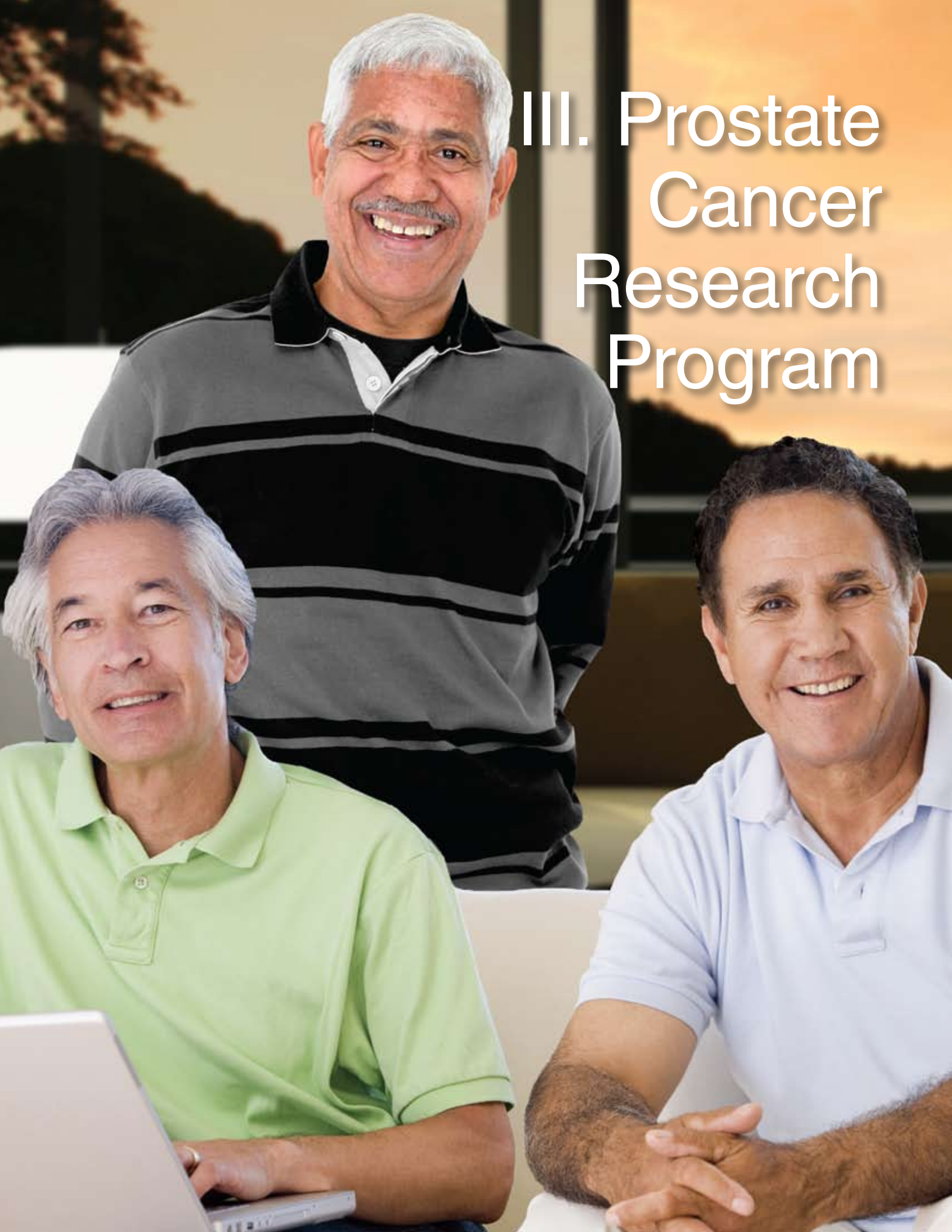
III. Prostate Cancer Research Program



Forging New Paths

Since its inception in fiscal year 1997 (FY97), the Prostate Cancer Research Program (PCRP), has received $890 million (M) in congressional appropriations and remains the world's second-largest funding agent of extramural prostate cancer research. The PCRP has used innovative approaches to funnel these funds directly into the best research to accelerate discovery, translate discoveries into clinical practice, and improve the quality of care and life of men with prostate cancer. By combining the expertise of the most talented prostate cancer scientists with the powerful perspective of consumer advocates, the PCRP is forging new paths toward its vision of conquering prostate cancer.

Vision

Conquer prostate cancer.

Mission

Support research that will eliminate prostate cancer.

Program Background

The Department of Defense (DOD) PCRP was established in FY97 by Appropriations Conference Committee Report No. 104-863, which provided $45M for research in prostate cancer. The PCRP remains a leader in funding extramural prostate cancer research, managing $890M through FY08 (see Figure III-1, PCRP Funding History). Since its inception, the PCRP has been forging new paths to conquer prostate cancer by emphasizing the need for innovative and collaborative research, development of research resources, and fostering new prostate cancer investigators through training. A total of 189 awards were made across these three categories in FY07.

- Innovative Research: Supporting innovative basic, translational, and clinical research in both the individual and multidisciplinary, collaborative group setting.
- Research Resources: Developing critical and cutting-edge research resources and technologies needed to move prostate cancer research forward, including a unique operational structure to expedite prostate cancer clinical trials.
- Training: Fostering the next generation of leading prostate cancer investigators through mentored research and training opportunities.

Since 1997, a total of 1,837 awards have been made across these three categories.

