decade.” The PCRCP’s extraordinary successes have led to continued congressional appropriations, totaling **\$810M through FY07**, and have made the program a leader in funding extramural prostate cancer research (see Figure III-1, PCRCP Funding History).

Since its inception the PCRCP has focused on making a positive impact on the lives of those affected by prostate cancer by fostering the transformation of outstanding laboratory science from **concept** to **reality**. The program’s multifaceted approach emphasizes training, research, and development of research resources.

- ❖ **Training:** Fostering the next generation of prostate cancer investigators through mentored research and training opportunities.
- ❖ **Innovative Research:** Supporting innovative basic, translational, and clinical research by both individual investigators and multidisciplinary collaborative groups with great potential to revolutionize the field and decrease the burden of prostate cancer.
- ❖ **Research Resources:** Developing cutting-edge research resources and technologies needed to move prostate cancer research forward, including a unique clinical trials operational structure to expedite prostate cancer clinical trials (as described on page III-20).

A total of **1,648 awards** were made across these three categories through FY06.

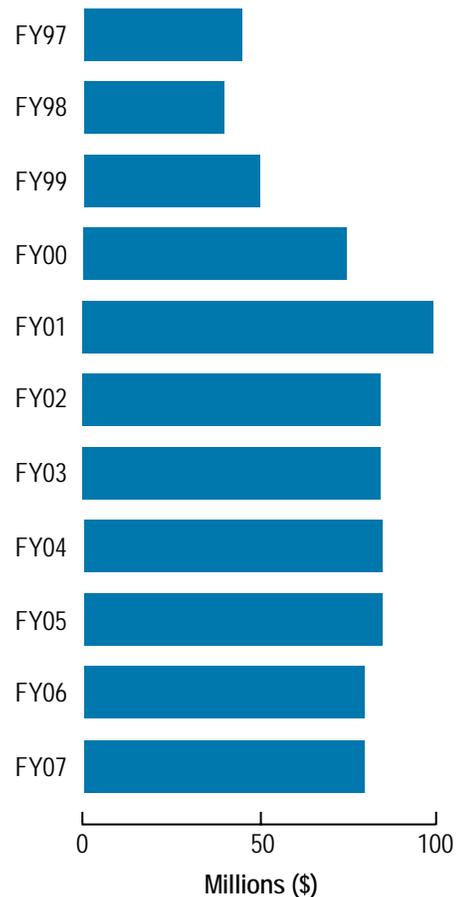


Figure III-1. PCRCP Funding History

## Making an Impact: The People

The combined efforts of scientists, research managers, and consumer advocates (prostate cancer survivors) are impacting the fight against prostate cancer. These people are working together to maximize their rate of return—to conquer prostate cancer.

### **The Honorable Ralph Burnett, J.D., National Prostate Cancer Coalition**

Since his prostate cancer diagnosis in 1996, Judge Ralph Burnett worked tirelessly as an advocate for patient rights and prostate cancer prevention. He served as Chairman of the National Prostate Cancer Coalition from 1999 to 2001. Judge Burnett served the PCRCP as a scientific peer reviewer, as a member of the Integration Panel, and as a member

of the IMPaCT (Innovative Minds in Prostate Cancer Today) Technical Planning Committee. He was actively engaged in planning for the IMPaCT meeting at the time of his death on May 10, 2007. He will be gratefully remembered for his prostate cancer advocacy and as noted by the National Prostate Cancer Coalition, as “a leader and a friend.”

## Consumer Advocates

A unique feature of the PCRCP is the active participation of consumer advocates—men living with prostate cancer—in virtually all facets of program execution. Approximately **270 consumer advocates** have served on peer and programmatic review panels for the PCRCP, providing distinctive viewpoints, a sense of urgency, and a face to the disease. Consumer advocates’ unique perspective complements the scientists’ expertise and helps ensure that funding decisions meet the needs of

men with prostate cancer, their families, and the clinicians who treat them. Further, by sharing what they have learned with their communities, consumer advocates enhance awareness of the state of prostate cancer research and forge even stronger links between the scientific and consumer advocate communities. More information about consumer advocate participation can be found in Section I, Overview.



**Virgil Simons (far left)**  
**The Prostate Net**  
**FY02–07 PCRCP Consumer**  
**Integration Panel Member**

“Marcel Proust said ‘The real voyage of discovery consists not of seeking new landscapes, but in viewing with new eyes.’ I think that we have to look at the goal of eliminating prostate cancer today in the context of research funding under intense pressure. We need to go beyond the way we’ve looked at that landscape and find a way to be much more creative in what we fund and how we do it. The task of the PCRCP is to see how we can interdict against the suffering and death from cancer by being open to really changing the way we do business, keeping in mind all those who have died or are dying, and who will need our help in the future. This [report] shows that the PCRCP is on the right track.”



**Artie L. Shelton, M.D.**  
**Colonel U.S.A. retired**  
**US TOO International, Inc.**  
**FY07 PCRCP Consumer Peer**  
**Reviewer**

“...I have the greatest admiration and respect for the scientific community for their dedicated professionalism and sacrifice in their efforts to find a cure for prostate cancer. In 1971, President Nixon declared ‘War on Cancer.’ With the knowledge and perseverance of the scientists who I had the distinct honor of working with, I feel that in the very near future we should be able to declare a VICTORY in the war against cancer...”

## Peer Review Panel Members

PCRP scientific peer review panels are organized by scientific discipline and specialty areas. Peer review panels are composed of leading investigators from scientific and clinical disciplines as well as consumer advocates. The primary responsibility of the scientific peer review panel is to review the scientific merit of proposals submitted to the program. To date, **1,700 scientists, clinicians, and consumer advocates** have brought their expertise to the PCRP scientific peer review process. Additional information about scientific peer review can be found in Section 1, Overview.



**Marianne Sadar,  
Ph.D.  
University of British  
Columbia  
FY99–05 Peer  
Reviewer**

“The DOD PCRP attracts and funds the highest quality and most innovative applications for prostate cancer research worldwide. Serving on the scientific peer review panel takes many days of intense work for the panel members to rigorously assess the scientific merit and disease relevance of each application. The results that stem from the DOD’s mandate and rigor of peer review has set this funding program as a world leader for innovative research that is advancing the search for a cure and improved clinical management of this disease that affects such a large percentage of men.”



**Natasha Kyprianou, Ph.D.  
University of Kentucky  
FY97–98, FY01–02, and FY04,  
Peer Reviewer**

“It is exciting to experience the impact that the DOD PCRP has had on prostate cancer research. I feel privileged to have had the opportunity to work with a tremendously talented group of individuals who are committed to dynamic research in finding the cure for prostate cancer. It is a creative journey that embraces the waves of translational research into the clinical setting while it enhances public awareness and support. Through the efforts of the CDMRP program for prostate cancer, the war against prostate cancer has expanded dramatically, as innovative minds are being recognized, high-risk ideas are materialized, new data are interpreted at a more assertive rhythm, and answers are generated at a rapid pace, leading to accurate prognostic and effective treatment possibilities. I believe that in the not-so-distant future patient advocates, scientists, clinicians, the government, and indeed the entire nation will witness the results of such phenomenal research creativity led by the DOD Prostate Cancer Research Program toward eradicating prostate cancer.”