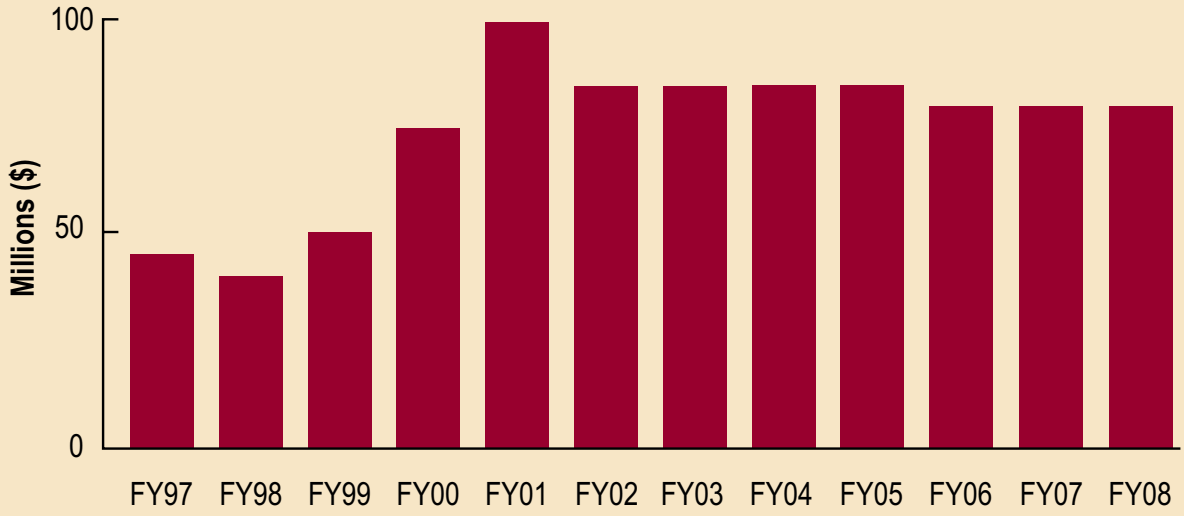


Figure III-1. PCRP Funding History

The Disease

- Prostate cancer is the most commonly diagnosed cancer in men.
- Prostate cancer is the second most common cause of cancer deaths in men.
- In 2008, approximately 186,320 men in the United States will be diagnosed with prostate cancer, and an estimated 28,660 will die from the disease.
- For reasons that are unclear, prostate cancer incidence rates are significantly higher in African American men compared to Caucasian men, and the death rate for African American men is more than twice that of Caucasian men.[1]
- 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, advanced prostate cancer may include:[1]

- 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.

[1] American Cancer Society, *Cancer Facts & Figures, 2008.*

Early Detection

Early detection of prostate cancer leads to the most successful treatment of the disease. The American Cancer Society (ACS) recommends that men talk to their doctor about the benefits, risks, and side effects of early prostate cancer testing. The following recommendations by the ACS for men with average and increased risk of prostate cancer may help in early detection of the disease.

Prostate-Specific Antigen (PSA) Blood Test

- The PSA test is recommended for men at age 50 with no major medical problems.
- Men at high risk of prostate cancer including African Americans and men with close relatives with history of disease before age 65 should be tested beginning at age 45.
- Men with several close relatives with prostate cancer are at even higher risk and may begin testing at age 40.
- A prostate biopsy is often recommended for men with high PSA levels.
- The PSA test can also be used to determine types of treatment or to monitor treatment.

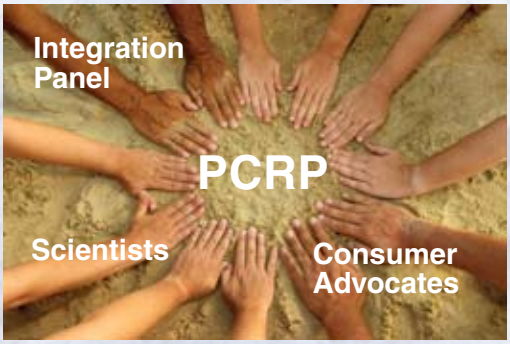
Digital Rectal Exam (DRE)

- The DRE exam is often used to identify prostate irregularities in the part of the gland that can be palpated from the rectum.
- Men at age 50 should have a DRE exam as well as PSA testing.
- Men at increased risk for prostate cancer should have a DRE exam and PSA test at age 40 or 45.
- DRE may be uncomfortable but is not painful.
- Although the DRE exam can sometimes find cancers in men with normal PSA, it is less effective than the PSA test; therefore, it should be done in combination with PSA testing.

Prostate Biopsy

- Prostate biopsy usually takes a few minutes and involves removing tissue from several different parts of the prostate gland through the rectum wall. The procedure is done with little discomfort.
- Some soreness may occur for a few days after the procedure, and some blood may be found in the urine, semen, and rectum for up to 2 months after the biopsy.

Building Partnerships



The successes of the PCRP have and continue to be critically dependent on strong partnerships. The combined efforts of consumer advocates, scientists serving as peer reviewers and funded investigators, and Integration Panel (IP) members work together to make major advances in the fight against prostate cancer. The collective contribution of these dedicated partners plays a pivotal role in maintaining the program's standard of scientific excellence.

Consumer Advocates

As active members of the PCRP, consumer advocates participate in the peer review of proposals as well as in setting program priorities and making funding recommendations. Approximately 285 consumer advocates have contributed to both peer and programmatic review since 1997. Consumer advocates' firsthand experiences with prostate cancer provide a unique perspective that is complementary to the expertise of the scientists and clinicians. This perspective keeps the urgency of curing the disease at the forefront of research and helps scientists understand the human side of how research will impact the community. Equally important, consumer advocates take what they have learned from the scientists back to their advocacy communities. This results in increased awareness of the importance of research and a stronger relationship between the scientific and consumer advocate communities.

"The scientists' careful consideration of the imaginative proposals we reviewed opened my eyes to the level of research taking place in cancer, its causes, detection, and treatment, and gave me much hope for the future."

Benjamin F. Fay
First State Prostate Cancer Support Group
FY07-FY08 Peer Reviewer

"Peer review provides a unique opportunity for survivors to interact with scientists conducting cutting-edge prostate cancer research. In turn, scientists value the input of consumer reviewers and incorporate those viewpoints into their deliberations in a meaningful way."

Benjamin Floyd
Prostate Cancer Network Group
FY07-FY08 Peer Reviewer

"Through reviewing research proposals seeking new funding, we Consumer Reviewers are able to report back to our community that there is reason for hope that the elusive key to intervention, before prostate cancer can even begin development, is within reach."

Charles Maack
US TOO
FY07 Peer Reviewer

"The minority consumer brings to the CDMRP critical knowledge and perspective, often first-hand, of the health disparities and the deleterious effects these disparities have on survivors and their families. Participation in the PCRP has given me the opportunity to make a tangible contribution to the fight to find the causes and cures of prostate cancer."

William Bright
US TOO
FY07-FY08 Peer Reviewer

Peer Review Panel Members

Scientific peer review is conducted by panels of expert scientists, clinicians, and consumer advocates who provide unbiased, expert advice on the scientific and technical merit of proposals submitted to the PCRP. Peer review panels are typically organized by scientific discipline and specialty areas. To date, more than 1,600 scientists, clinicians, and consumer advocates have brought their expertise to the PCRP scientific peer review process.

"The mission of the PCRP, to support highly innovative prostate cancer research, remains a critical counterpoint to traditional funding mechanisms. Not only have I had the honor of reviewing some truly great science, I've also met some really fantastic scientists who have become my collaborators and friends for a lifetime and consumers who remind us all every year why we keep coming back!"

Briana Jill Williams, Ph.D.
LSU Health Sciences Center
FY07 Peer Reviewer

"The unique aspect of the DOD PCRP, involving the consumer reviewers, helps maintain the focus of reviews on what is, more than interesting science, the fastest potential way forward to effective therapy."

Lisa Butterfield, Ph.D.
University of Pittsburgh
FY07 Peer Reviewer

"The PCRP review process was gratifying because many of the proposals permit investigators to do highly innovative research, and I believe many of them have a potential to really make a difference. The CDMRP process has truly been the stage for novel research."

Mohamed Khan, M.D., Ph.D.
FACRO, FAANM
Roswell Park Cancer Institute
FY07 Peer Reviewer

"The Prostate Cancer Research Program emphasizes innovation as a major funding criterion. By this mechanism nascent ideas gain fruition and, by constantly emphasizing specific funding mechanisms, newer interdisciplinary scientists are brought into the fold of cancer research. The most gratifying part is the inclusion of consumer reviewers—by considering the human element of the disease those ideas most suited for translational research are never lost."

Dr. Raj Tiwari, Ph.D.
New York Medical College
FY07 Peer Reviewer

Integration Panel Members

The PCRP IP is composed of 14 prominent scientists, clinicians, and consumer advocates with varied expertise in prostate cancer. IP members use their knowledge and expertise to develop and recommend an annual vision and investment strategy for the PCRP that focuses on scientific innovation, partnerships, training, and resource and clinical development. Additionally, IP members review proposals and suggest a broad-based research portfolio that best meets the program's vision and mission. Further details about the functions of the IP are summarized in Section I, Overview.

"The Department of Defense Prostate Cancer Research Program is rigorous and provides substantial support for innovative research to end death and suffering from prostate cancer. It is my honor to serve this fine group."

Howard R. Soule, Ph.D.
Prostate Cancer Foundation
FY08 Integration Panel Chair and
FY01-FY08 Integration
Panel Member

"Being a member of the Prostate Cancer Integration Panel is one of the most gratifying and important jobs that I can imagine. The work of the DOD, and the Integration Panel, in particular, gives me hope that one day my patients will get better care. I am glad to play a small role in this critical and strategic process."

Oliver Sartor, M.D.
Tulane Medical School
FY09 Integration Panel
Chair-Elect and FY06-FY09 Member

FY08 PCRP IP Members

Howard Soule, Ph.D. (Chair)
Prostate Cancer Foundation

A. Oliver Sartor, M.D. (Chair-Elect)
Tulane University School of Medicine

Timothy Ratliff, Ph.D. (Chair Emeritus)
Purdue Cancer Center

Cheryl Lee, M.D. (Executive Committee Member-at-Large)
University of Michigan

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

Philip Arlen, M.D.
National Cancer Institute

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

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

Natasha Kyprianou, Ph.D.
University of Kentucky

Donald Miller, M.D., Ph.D.
James Graham Brown Cancer Center, University of Louisville

Howard Sandler, M.D.
University of Michigan

Westley Sholes, M.P.A.
California Prostate Cancer Coalition

Donald Tindall, Ph.D.
Mayo Clinic

John Willey
National Prostate Cancer Coalition

"Prostate cancer is a disease unique in that its diagnosis does not immediately result in solutions but rather in questions based on the vagaries and diversity of the disease itself. For me, only research can begin to codify the structure of understanding that ultimately leads to informed, and effective, choice for the patient, his family, and their future. From my perspective, the DOD Prostate Cancer Research Program maintains a vision of patient-centered research that stresses results designed to reduce the disparities, suffering, and death caused by prostate cancer."

Virgil Simons
FY02-FY08 Integration
Panel Member

"IP members help the Prostate Cancer Research Program to reach its goals in the most effective way. I am honored to be a member and pleased to see the PCRP making such great progress in setting its goals and delivering the results needed to benefit thousands of prostate cancer patients."

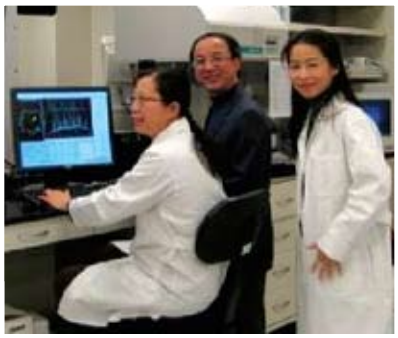
Shuk-mei Ho, Ph.D.
University of Cincinnati
FY08 Integration
Panel Member

"I have personally witnessed many examples of how the Prostate Cancer Research Program has provided critical support to young investigators who are just beginning their careers. Thus, new ideas and expertise have been brought to focus on prevention, detection, prognosis and treatment of prostate cancer. Future generations will greatly benefit from this research."

Donald J. Tindall, Ph.D.
Mayo Clinic
FY07-FY08 Integration
Panel Member

The Scientific Community

Prostate cancer researchers are, of course, vital partners in the PCRP. The program has funded nearly 1,500 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.



PCRP in the News...

PCRP's focus on funding innovative, high-risk, high-impact research has resulted in exciting breakthroughs that have impacted prostate cancer and resulted in media headlines. Samples of those headlines are:

- New, Non-Invasive Prostate Cancer Test Beats PSA in Detecting Prostate Cancer, Researchers Report. American Association for Cancer Research Press Release, February 1, 2008
- Study Suggests Adjusting PSA Scores for Obese Men or Cancers May Be Missed. DukeHealth.org, November 26, 2007
- New Genetic Variant Associated with Prostate Cancer in African Americans. The University of Chicago Medical Center Press, November 1, 2007
- Congressional Funding Has IMPaCT on Prostate Cancer Research. *Oncology Times*, October 10, 2007
- Hitting Advanced Prostate Gently May Improve Quality of Life. *MedPage Today*, September 17, 2007
- Income Not Race Cited as Reason for Prostate Mortality Excess in Minorities. *MedPage Today*, September 11, 2007
- Encourage Diet and Lifestyle Interventions in Low-Risk Prostate Cancer. *Medscape Medical News*, September 10, 2007
- Red Wine Compound Shown to Prevent Prostate Cancer. University of Alabama Media Relations, August 31, 2007
- Veterinary Scientists Explore Poultry Virus Approach to Human Prostate Cancer. *Virginia Tech News*, April 9, 2007
- Inflammation May Play Role in Metastasis of Prostate Cancer. University of California, San Diego Communications, March 19, 2007
- Experimental Agent Blocks Prostate Cancer in Mice. The Ohio State University Medical Center, May 22, 2008
- PSMA's Role in Aggressive Prostate Cancer. Nemours Biomedical Research, August 4, 2008
- Synthetic Molecules Advance PC Drug Development, The Ohio State University Medical Center, August 17, 2008