## Integration Panel Members

The PCRP Integration Panel (IP) is composed of exceptional scientists, clinicians, and consumer advocates who use their expertise to recommend effective investment strategies, innovative research agendas, and broad-based research portfolios. Further details about the functions of the IP are summarized in Section I, Overview.

### FY07 PCRP IP Members

Timothy Ratliff, Ph.D. (Chair), Purdue Cancer Center  
Howard Soule, Ph.D. (Chair-Elect), Prostate Cancer Foundation

A. Oliver Sartor, M.D. (Executive Committee Member-at-Large), Dana-Farber Cancer Institute

Virgil Simons (Executive Committee Member-at-Large), The Prostate Net

The Honorable Ralph Burnett, National Prostate Cancer Coalition (deceased)

Peter Choyke, M.D., National Cancer Institute

Angelo DeMarzo, M.D., Ph.D., Johns Hopkins University School of Medicine

Robert Dreicer, M.D., The Cleveland Clinic Foundation

Cheryl Lee, M.D., University of Michigan

Donald Miller, M.D., Ph.D., University of Louisville

Gail Prins, Ph.D., University of Illinois at Chicago

Martin Sanda, M.D., Beth Israel Deaconess Medical Center

Howard Sandler, M.D., M.S., University of Michigan Medical School

Donald Tindall, Ph.D., Mayo Clinic

John Willey, National Prostate Cancer Coalition



**Timothy Ratliff, Ph.D.**  
Purdue Cancer Center  
FY07 Integration Panel  
Chair

“Working on the DOD Prostate Integration Panel has been very rewarding for several reasons, including the commitment to support training, support for underserved populations, and the flexibility for funding innovative science through novel mechanisms. The DOD is akin to the light cavalry in that they are relatively small, flexible in approach and implementation, and out in front leading the way.”



**Donald M. Miller, M.D.**  
University of Louisville  
FY05–07 Integration Panel  
Member

“I have been fortunate to participate in the Prostate Cancer Research Program of the DOD as a grantee, grant reviewer, and more recently, as a member of the PCRP Integration Panel. It has been a privilege to be associated with a program that is completely dedicated to helping men with prostate cancer. I believe that it has changed the face of prostate cancer research in a remarkable way. The very strong emphasis on consumer involvement and translational research has had a very strong impact on the development of new insights into prostate cancer causation and treatment.”



## The Scientific Community

Both early-career scientists and established prostate cancer experts are exploring the cutting edge of science and medicine and developing collaborative efforts to conquer prostate cancer. To date, the program has funded **more than 1,620 researchers**. These individuals are focusing their efforts on unraveling the complexity of prostate cancer, improving early detection and diagnosis, developing better treatment approaches, improving the quality of life of affected persons, and ultimately preventing prostate cancer.

# Making an Impact:

## The First Decade

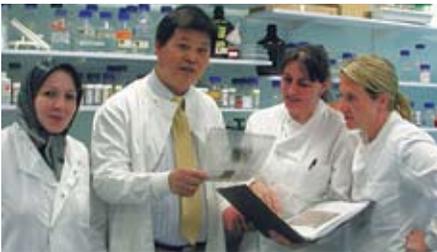
The PCRP is committed to making a difference in the lives of men with prostate cancer. This commitment has been realized through a spectrum of initiatives over the past 10 years that ultimately aim to accelerate the transformation of state-of-the-art research from concept to reality. Whether fostering the prostate cancer investigators of the future, supporting cutting-edge basic research on the prostate cancer disease process, promoting the formation of multidisciplinary partnerships, or sponsoring novel clinical and translational studies, the PCRP is focused on transitioning basic science into the clinic and, ultimately, conquering prostate cancer.





## Making an Impact... through Innovative Research

Since its inception, a hallmark of the PCRP has been to fund innovative, high-risk, high-impact research. These breakthrough studies not only result in critical advances in our understanding of prostate cancer but also lay the groundwork for the development of improved methods for prevention, detection, and treatment of the disease. Innovations in prostate cancer research span multiple areas, including environmental carcinogenesis, biomarker development, tumor imaging, radiation therapy, novel therapies and quality of life, as highlighted on the following pages.



**Youqiang Ke, Ph.D. (second from left) and colleagues**  
University of Liverpool, United Kingdom

### The Power of Applied Knowledge in Biomarker Development

Dr. Youqiang Ke of the University of Liverpool, United Kingdom, recipient of an **FY04 Exploration–Hypothesis Development Award**, has identified two potential biomarkers that may improve the detection and diagnosis of prostate cancer stages. Dr. Ke discovered that the ribosomal protein L19 (RPL 19) gene was differentially expressed between benign and malignant prostate cells. Further studies correlated Gleason score with RPL 19 staining intensity. Staining intensity was significantly stronger in highly malignant tissues compared to less malignant tissues. In addition, a

unique signature for benign prostatic hyperplasia (BPH) was attained by RPL 19 staining. Dr. Ke also examined osteopontin (OPN) expression in a study of 116 prostate samples. The OPN marker was weak in normal and BPH samples. Strikingly, carcinoma samples showed significant levels of OPN staining. Additional data correlated OPN staining with tumor aggressiveness. Finally, the degree of OPN staining inversely correlated with patient survival. From the results thus far, these candidate markers may serve as powerful predictors of tumor aggressiveness and aid in treatment decisions.



**Paul Cho, Ph.D.**  
University of  
Washington



**Danny Song, M.D.**  
Johns Hopkins University

### Improving How Seeds Are Pinpointed for Brachytherapy

Prostate brachytherapy, the implantation of radioactive seeds directly into the prostate to deliver localized radiotherapy, is an effective treatment for early-stage prostate cancer. Individual seed positions are optimized for maximum dose coverage of the prostate through computer simulation prior to implant, but the elasticity of the prostate gland, procedure-induced swelling, and other uncertainties often lead to discrepancies between the planned and actual seed locations. The ability to accurately pinpoint the seeds near tumors will greatly enhance the effectiveness of this therapy while minimizing damage to healthy tissues. Two prostate cancer researchers have come up with new strategies to address this problem using combined ultrasound and fluoroscopy imaging techniques. Dr. Paul Cho, an **FY02 Idea Development Awardee** at the University of Washington, has developed an advanced computer software system with an easy-to-use interface that images the fine contours of the

prostate and localizes tumors while compensating for patient movement. To date, Dr. Cho's work has shown that this intraoperative fluoroscopy-based dose assessment system can accurately guide the implantation of additional seeds in brachytherapy patients to more adequately bombard tumors with radiation. In a related study, Dr. Danny Song of Johns Hopkins University is currently enrolling patients to investigate a similar combined ultrasound-fluoroscopy strategy for seed placement. With the support of an **FY05 Clinical Trial Award**, Dr. Song is specifically investigating the safety of registered ultrasound and fluoroscopy (RUF), which closely parallels Dr. Cho's approach. Dr. Song will compare standard seed placement techniques with RUF to fairly evaluate its usefulness. The efforts of these investigators have the potential to catalyze the translation of combined ultrasound-fluoroscopy imaging strategies for seed placement into the clinic to enhance the effectiveness of brachytherapy.