Breaking New Ground

Finding solutions to improve methods of prevention, early detection, treatment, and quality of care are the hallmarks of successful PCRP-funded investigators. Some PCRP-supported projects are reflected in the following five areas of development that will impact the lives of men with prostate cancer:

Therapeutics

- Phase III clinical trial of the Proteasome inhibitor, Bortezomib (PS-341, Velcade®)
- Phase I/II clinical trial of DNA-based vaccine targeting prostate acid phosphatase
- Phase I/II study of combination neoadjuvant hormone therapy and OGX-011 (clusterin antisense oligo) prior to radical prostatectomy
- Phase II clinical trial of anti-PSMA designer T cells in advanced prostate cancer
- Development of vaccine immunotherapy

Therapeutics in Combination

- Phase III clinical trial of the Proteasome inhibitor, Bortezomib (PS-341, Velcade) combined with chemotherapeutic agents for advanced prostate cancer
- Synergistic effects of gossypol and chemotherapeutics
- Chemoenhancement of radiation therapy
- Laser-activated vascular barrier disruption enhances tumor drug delivery
- Synergistic effects of calcitriol with ibuprofen, naproxen, or other NSAIDs in prostate cancer growth inhibition

Technologies

- 3T perfluorocarbon-filled endorectal magnetic resonance spectroscopic imaging of prostate
- Multichannel robotic system for concurrent delivery and immobilization of interstitial therapeutic agents
- Intraoperative ultrasound-fluoroscopy fusion enhances prostate brachytherapy quality
- Robotic image-targeted prostate cancer biopsy

Nutritional Inhibitors of Prostate Cancer

- Phenyl isothiocyanate inhibits prostate cancer cell growth
- Ketogenesis and ketogenic diet inhibit prostate cancer progression
- Metabolism in prostate cancer progression

Biomarkers

- TMPRSS2:ETS gene fusion as diagnostic and prognostic marker of prostate cancer
- 64Cu-DOTA-[Lys3]BBN and 18F-FB[Lys3]BBN as diagnostic marker for GRPR-positive prostate cancer
- Membrane cholesterol mediates prostate cancer survival pathways
- Ribosomal protein L19 as putative marker of prostate cancer
- 1q, 7q, 8p, and Xq are susceptible chromosomal regions for prostate cancer

Epidemiological

- Obesity as risk factor for aggressive prostate cancer
- High PSA levels in recurrent cancer after surgery as risk factor for prostate cancer death
- Estradiol and bisphenol A developmental exposure increases prostate cancer susceptibility
- Race and socioeconomic status underlie disparity in prostate cancer treatment between Caucasians and African Americans
- Two insulin-like growth factor gene variants strongly associated with prostate cancer risk among African Americans, Native Hawaiians, Japanese, Latinos, and Caucasians

PCRP Investigators in Focus

From Novice to Expert… Pushing the Leading Frontiers of Discovery and Innovation in Prostate Cancer

The PCRP is committed to fostering prostate cancer researchers who forge new paths toward conquering prostate cancer. Several investigators have received multiple awards from the PCRP, which has supported their research from early in their careers and as they have become established prostate cancer researchers. Drs. Douglas McNeel, Marianne Sadar, and Folakemi Odedina are outstanding examples of researchers who have prospered with PCRP funding.

Following the Yellow Brick Road to a Prostate Cancer Vaccine

Douglas McNeel, M.D., Ph.D.
University of Wisconsin-Madison

Priming the immune system so that it can see tumors as foreign bodies and mount an attack against them is the goal of therapeutic cancer vaccines. Developing such a cancer vaccine for prostate cancer has been the focus of Dr. Douglas McNeel's work since he started as a postdoctoral fellow at the University of Washington with an FY99 Postdoctoral Traineeship Award evaluating prostatic acid phosphatase (PAP) as a candidate antigen for the development of a DNA cancer vaccine. Dr. McNeel demonstrated that some patients with prostate cancer have low-level immune responses directed against PAP, suggesting that these might be enhanced by vaccines. Building on this work, Dr. McNeel received an FY02 New Investigator Award to develop improved vaccines and methods of vaccinating patients with prostate cancer. He established that key portions of PAP activate CD4 and CD8 T cells in the immune system and tested the safety and immunological efficacy of a DNA vaccine encoding PAP in a rodent model. No toxicities were observed, and high levels of PAP-specific helper T cells and CD8 T cells were generated. These findings led to an FY05 Clinical Trial Award (CTA) for a Phase I PAP DNA vaccine trial in prostate cancer patients with rising prostate-specific antigen (PSA) levels after surgery or radiation therapy (stage D0). Results to date indicate that the PAP DNA vaccine can elicit an IFN-gamma secreting CD8 T cell immune response to PAP. Also, several of the patients have experienced an extended PSA doubling time following completion of the immunization series. The success of this Phase I clinical trial has led to an FY07 CTA for a Phase II trial targeting the stage D0 patient population and comparing vaccination with the PAP DNA vaccine plus GM-CSF versus GM-CSF alone. The study will examine the effect of serial intradermal vaccinations with a PAP DNA vaccine plus GM-CSF on time to disease progression.

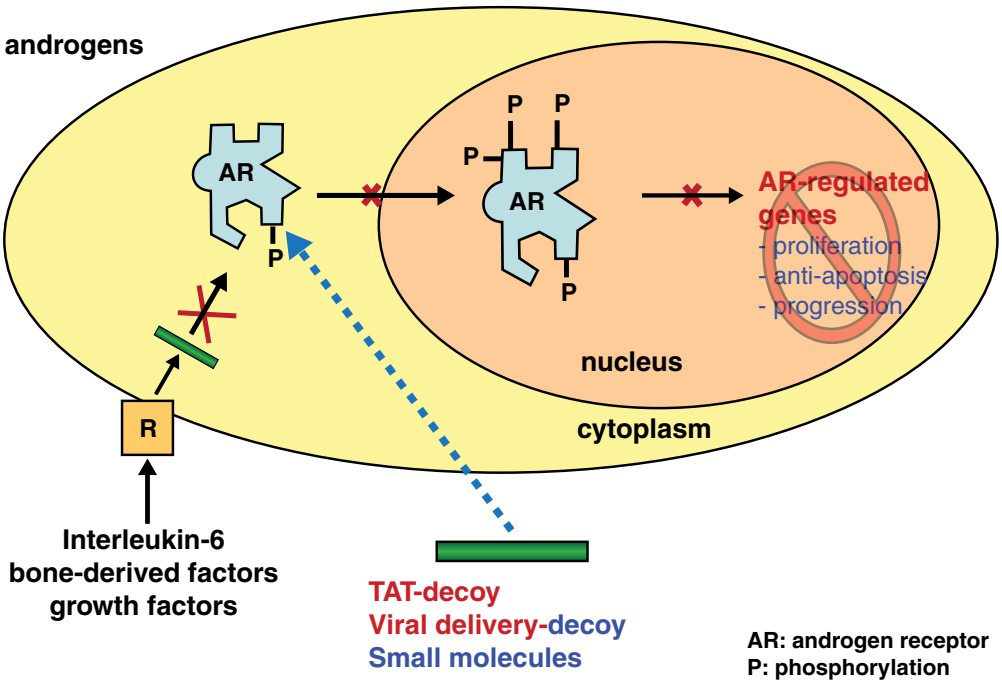
In addition to being a successful translational researcher fostered by the PCRP, Dr. McNeel has also helped mentor new investigators in the field of prostate cancer research, including Dr. Laura Johnson, recipient of an FY03 Postdoctoral Traineeship Award, and Mr. Brian Olson, recipient of an FY06 Predoctoral Traineeship Award.

Photo credit: Department of Medicine, University of Wisconsin School of Medicine and Public Health.

Blocking Prostate Cancer's Final Blow

Marianne Sadar, Ph.D.
British Columbia Cancer Agency

The growth of prostate cancer cells depends on androgens, which stimulate cell growth via the androgen receptor (AR). Androgen deprivation therapy for prostate cancer initially slows tumor growth. However, the AR can also be stimulated by cellular signals that are independent of androgens. These pathways can flourish to contribute to androgen-independent (or hormone refractory) disease, for which there are currently no effective therapies. To halt the progression of prostate cancer to the lethal stage, Dr. Marianne Sadar, of the British Columbia Cancer Agency, has focused her work on preventing androgen-independent activation of the AR. Beginning with an FY99 New Investigator Award and followed by Idea Development Awards in FY00, FY03, FY04, and FY06, the PCRP supported Dr. Sadar as she developed a novel in vivo model of androgen-independent prostate cancer. This model has enabled her to study the best approaches to blocking AR activation. She has discovered that this activation is dependent on key regions of the N-terminal domain (NTD) of the AR, which interacts with stimulatory proteins such as the cytokine interleukin-6. Dr. Sadar is now focused on developing peptides that can act as decoys for the AR NTD, blocking interaction with stimulatory molecules. With an FY06 Idea Development Award, Dr. Sadar is mapping the regions of the AR NTD more discretely to enable the development of smaller decoy molecules that will block tumor growth and delay or even prevent prostate cancer progression to androgen independence and lethality. In addition, Dr. Sadar has identified 23 marine sponge extracts that block activation of the AR and has shown that one of these compounds has the ability to reduce prostate cancer in animal models with no apparent systemic toxicity.

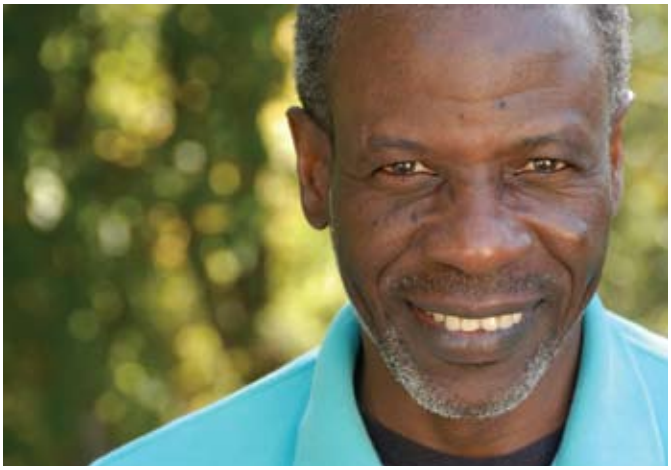


"Development of a novel class of antagonists that block activation of the amino-terminal domain of the androgen receptor for the treatment of prostate cancer"

Forging a New Path in Prostate Cancer Disparity Research for African American Men

Folakemi Odedina, Ph.D.
Florida Agriculture and Mechanical University (FAMU)

African American men are disproportionately affected by prostate cancer, compared to other ethnic groups (60 percent higher incidence compared to Caucasian men), and are 2.4 times more likely to die from the disease. Dr. Folakemi Odedina, recipient of a PCRP FY00 New Investigator Award (NIA), FY03 HBCU Collaborative Partnership Award (CPA), and FY06 Health Disparity Research Award (HDRA), has focused her investigations on prostate cancer disparities in disproportionately affected populations. Dr. Odedina's research seeks to delineate the causes that contribute to the high incidences of prostate cancer morbidity and mortality and to develop interventions that will alleviate the burden of prostate cancer in the African American population. The initial FY00 NIA supported the development of culturally sensitive questionnaires studying African American prostate cancer screening behavior, data collection, and analysis of study variables to validate the proposed theoretical framework.



Using the FY03 CPA, Dr. Odedina expanded her studies to address the needs of African American communities in Florida. Dr. Odedina partnered with Dr. Nagi Kumar and colleagues at the Moffitt Cancer Center to establish the Center for Minority Prostate Cancer Training and Research Program at FAMU. The Center's main objective is to eliminate the disparity in prostate cancer morbidity and mortality among African American men in Florida. To accomplish this goal, Dr. Odedina has employed a multifaceted approach to help researchers develop highly competitive grant proposals in prostate cancer disparities; increase the number of FAMU researchers trained in prostate cancer; and develop culturally appropriate and literacy-sensitive intervention tools that would effectively communicate information about prevention and screening to the targeted communities.

With the FY06 HDRA, Dr. Odedina has focused further investigations on how African American men make decisions about prostate cancer prevention and screening. These investigations involve development and validation of an Integrative Personal Model of Prostate Cancer Disparity, or PIPCaD. This model uses focus group discussions and survey methodology to ascertain how various African American cultural beliefs, values, and behaviors influence decision making.