**Leo Cheng, Ph.D.**  
**Massachusetts General Hospital**

#### **Magnetic Resonance Spectroscopy: An Objective Technique for the Quantification of Prostate Cancer Pathologies**

In the past, high-resolution magic angle spinning (HRMAS) spectroscopy was restricted to the determination of the physical structures of small molecules and some proteins. This branch of magnetic resonance spectroscopy has only recently been extended to studies of more complex molecules in cells and tissues isolated from patients. Dr. Leo Cheng of Massachusetts General Hospital, recipient of an **FY03 Idea Development Award**, has taken full advantage of this new technique and has begun to translate this imaging modality into the clinic for prostate cancer detection and diagnosis. By definition, HRMAS spectroscopy requires that samples be spun at very high rates, which can disrupt tissue architecture and prevent accurate pathological analysis. To address this roadblock, Dr. Cheng engineered a method that provides quantifiable, high-resolution data for prostate

metabolites at spinning speeds that do not damage prostate tissue architecture. Dr. Cheng focused on three lipid molecules—choline, phosphocholine (PC), and glycerophosphocholine (GPC)—whose metabolism often increases with the progression of prostate cancer. To measure these metabolites, Dr. Cheng has integrated  $^{31}\text{P}$  edited  $^1\text{H}$  spectroscopy with HRMAS techniques to reliably quantify the concentrations of choline, PC, and GPC in human prostate biological samples based on the unique phosphorus signal of each metabolite. The metabolic profile generated by these molecules was remarkably consistent, even after long-term storage. When combined, HRMAS and  $^{31}\text{P}$  edited  $^1\text{H}$  spectroscopy may one day measure the aberrant metabolism of a tumor for the diagnosis and treatment of prostate cancer in the clinic.



**Xiaoyuan Chen, Ph.D.**  
Stanford University

### Imaging of Primary Prostate Cancers

New targets for drug discovery benefit men with prostate cancer as they offer the promise of new therapies or tools for diagnosis. Gastrin-releasing peptide receptors (GRPRs) are overexpressed in human prostate cancer, but little with respect to drug or agent development has focused on these targets. Seizing this opportunity to better patients' lives, **FY02 New Investigator Awardee** Dr. Xiaoyuan Chen of Stanford University has developed radiolabeled bombesin (BBN) analogs to bind to GRPRs for imaging of prostatic lesions. To date, Dr. Chen has identified a series of analogs that have shown promising results in vivo. Animal models have revealed rapid uptake by hormone-refractory tumors with limited uptake by other organs. Dynamic scans of tumors indicated that the tumors were clearly visualized between 10 and 30 minutes after injection. In addition, the images generated could be processed very quickly; in some cases, it took less than 15 minutes on a standard personal computer. This agent may also be applied to the imaging of metastatic cancer.



**Dr. Shuk-mei Ho, Ph.D.**  
University of Cincinnati

### Estrogens in Prostate Cancer

Dr. Shuk-mei Ho of the University of Cincinnati has received **multiple awards from the FY97, FY00, FY03, and FY05 PCRCP** to examine the involvement of the female hormone estrogen and estrogen-like compounds in prostate cancer. Her earlier funded work identified paradoxical roles for estrogen receptor (ER) beta in inhibiting prostate cancer progression but promoting metastasis. More recently, in conjunction with Dr. Gail Prins at the University of Illinois at Chicago, she demonstrated for the first time that increased prenatal exposure to environmentally relevant doses of agents that mimic the actions of estrogen predisposes prostate tissue to precancerous lesions and tumor development later in life. One such agent is bisphenol A (BPA), which is commonly found in plastics and also occurs naturally in placental and fetal tissue. Dr. Ho's group has also identified a gene that is epigenetically regulated by estradiol or BPA exposure. This gene is a critical link in establishing a mechanism of xenoestrogen carcinogenesis. Elucidation of the critical role of estrogens and ER beta in prostate cancer has generated intense interest in developing new preventive or treatment agents that block harmful estrogenic signaling in the prostate. Dr. Ho's discovery of multiple variants (isoforms) of ER beta with different tissue distributions and actions should facilitate such efforts by permitting the design of agents that specifically inhibit the deleterious effects of estrogen in prostatic tissue with minimal side effects.



**Monique Cherrier, Ph.D.**  
University of Washington

### **Technology Meets Quality of Life: How to Make a New Treatment Strategy Even Better from the Patients' (and Doctors') Point(s) of View**

Chemotherapies that focus on androgen suppression are a new weapon in the clinic against metastatic prostate cancer. Intermittent androgen suppression (IAS) therapy represents a novel androgen suppression-based treatment regimen in which treatment is periodically stopped and then restarted. IAS therapy reduces many of the physiological side effects of conventional hormone-suppressive therapy such as loss of libido, weight gain, osteoporosis, fractures, and anemia. While the ability of IAS to minimize physiological side effects is well studied, many who undergo this type of treatment have experienced mood changes and memory problems. Dr. Monique Cherrier of the University of Washington, an **FY02 Idea Development Awardee**, and collaborators Drs. Celestia Higano and Satoshi

Minoshima have examined the mechanisms underlying these changes. Using a diagnostic tool called positron emission tomography, Dr. Cherrier investigated the effects of IAS treatment on brain blood flow. The measurements strongly suggested that the regions of the brain affected by IAS therapy could produce changes in mood, cognition, and working memory. Follow-up studies with a battery of cognitive tests further confirmed this hypothesis. Therefore, IAS may alter behavior and other cognitive functions by creating deficiencies in how blood flows in the brains of men receiving IAS. Dr. Cherrier's work promises to benefit patients of IAS therapy as scientists now understand the nature of the side effects of IAS. A variety of approaches are now under study to relieve these side effects.

## Making an Impact: Team Science

The work of independent investigators has been pivotal in advancing the understanding of prostate cancer development and progression. To take these findings to the next level, the PCRP has supported the development of multidisciplinary, multi-institutional collaborative networks, or consortia that conduct the types of large and far-reaching studies that cannot be accomplished by individual researchers. As described in the following highlights, the synergy promoted among such groups will accelerate the solution of major overarching questions with the potential to revolutionize prostate cancer research and clinical care.



**Robert Matusik, Ph.D.**  
Vanderbilt Prostate Cancer Center



**Flora Ukoli, M.P.H.**  
Meharry Medical College

### Working Together to Challenge Prostate Cancer Disparity

The Vanderbilt Prostate Cancer Center (VPCC) has become a premier research facility under the leadership of Dr. Robert Matusik and early support from an [FY99 Prostate Cancer Center Initiation Award \(PCCIA\)](#). Studies at VPCC have enhanced our understanding of the roles of transforming growth factors in prostate cancer. Further, Dr. Matusik's group has teamed with Dr. Flora Ukoli of Meharry Medical College (MMC) through an [FY04 Historically Black Colleges and Universities \(HBCU\) Collaborative Partnership Award \(CPA\)](#) to develop a program at MMC focused on prostate cancer disparity in African Americans.

With mentorship from VPCC investigators, MMC researchers are assessing the role of lycopene (a nutrient from tomatoes) in prostate cancer risk in African American men. Nigerian men, who consume more tomato-based foods, have lower rates of prostate cancer. A second study investigates whether thiazolidinediones, drugs used to treat type II diabetes, may reduce prostate cancer progression. Team science award mechanisms such as the PCCIA and CPA have established new partnerships to expand the community of prostate cancer researchers focused on improving the lives of all men.



**Investigators from the North Carolina–Louisiana Prostate Cancer Project**  
Back row, left to right: Joseph Su, Ph.D. (LSU), Gary Smith, Ph.D. (RPCI), Elizabeth Fontham, Dr.Ph. (LSU), James Mohler, M.D. (RPCI and UNC)  
Front row, left to right: Jane Schroeder, Ph.D. (UNC) and Jeannette Bensen, Ph.D. (UNC)

#### Understanding Health Disparity in Prostate Cancer

Dr. James Mohler, of Roswell Park Cancer Institute (RPCI) and the University of North Carolina at Chapel Hill (UNC), and co-Director Dr. Jeannette Bensen of UNC are leading the North Carolina–Louisiana Prostate Cancer Project with the support of an **FY02 Consortium Award**. The overarching theme of this large, multi-institutional and multidisciplinary effort is to uncover the factors responsible for the inordinately high mortality rate from prostate cancer in African Americans, which is about two and a half times that for Caucasian Americans.<sup>2</sup> Dr. Mohler assembled a team of leading clinicians, epidemiologists, and basic scientists from 11 institutions/organizations to tackle this problem. In addition to Dr. Mohler and Dr. Bensen, Dr. Elizabeth Fontham and Dr. Joseph Su of the School of Public Health at Louisiana State University Health Sciences Center (LSUHSC), Dr. Jane Schroeder, Dr. Paul Godley, and Dr. Merle Mishel of UNC, and Dr. Gary Smith of RPCI are playing a major role in accomplishing the goals of this consortium. A total of 2,000 men with newly diagnosed prostate cancer will participate and will be divided into four groups: 500 African Americans

and 500 Caucasian Americans from North Carolina and analogous cohorts from Louisiana. These populations were chosen for their unique differences in prostate cancer mortality among the African American populations. African Americans in North Carolina have one of the highest and African Americans in Louisiana have one of the lowest mortality rates among African Americans from prostate cancer while Caucasian Americans in the two states have similar mortality rates that are less than either African American group. Investigators in the consortium are conducting a comprehensive and coordinated characterization of racial differences in diet, genetics, tumor biology, and interaction with the health care system. Biological samples (prostate tissue, adipose tissue, blood, urine, and toenails) are also being collected and will provide an invaluable resource that will allow in-depth assessments of differences in host and tumor biology among the different cohorts. This study will provide valuable information to help target public health efforts to reduce prostate cancer mortality in general and among African American men especially.

<sup>2</sup> CA: A Cancer Journal for Clinicians–Cancer Statistics 2007: Vol 57; No. 1; Jan/Feb 2007.



Leland W.K. Chung, Ph.D. (center) and colleagues  
Emory University

### Targeting the Lethal Phenotype of Prostate Cancer

The **FY02 Consortium Award** funded the establishment of an unprecedented multi-institutional initiative to identify new therapeutic targets and concepts for treating the lethal phenotypes of metastatic, hormone-refractory prostate cancer. The consortium, previously led by Dr. Jonathan Simons (formerly of Emory University and now at the Prostate Cancer Foundation) and now directed by Dr. Leland W. K. Chung of Emory University, addresses a critical issue in prostate cancer research—there are currently few therapeutic agents to extend the survival of men with advanced prostate cancer. Dr. Chung and Dr. Simons assembled and managed five multidisciplinary, synergistic teams of leading researchers and clinicians in prostate cancer from 11 universities and 8 states to tackle this problem by elucidating the signaling pathways that regulate lethal prostate cancer growth, survival, and metastasis to bone and other organs. The endpoint of this major effort is to develop and bring to clinical trials exciting new therapeutics to improve the outcome of patients with advanced prostate cancer. Dr. Simons developed

and implemented novel, team science initiatives to foster synergy, free exchange of ideas, and progress and data sharing. Web-based videoconferencing and online data-sharing technologies connected basic scientists (in tumor biology, bone physiology, molecular genetics, pharmacology, and biostatistics) and physician scientists (urologists, pathologists, radiation oncologists, and medical oncologists) in real time across space. As this project approaches completion, three novel strategies that were conceived within the consortium and developed through basic and translational research steps represent the most promising candidates for entry into clinical trials: A monoclonal antibody that blocks the insulin-like growth factor receptor and inhibits bone metastases, 2-methoxyestradiol that also interferes with bone metastases, and the use of a cholesterol-lowering “statin” to inhibit prostate cancer growth and progression. Through innovations in executing a major team science effort, Dr. Simons, Dr. Chung, and all other participants in this consortium are making an impact on prostate cancer.



**Clinical Consortium Investigators**

#### **Clinical Consortium**

A major impediment to the rapid evaluation of new therapies for prostate cancer is the lack of sufficient resources to support the infrastructure needed to conduct a clinical trial. In FY05, the PCRCP responded to that barrier by developing a unique mechanism, the **Clinical Consortium Award**.

This major, multi-institutional effort is designed to rapidly develop, activate, and execute Phase I/II and Phase II clinical trials in prostate cancer by providing critical resources such as personnel and information technology infrastructure—gaps often difficult to fill with current funding mechanisms. The investigators, led by Dr. Howard Scher at Memorial Sloan-Kettering Cancer Center, represent leading clinicians and scientists who are working collaboratively to bring therapeutic interventions to the bedside. Since the start of the consortium award in January 2006, 366 patients have already been accrued across 26 Phase I/II and Phase II trials. These investigators are not only implementing and carrying out trials at a highly accelerated pace, they

are also creating a paradigm for successful team science and conducting clinical trials in prostate cancer. Additionally, they are combining their efforts with other large interdisciplinary initiatives such as the National Cancer Institute's Specialized Programs of Research Excellence program to capitalize on available resources for valuable correlative studies. This represents the consortium's commitment to reach out to the scientific community to further advance their goals. Cognizant of their respective roles as leaders in the field of prostate cancer clinical research, these investigators have combined their collective expertise to focus their research priorities. With an eye to the future, they have put together draft business plans to ensure their sustainability beyond the term of this award. The consortium as a whole represents a powerful and synergistic initiative ensuring that the most promising therapeutics are evaluated rapidly in the clinic with the goal of prolonging the lives of prostate cancer patients.

## Making an Impact... by Eliminating Health Disparity

Health disparity refers to differences in disease burden (risk, incidence, prevalence, and/or mortality) across populations that vary by ethnicity/race, socioeconomic status, age, health care access, or other characteristics. The PCRP has been committed to supporting basic, translational, and clinical research in prostate cancer health disparities since FY97/98. Special emphasis has been placed on disparities within the African American community, which has the highest incidence and mortality of

prostate cancer of any racial or ethnic group in the United States. As described in the following highlights, PCRP investigators are elucidating the complex socioeconomic, environmental, and genetic factors underlying prostate cancer health disparities with an eye toward transforming this knowledge into better means for preventing, detecting, treating, and reducing the impact of the disease in men at highest risk.