With funds from the PCRP, Dr. Odedina has transformed herself from a new investigator in prostate cancer research to a leader in the study of prostate cancer health disparities and has made a substantive contribution to identifying the underlying causes of prostate cancer disparity in African American men.

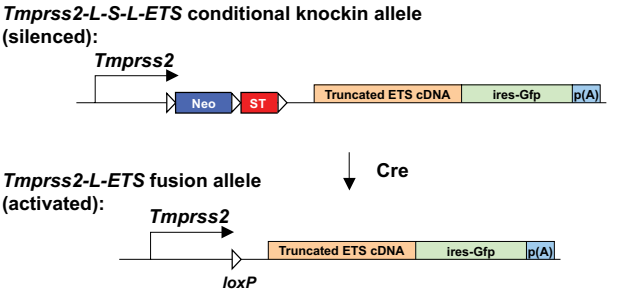
Exploiting Major Discoveries in Gene Fusion Toward Curing Prostate Cancer: TMPRSS2-ERG

In 2005, with support from multiple PCRP awards, Dr. Arul Chinnaiyan and colleagues at the University of Michigan discovered the gene fusion TMPRSS2–ERG (transmembrane protein, serine 2–ETS-related gene). Fusion of the androgen-regulated TMPRSS2 to ETS family transcription factor genes such as ERG or ETV1 (Ets variant gene 1) by chromosomal translocation events causes these genes to become androgen-responsive and upregulated in prostate cancer. This genetic lesion holds promise as both a diagnostic and prognostic marker for prostate cancer, perhaps providing an important supplement to the well-known marker PSA. Fusions of TMPRSS2 to ETS family genes such as ERG and ETV1 are found in 50-60 percent of prostate cancers. They have been postulated to play a role in prostate cancer development and may shed light on the mechanisms of prostate cancer initiation. Similar to Bcr-Abl, the well-known fusion gene product of the Philadelphia chromosome in chronic myelogenous leukemia, these fusion genes may also prove amenable to the development of therapeutic targets, expanding this paradigm to solid tumors. Several current awards supported by the PCRP are aimed at studying numerous aspects of this gene fusion.

Murine Model of TMPRSS2/ERG-/ETV1 Gene Fusion

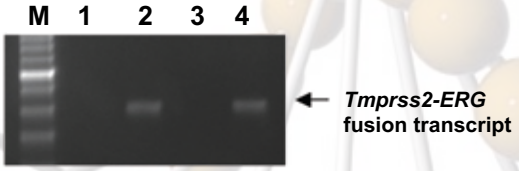
Stuart Orkin, M.D.
Children's Hospital, Boston

Dr. Stuart Orkin, recipient of an FY06 Idea Development Award, is developing a mouse model incorporating the TMPRSS2/ERG or /ETV1 gene fusion product. Dr. Orkin will utilize Cre/Lox technology for the conditional knock-in of alleles to express truncated human ERG or ETV at the mouse endogenous Tmprss2 locus. This novel murine model of the human disease state should significantly advance understanding of the mechanisms of pathogenesis of prostate cancer and provide an effective preclinical system to test novel therapies.



L: loxP; S or ST: stopper cassette; ETS: human ERG or ETV1; p(A): poly(A) signal.

Knockin alleles of both Tmprss2 and ERG generated by introducing loxP sites to permit Cre-mediated interchromosomal recombination



M: marker lane; 1, 3: WTs; 2, 4: *Tmprss2-ERG* knockins
Expression of the Tmprss2-ERF transcript

TMPRSS2-ETS Rearrangements in a Population-Based Prostate Cancer Cohort

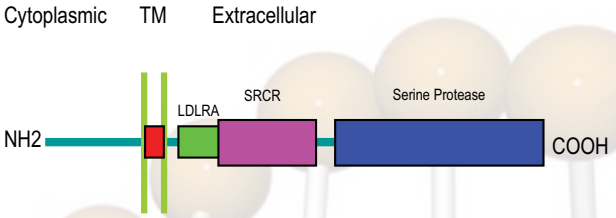
Sven Perner, M.D.
Weill Medical College at Cornell University

Dr. Sven Perner is investigating the frequency of TMPRSS2 and ERG/ETV1 gene rearrangements, which occur on chromosome 21, and the utility of this as a measure of invasive disease in a large clinical cohort. Dr. Perner, an FY06 Postdoctoral Prostate Cancer Training Award recipient, will access the Physicians Health Study collection of over 2,000 prostate cancer cases to determine the status of the TMPRSS2–ERG gene rearrangement and ERG transcription expression. This information will then be correlated with clinical parameters including androgen levels, development of metastases, and cancer-specific death. By correlating rearrangement status and expression levels with these disease outcomes, Dr. Perner hopes to determine whether these genomic assays can be employed as prognostic biomarkers that could be valuable indicators of the potential for advanced-stage disease.

Characterization of the TMPRSS2 Protease as a Modulator of Prostate Cancer Metastasis

Yu Sun, Ph.D.
Fred Hutchinson Cancer Research Center

While TMPRSS2 may be involved in the cleavage of extracellular matrix proteins to allow tumor cells to invade surrounding tissues, its functional role in invasion and metastasis has not been elucidated. Through an FY07 Postdoctoral Prostate Cancer Training Award, Dr. Yu Sun is proposing to investigate TMPRSS2 mechanisms and develop a mouse model of TMPRSS2 expression to help other researchers learn more about this potential therapeutic target. Dr. Sun will examine TMPRSS2 activity against barriers to invasion-like extracellular matrix components and signaling factors to focus on how it promotes invasion. He will also cross mice that overexpress TMPRSS2 with mice known to develop non-metastatic primary tumors to identify and confirm particular functions of the protein. This research has the potential to help researchers exploit TMPRSS2 activity to develop new therapies for prostate cancer patients.



TMPRSS2 protease linear structure (functional domains)

Biological Effects of TMPRSS2-ERG Fusion Isoform in Human Prostate Cancer

Jiaghua Wang, Ph.D.
Baylor College of Medicine

Dr. Jiaghua Wang is using an FY07 New Investigator Award to examine the biological effects of TMPRSS2-ERG in prostate epithelial cells and mouse models to further understand the role of this gene fusion in the initiation and progression of prostate cancer. Dr. Wang plans to examine the correlation between different forms of TMPRSS2-ERG gene fusions and lowered expression of the tumor suppressor genes Syk and MTSS1. Teasing apart the mechanism of altered gene expression in response to TMPRSS2-ERG will be an important step in discovering its role in prostate cancer.