**Thomas Denberg, M.D., Ph.D.**  
University of Colorado Health Sciences Center

### Influence of Race and Social Class in Prostate Cancer Treatment

African American men with localized prostate cancer undergo radical prostatectomy (RP) less often than Caucasian men, even though many urologists consider RP the best treatment. Dr. Thomas Denberg of the University of Colorado Health Sciences Center is examining the factors underlying this discrepancy through an **FY04 Health Disparity Research Award**. He found that urologists, when asked to suggest treatment for hypothetical patients with the same diagnosis but of different races and social classes, recommended RP 14 percent less often

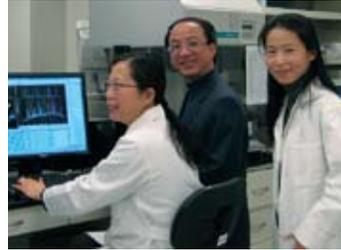
for low-income/widowed African Americans than for middle-income/married African Americans. In contrast, the difference was only 4 percent for low-income/widowed versus middle-income/married Caucasians. These findings suggest that both race and socioeconomic status may contribute to disparities in prostate cancer treatment and may aid in the development of physician training programs to improve the care of African Americans with prostate cancer.



**William Isaacs, Ph.D.**  
Johns Hopkins University

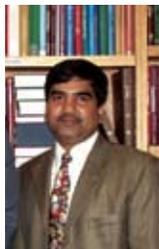
### **In Search of Prostate Cancer Genes**

Discovering genes that cause prostate cancer may lead to breakthroughs in our understanding of the disease. Dr. William Isaacs of Johns Hopkins University, recipient of **FY97 and FY00 Idea Development Awards**, and Dr. Jianfeng Xu of Wake Forest University, recipient of an **FY99 Idea Development Award**, used microsatellite markers (small, unique sequences associated with specific locations on each of our 23 chromosomes) to rapidly screen the genome for locations that are similar among men with prostate cancer but differ from the “normal” population. The researchers analyzed over 200 high-risk prostate cancer families of Ashkenazi Jewish, African American, or European American descent and found several prostate cancer susceptibility regions at chromosomes 1q, 7q, 8p,



**Jianfeng Xu, M.D.,  
Dr.Ph., (center) and  
colleagues**  
Wake Forest  
University

and Xq. In more recent studies combining genetic linkage analyses with somatic deletion analysis of 55 prostate tumors, they uncovered two small regions on chromosome 8p associated with prostate cancer genes. Currently, these investigators are using representational oligonucleotide microarray analysis and single nucleotide polymorphism arrays to study germline DNA variations, such as copy number polymorphisms (CNPs), and their association with prostate cancer. The researchers analyzed 90 patients with a strong family history of prostate cancer and early onset of disease and identified 13 novel CNPs. The team is continuing their effort to identify the actual cancer-causing gene(s) at these and other locations of the genome.



Ravishankar Jayadevappa, Ph.D.  
University of Pennsylvania

### Effects of Differential Prostate Cancer Treatments on Quality of Life

Dr. Ravishankar Jayadevappa of the University of Pennsylvania received an **FY03 Health Disparity Research Award** to study the quality of life effects of different treatments for prostate cancer as they relate to the African American community. Specifically, Dr. Jayadevappa focused on improving the quality of life in African American and Caucasian American men 65 years of age or older. Nearly 600 patients participated, who were treated with either RP or external beam radiation therapy (EBRT). Patients were followed up at 3, 6, 12, and 24 months thereafter, and clinical data were extracted from their medical records. Each patient completed a patient satisfaction care survey and a health-related quality of life survey (HRQoL) at each follow-up. Dr. Jayadevappa found that satisfaction with care did not differ between African American and

Caucasian American men or between men treated with RP and those treated with EBRT. However, important differences were observed in HRQoL between the various groups. African American men took longer to return to their baseline HRQoL scores than did Caucasian American men. Additionally, the RP group had significantly improved HRQoL scores compared to the EBRT group at the 12-month follow-up. Based on these results, Dr. Jayadevappa hypothesizes that therapeutic decisions should not be based primarily on age. These findings highlight the need for discussion with patients and families about expectations before treatment and the need for post-treatment support services, particularly for African American men for whom HRQoL may be compromised for a significant period of time after therapy.

## Making an Impact... by Training the Researchers of the Future

The PCRP understands that continued advances in prostate cancer research depend upon a highly trained cadre of both basic and clinical investigators. As such, training of outstanding scientists at the undergraduate, graduate, postdoctoral, and clinical fellow levels remains a top priority. A cross-section of some of the most promising trainees and training programs is profiled on the following pages.



**Jamie Cesaretti, M.D.**  
Mount Sinai School of  
Medicine

### **Genes and Adverse Radiotherapy Responses** FY03 Physician Research Training Awardee

Dr. Jamie Cesaretti of Mount Sinai School of Medicine is studying the off-target effects of prostate cancer radiotherapy, such as erectile dysfunction, urinary morbidity, and rectal bleeding, at the Mount Sinai School of Medicine. In some cases, these complications are explainable due to dosage or pre-existing conditions. However, for others there are no clear reasons for the co-morbidities. Dr. Cesaretti is investigating these cases through a genetic approach, examining the effect of the ATM gene and its variants. This gene was chosen as a focus due to the role it is known to play in irradiation responses in cells. Dr. Cesaretti found that those patients who possessed an altered ATM gene were more likely to develop adverse radiotherapy responses after receiving brachytherapy. This finding may be a valuable tool for both physicians and patients when contemplating therapeutic options.



**Ingo Mellinghoff, M.D.**  
University of California,  
Los Angeles

### **Regulation of Androgen Receptor Function by ErbB Receptor Tyrosine Kinases**

While androgen deprivation therapy is initially very successful for reducing the tumor burden associated with early-stage prostate cancer, the adaptability of the disease to produce hormone-refractory cancer cells renders this an ineffective long-term treatment. Many studies strongly suggest that the androgen receptor (AR) plays a critical role in the development of hormone-insensitive cancer cells. Dr. Ingo Mellinghoff of the University of California, Los Angeles, has conducted studies that point to an additional level of complexity on how the AR does its job. Dr. Mellinghoff's research, supported by an **FY03 Physician Research Training Award**, strongly suggests that the activity of the AR is regulated by another receptor called the epidermal growth factor receptor, known as ErbB. This finding strongly supports that other therapies that target Her2/ErbB, such as the breast cancer drug Herceptin®, may prove efficacious against prostate cancer progression.

### Delivering a One–Two Punch to Prostate Cancer

Recent studies suggest that combination therapy for cancer treatment offers enhanced efficacy at lower doses while minimizing side effects. Dr. Jacqueline Moreno and colleagues at Stanford University School of Medicine have demonstrated the promise of this approach for prostate cancer treatment. With the support of an [FY04 Postdoctoral Traineeship Award](#), Dr. Moreno examined the combined effects of two agents on prostate cancer proliferation. The first agent investigated was 1,25-dihydroxyvitamin D3 (calcitriol), which is a well-established inhibitor of human prostate cancer cell growth. Dr. Moreno discovered that calcitriol blocked the synthesis and growth-stimulatory activities of prostaglandins (PGs) in prostate cancer cells by reducing the expression of cyclooxygenase (COX)-2, a key enzyme of PG synthesis. Calcitriol also enhanced

the expression of a putative tumor suppressor that converts PGs into inactive metabolites. Dr. Moreno then assessed the antiproliferative effects of calcitriol in conjunction with various COX-1 and -2 inhibitors known as nonsteroidal anti-inflammatory drugs (NSAIDs). The combination of calcitriol with ibuprofen, naproxen, or other NSAIDs synergistically inhibited prostate cancer cell growth at 2- to 10-fold lower concentrations than the individual drugs. Based on these results, a Phase II clinical trial (not funded by the PCRFP) was initiated to examine the efficacy of calcitriol and naproxen in men with advanced, relapsing prostate cancer. Such combined treatment strategies may offer new hope to prostate cancer patients for whom other therapies have not been successful.



## Making an Impact... by Training the Next Generation of Scientists to Address the Needs of the African American Community

The incidence and mortality rates of prostate cancer remain significantly higher in African American men than in Caucasian American men. The PCRCP **Collaborative Undergraduate Historically Black Colleges and Universities (HBCU) Student Summer Training Program (STP) Award** was created to encourage HBCU students to pursue careers in prostate cancer research and serve as sources of information on prostate cancer treatment and screening for their families and communities. Since the creation of this award mechanism in FY04, 11 STP awards have been granted to 9 laboratories having expertise in prostate cancer research (see Table III-1). To date, **90 HBCU students** received hands-on comprehensive training in prostate cancer. Students were selected by means of a highly competitive selection process at each participating mentoring institution. Through the various summer programs, all STP interns had an opportunity to attend workshops, seminars, laboratory meetings, journal clubs, and weekly seminars. All summer training experiences for the STP students culminated in workshops or symposia where each student had

**Marva M. Price, Dr.P.H., R.N., F.A.A.N.P.,  
F.A.A.N., FY04 and FY06 Collaborative  
Undergraduate HBCU Student STP Award  
Principal Investigator**

“If more university nursing and medical faculty would give of themselves to mentor our undergraduate students—our next generation—we can multiply our expertise and feel certain that we can further prostate cancer research much farther than any one of us can do alone in our lifetimes.”

an opportunity to give a poster or oral presentation on his or her summer research project. Although the program has only been in existence since 2004, it has already been shown to be extremely successful. Students have been so inspired by their summer training experiences that many have expressed to their mentors the commitment to pursue studies in prostate cancer research at the Ph.D. and/or M.D. levels.

Table III-1. Summary of the PCRP Collaborative Undergraduate HBCU Student STPs

Fiscal Year	Mentor Institution	HBCU	Total Trained
2004	Stevens Institute of Technology	Jackson State University	14
2004	Duke University	North Carolina Central University	13
2004	The University of Texas M.D. Anderson Cancer Center	Texas Southern University	8
2005	University of North Texas Health Science Center, Fort Worth	Tuskegee University University of Houston, Texas Southern University	10
2005	University of Delaware	Delaware State University, Lincoln University	9
2005 and 2006 (2 awards)	University of Iowa	Lincoln University	13
2005	Baylor College of Medicine	Prairie View A&M University	7
2005	Moffitt Cancer Center & Research Institute at the University of South Florida College of Medicine	Florida A&M University	8
2006	University of North Carolina, Chapel Hill	Shaw University	4
2006	Duke University	Bennett College	4
<b>TOTAL</b>			<b>90</b>

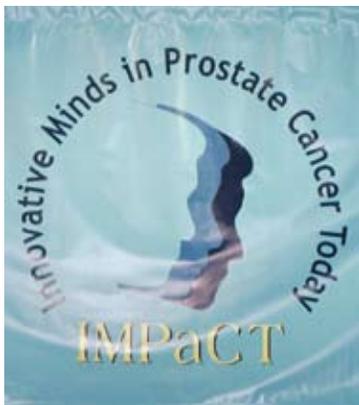


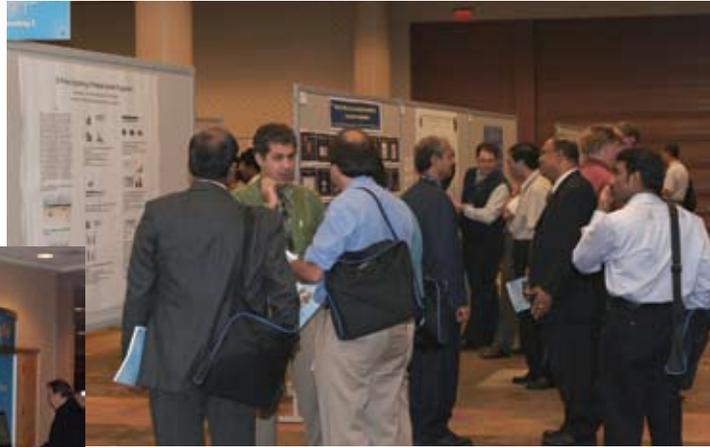
HBCU Undergraduate Students Supported by the PCRP

## IMPACT Meeting

The PCRP celebrated 10 years of research progress and excellence at the inaugural **Innovative Minds in Prostate Cancer Today (IMPACT)** meeting in Atlanta, Georgia, September 5–8, 2007. Scheduled to coincide with National Prostate Cancer Awareness Month, the IMPACT meeting, attended by more than 850 scientists, clinicians, and consumer advocates, provided a forum for the exchange of ideas and exploration of innovative avenues of research supported by the PCRP that will advance the

prostate cancer field. Through the involvement of consumers and scientists, the IMPACT meeting recognized the program's successes in funding innovative and high-impact research, addressing health disparities, and training the next generation of prostate cancer researchers.





# The Program Today

## Fiscal Year 2006 Summary

The PCRCP was sustained through a congressional appropriation of \$80M in FY06 to support peer-reviewed prostate cancer research. The FY06 program offered **11 award mechanisms** in the areas of clinical research, innovation, training, and research resources. One award mechanism, the Prostate Cancer Training Award (PCTA), was new for FY06. The PCTA combined research training opportunities for promising predoctoral students, postdoctoral researchers, medical students, residents, and fellows into a single mechanism. This award reflects the PCRCP's goal of maintaining a strong and diverse pipeline of researchers and clinicians who will continue to make advances for years to come.

A total of **1,176 proposals** was received across the 11 award mechanisms, and **194 awards** were made as shown in Table III-2. The multidisciplinary research portfolio developed by the FY06 PCRCP, which encompasses basic, clinical, and population-based research, is illustrated in Figure III-2.

**2006** 1,176 Proposals Received  
**2006** \$80M in Appropriations  
**2006** 194 Awards

Table III-2. Funding Summary for the FY06 PCRCP

Categories and Award Mechanisms	Proposals Received	Awards	Investment
<b>Clinical Research</b>			
Clinical Trial	19	3	\$3.1M
<b>Innovative Research</b>			
Exploration–Hypothesis Development	200	25	\$2.8M
Health Disparities Research	47	8	\$3.6M
Idea Development	582	66	\$36.6M
New Investigator	144	23	\$7.7M
<b>Training/Recruitment</b>			
Collaborative Undergraduate HBCU Student STP	4	3	\$0.6M
HBCU Collaborative Partnership Training	7	2	\$1.5M
Health Disparity Training–Prostate Scholar	6	3	\$0.5M
Physician Research Training	23	6	\$3.4M
Prostate Cancer Training	138	53	\$5.5M
<b>Research Resources</b>			
Clinical Consortium Sites	6	2	\$1.8M
Supplements to Prior Year Awards	N/A	N/A	\$2.4M
<b>TOTAL</b>	<b>1,176</b>	<b>194</b>	<b>\$69.5M</b>