Functional Characterization of TMPRSS2-ERG Using Protein Arrays

Larisa Litovchick, M.D., Ph.D.
Dana-Farber Cancer Institute

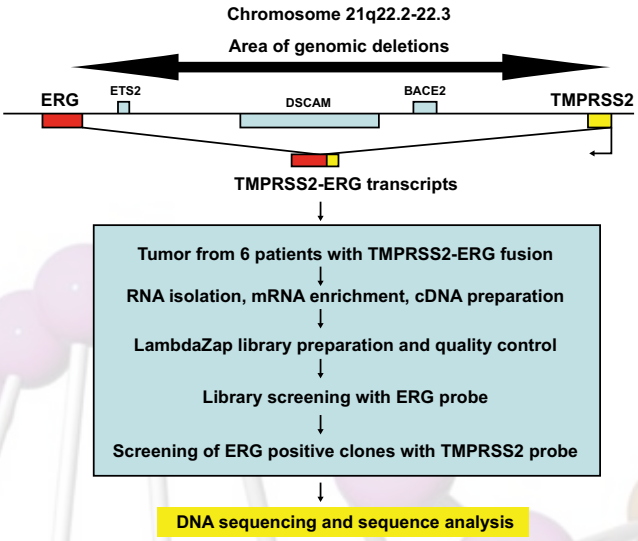
Dr. Larisa Litovchick is probing the molecular consequences of TMPRSS2-ERG gene fusions with support from an FY07 New Investigator Award. These gene fusions often result in aberrant expression of truncated forms of the transcription factor ERG. To gain insight into the mechanisms of how ERG contributes to prostate cancer, Dr. Litovchick is using newly developed proteomics and genomics tools to identify proteins that interact with truncated ERG and to discover genes that are targeted by the ERG protein complex. Once identified, further studies are designed to elucidate the roles of molecules found within the ERG complex and their contribution to aberrant gene expression in prostate cancer.

Structure and Function of the Splice Variants of TMPRSS2-ERG, a Prevalent Genomic Alteration in Prostate Cancer

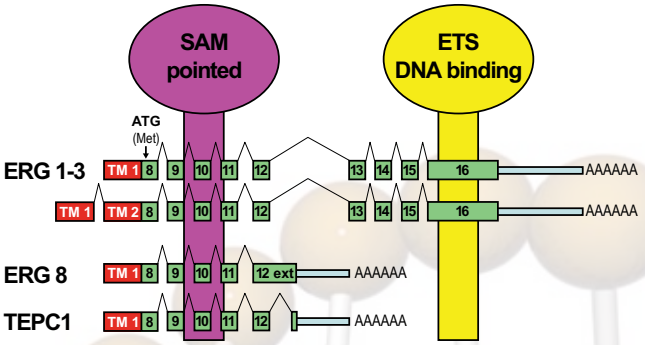
Shiv Srivastava, Ph.D.
Uniformed Services University of the Health Sciences
(L-R – Drs. Taduru Sreenath, Albert Dobi, Shiv Srivastava, Ying Hu, Gyorgy Petrovics)

Dr. Shiv Srivastava, along with co-Principal Investigators Drs. Albert Dobi and Taduru Sreenath, are recipients of an FY07 Idea Development Award. These scientists plan to examine the expression and function of the major TMPRSS2-ERG splice variants in prostate cancer cells. Despite the large body of data on the TMPRSS2-ERG fusion junctions, virtually nothing is known about the relative abundance or function of full-length TMPRSS2-ERG transcripts expressed in prostate tumors. Recent results from this group show that higher levels of the shorter TMPRSS2-ERG transcripts lacking the Ets domain (ERG 8 and TEPC) are present in prostate tumors in addition to the longer TMPRSS2-ERG transcripts (ERG 1-3). Evaluations of clinico-pathologic association and functional contribution of the specific TMPRSS2-ERG splice variants are needed in light of frequent ERG overexpression due to TMPRSS2-ERG fusion in prostate cancer. Dr. Srivastava and colleagues hope to establish function and correlation of these fusion gene products with the severity of the prostate cancer phenotype and, in the process, develop more precise prognostic tools and therapeutic targets.

Strategy for identifying full-length transcripts of the ERG locus in human prostate tumor specimens



Full-length ERG transcript types in prostate tumor cells



Targeting an Important Pathway in Prostate Cancer Progression: Signal Transducer and Activators of Transcription (STAT) and the Androgen Receptor (AR)

The STAT family of transcription factors is composed of seven members (STAT1-4, 5a, 5b, and 6), and their protein expression has been found in various cancer malignancies. Activation of STAT occurs via cytokine and growth factor signaling. Activated STAT dimerize, forming multiprotein complexes that translocate to the nucleus to induce expression of genes involved in proliferation, differentiation, and survival. Recent studies have shown that STAT5 is important in prostate cancer cell viability, is highly expressed in high-grade human prostate cancers, and is a marker for disease recurrence. Importantly, STAT5 and the AR were found to be involved in a feedback loop in prostate cancer cells in which activated STAT5 enhances AR activity and AR in turn increases the activity of STAT5. Furthermore, the interaction of STAT5 and liganded AR increases nuclear translocation of both proteins to increase expression of target genes involved in proliferation. These observations are important in understanding the mechanism underlying hormone-independent prostate cancer progression and points to new avenues for targeted therapy. Several PCRP investigators are working to unravel the mechanism of STAT5 and AR action in prostate cancer progression.

Therapeutic Target Proteins for Prostate Cancer

Marja Nevalainen, M.D., Ph.D.
Thomas Jefferson University

Dr. Marja Nevalainen of Thomas Jefferson University is investigating the transcription factor Stat5 as a potential therapeutic target or biomarker for androgen-independent prostate cancer. Dr. Nevalainen received an FY04 New Investigator Award to conduct preliminary work showing that Stat5 was important for survival of prostate cancer cells in culture and in mouse tumor models. Examination of human prostate specimens also showed that Stat5 was strongly expressed in high-grade tumors, particularly those refractory to hormone deprivation therapy. Dr. Nevalainen is following up these findings with an FY06 Idea Development Award to investigate the functional interaction between Stat5 and the androgen receptor in prostate cancer. Dr. Nevalainen's work is at the forefront of research for this exciting new potential anti-cancer target.