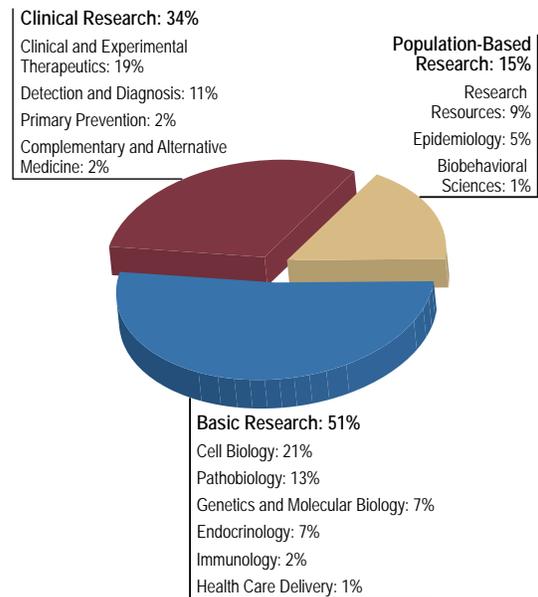


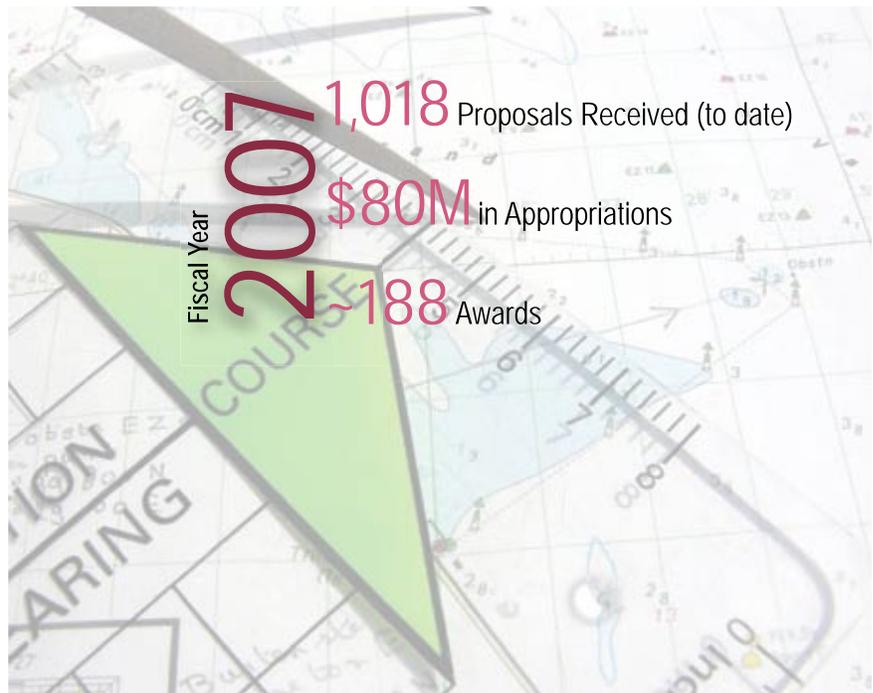
Figure III-2. FY06 PCRCP Portfolio by Research Area

# Charting the Course: The Second Decade of the PCRP

## The Vision for Fiscal Year 2007

Congress appropriated \$80M to continue the PCRP in FY07, the **10th anniversary** of the program. On this occasion, the IP members (see Section 1, Overview), during its FY07 vision setting meeting, critically and thoughtfully re-examined the PCRP—its past, its present, and its future. The outcome was a newly charted course for the next decade that builds upon the PCRP’s legacy of success in training and research and adopts new commitments to increase the PCRP’s focus on collaborations and on translational research. The course for the next decade is built upon the following:

- ❖ **Renewing Existing Commitments to Training:** Support of exceptional training opportunities for undergraduates, predoctoral students, postdoctoral Ph.D.s, and postdoctoral M.D.s is essential to ensure future progress in prostate cancer research. Also essential is alleviating the critical shortage of physician scientists. To achieve these goals, the PCRP is continuing its Collaborative Undergraduate HBCU Student STP Award, Prostate Cancer Training Award, and Physician Research Training Award mechanisms.
  
- ❖ **Renewing Existing Commitments to Individual Investigator-Initiated Research:** Support of innovative, high-impact investigator-initiated research has been a hallmark of the PCRP since its inception in FY97. These efforts are continuing via the PCRP’s Idea Development Award and New Investigator Award mechanisms.



- ❖ **Renewing Existing Commitments to Prostate Cancer Health Disparity Research:** Health disparity research focuses on factors that contribute to differences in disease experience across populations and has been an important focus of the PCRCP since FY98. Health disparity research continues to be an area of strong programmatic interest and has been incorporated as a focus area across most FY07 award mechanisms.
- ❖ **Identifying Program Focus Areas:** In addition to health disparity, other areas of programmatic focus were identified and published in the FY07 Program Announcements to assist investigators in developing proposals that will advance the PCRCP's mission of supporting research that will eliminate prostate cancer. These areas include biomarkers, imaging, and quality of life.
- ❖ **Increasing Emphasis on Collaboration:** In an era of exponentially rising research complexity, it is becoming increasingly important to foster multi-investigator collaborations. During the FY07 vision setting meeting, members of the IP addressed this issue and offered the Synergistic Idea Development Award. As with the PCRCP's Idea Development Award, this new mechanism supports innovative, high-impact studies on a critical research problem or question. The key difference is that the Synergistic Idea Development Award supports up to three collaborators with diverse expertise to collaborate as equal investigators who share equal responsibility for achieving research goals. Each investigator will receive his or her own individual award.
- ❖ **Increasing Emphasis on Translational Research:** A major gap in prostate cancer research funding that was identified at the FY07 vision setting meeting involved limited availability of funding for investigators to carry out the translational research efforts required to advance promising lead agents to clinical trials. To address this gap, members of the IP recommended the Laboratory-Clinical Transition Award: Stage I. The Stage I award focuses on validating novel therapeutics for prostate cancer from an identified lead agent up to but not including current Good Manufacturing Practice (cGMP) production of that agent for use in clinical trials. Stage II, which is anticipated to be offered in FY10, is intended to fund the cGMP production of validated lead agents. Further, to continue its support of agents in later stages of clinical development, the PCRCP is again offering the Clinical Trial Award to fund Phase I, II, and I/II studies of novel interventions for prostate cancer prevention, detection, diagnosis, or treatment.

Enthusiasm for the program continues among researchers, as a total of **1,018 proposals** was received across the **8 award mechanisms**, as shown in Figure III-3. Approximately 188 awards are expected. Appendix B, Table B-2, summarizes the congressional appropriations and the investment strategy executed by the PCRCP for FY06 and FY07.

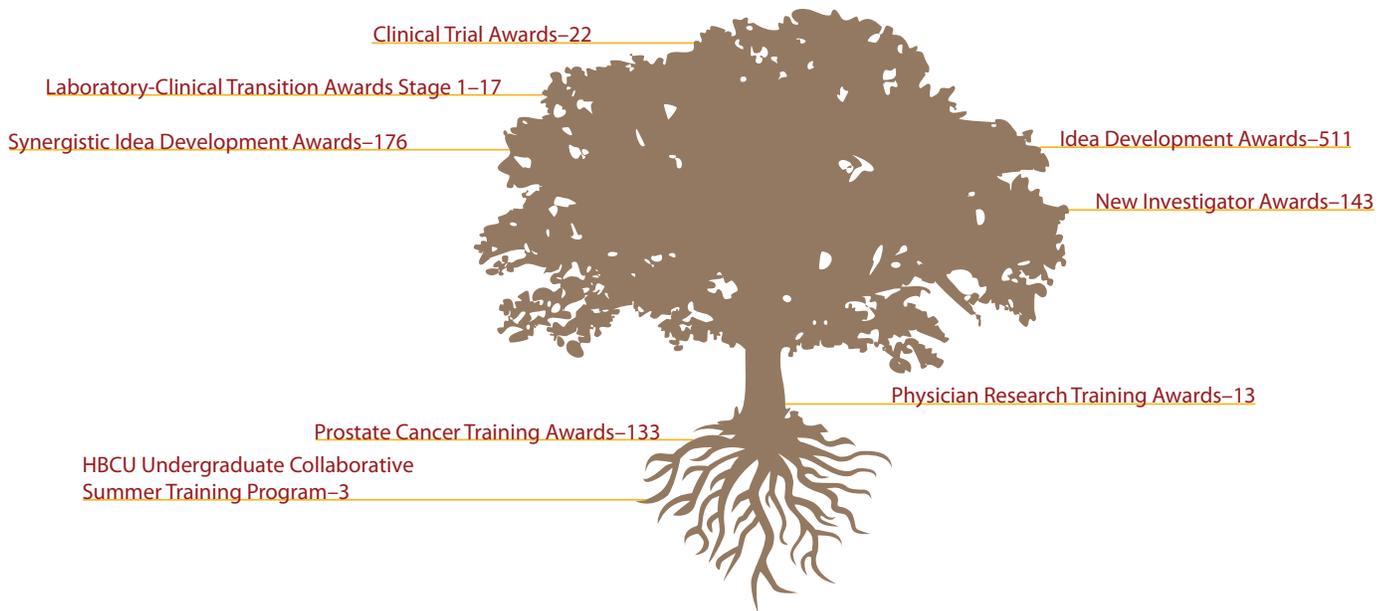


Figure III-3. Award Mechanisms Offered and Proposals Received for the FY07 PCRCP

## PCRP: Making an Impact

The progress funded researchers have made is exciting, and there is much enthusiasm for the continued success of the PCRP. The following product time line shows samples some of the scientific and programmatic accomplishments made possible by this program.

### 2004

- Discovered that signaling through ErbB (the receptor targeted by the breast cancer therapeutic Herceptin) regulates AR function.
- $^{64}\text{Cu}$ -DOTA-[Lys3]BBN and  $^{18}\text{F}$ -FB-[Lys3]BBN reported in the literature as able to detect GRPR-positive prostate cancer. Validation studies continue.
- Established the Collaborative Undergraduate HBCU Student STP Award to encourage HBCU students to pursue careers in prostate cancer research.

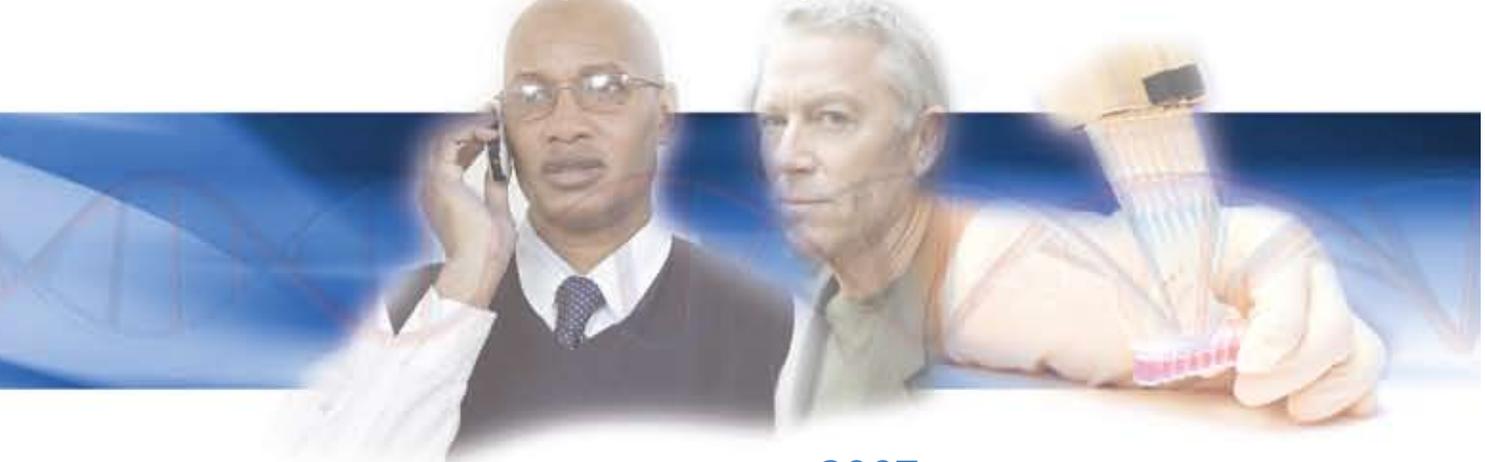


### 2005

- In vitro study completed that revealed that a combination of calcitriol with ibuprofen, naproxen, or other NSAIDs could synergistically inhibit prostate cancer cell growth.
- One of the first reports that magic angle spinning-based nuclear magnetic resonance imaging could be used to predict metabolic profiles of the prostate.
- Identified obesity as a risk factor for aggressive prostate cancer. In addition, found that among men with recurrent cancer after surgery, a rapid PSA doubling time increases the risk for death from prostate cancer. These findings may aid the identification of high-risk patients for early and aggressive treatment.
- Identified recurrent gene fusions in prostate cancer, which may serve as both novel biomarkers and therapeutic targets.
- Established the Clinical Consortium to facilitate the rapid execution of novel clinical trials.
- Identified a role for membrane cholesterol in mediating prostate cancer survival pathways. Anti-cholesterol drugs known as statins may be useful for prostate cancer treatment.

## 2006

- Innovative report completed on how radiotherapy specifically affects the genetic information inside cells. This finding may be a valuable tool for both physicians and patients when contemplating therapeutic options and may be useful to stem the side effects of such treatments in the future.
- Seminal report on how developmental exposure to estradiol and bisphenol A increases susceptibility to prostate carcinogenesis.
- Race and socioeconomic status may underlie the discrepancies in prostate cancer treatment between Caucasian and African American men.
- Identified two correlated variants of the insulin-like growth factor gene that were strongly associated with prostate cancer risk among African Americans, Native Hawaiians, Japanese, Latinos, and Caucasians.
- Ribosomal Protein L19 identified as a putative prostate cancer biomarker.
- Intermittent androgen suppression can alter brain metabolism, resulting in cognitive deficits. This is the first step toward understanding how to treat these side effects.



## 2007

- Among men with high incidences of prostate cancer, several prostate cancer susceptibility regions were identified at 1q, 7q, 8p, and Xq.
- Clinical study completed that identified differential post-treatment recovery pattern and thus the need for support services post-treatment.
- Validation that intraoperative ultrasound-fluoroscopy fusion can enhance prostate brachytherapy quality.
- Commemorated 10 years of breakthroughs at the inaugural Innovative Minds in Prostate Cancer Today (IMPACT) meeting in Atlanta, Georgia, September 5–8.