Targeting the Tumor Suppressor STAT5B

Alexander Kazansky, Ph.D.
Baylor College of Medicine

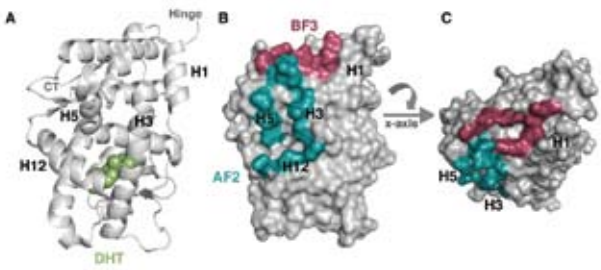
Dr. Alexander Kazansky, an FY02 New Investigator Award recipient, examined the molecular mechanisms surrounding the transcription factor STAT5 and, more importantly, the anti-cancer activity of a naturally occuring inhibitory dominant negative truncated variant, STAT5B. Dr. Kazansky's experiments showed that while STAT5B is important for aggressive growth and invasiveness in prostate cancer cells, expression of the STAT5B variant significantly reduced these carcinogenic properties. Dr. Kazansky then worked to express these proteins in TRAMP mice prone to develop prostate tumors and found that mice with the STAT5B variant had significantly reduced tumor growth compared to their STAT5-expressing counterparts. Dr. Kazansky is taking the next step by patenting a cell-based high-throughput screening assay for identifying new anti-cancer agents that switch proto-oncogenic STAT5B to the tumor suppressor form STAT5B.

Forging New Avenues in Androgen Receptor Therapy

Inhibitors for Androgen Receptor Activation

Robert Fletterick, Ph.D., University of California, San Francisco

The androgen receptor (AR) is known to be a central factor in the development of prostate cancer and drives early disease progression with endogenous androgens. A chemical that blocks AR activity would prevent prostate cancer development regardless of whether the receptor requires androgen activation. Dr. Robert Fletterick, recipient of an FY05 Idea Development Award, is using X–ray crystallography to visualize receptor sites on the AR, focusing on hormone-driven activation function 2 (AF-2) and, as a result, has found a novel allosteric site called BF-3. Dr. Fletterick is currently screening for compounds that show strong binding to these areas and antagonize coactivator binding, and he has found preliminary candidates in a thyroid hormone analog and aspirin-related compounds. Cellular assays show that these compounds inhibit transcription, and they could develop into promising prostate cancer therapeutics.

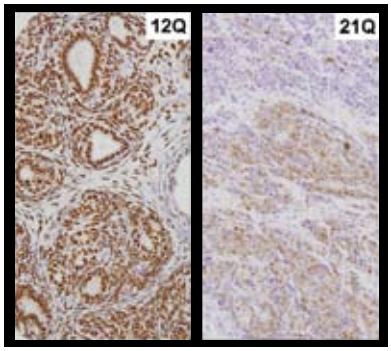


Location of AF-2 and BF-3. A. Schematic of AR LBD showing the location of the DHT, key AF-2 helices (3,5, and 12) and H1. B. Space filling model of AR LBD showing key residues in AF-2 (cyan) and BF-3 (red). C. As in Fig. B, but rotated 90° to reveal BF-3.

Humanized Androgen Receptor Mice: A Genetic Model for Differential Response to Prostate Cancer Therapy

Diane Robins, Ph.D., University of Michigan

Small differences in the length of the polyglutamine tract, encoded by CAG repeats, in the androgen receptor (AR) are thought to contribute to variable AR signaling activity in human prostate cancer initiation and progression. A complete understanding of these allelic differences may uncover interacting signaling pathways that could provide new insights into prostate cancer progression and help predict response to therapy. FY07 Idea Development Award recipient Dr. Diane Robins plans to investigate the small differences in AR activity caused by variations in the N-terminal polyglutamine tract in a "humanized androgen receptor" knock-in mouse model that mimics AR variations found in humans. The defined genetic background of the mouse alleviates some of the genetic complexities associated with human studies, thereby allowing investigation of these subtle differences in AR signaling. Additionally, study of these variations within the context of a conditional PTEN knockout (phosphatase and tensin homolog deleted on chromosome 10) more closely resembles the study of human disease and will help to identify factors important in the response to therapy.



End-stage mouse prostate tumors. Tissue array of short tract AR (12Q) well-differentiated tumor phenotype and median length AR (21Q) with poorly differentiated phenotype.

Photo credit: Photo courtesy of U-M Photo Services, Martin Vloet

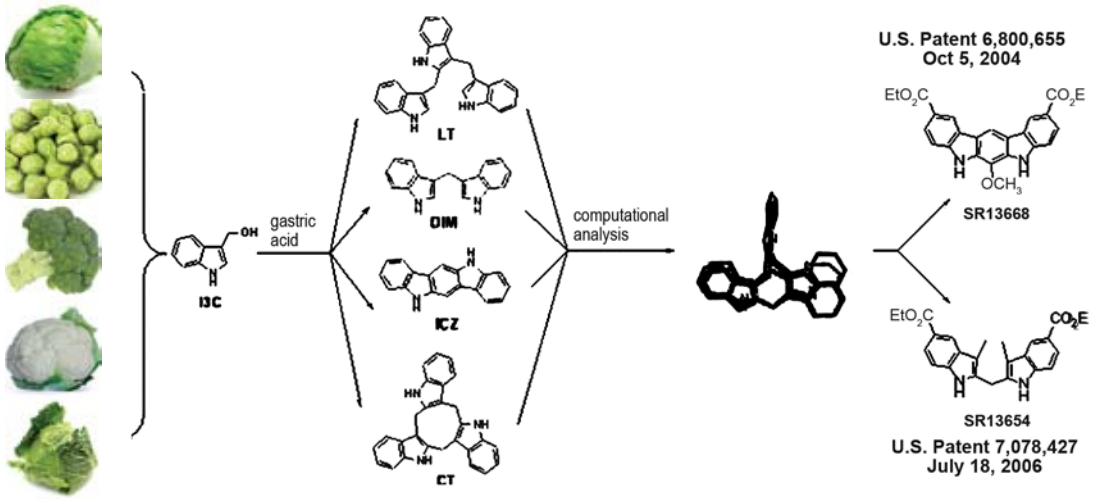
Forging New Paths by Combining Novel Therapies to Increase Clinical Benefit

To achieve the greatest impact in treating prostate cancer, various combinations of therapy are being investigated by PCRP researchers. Advancement in understanding the molecular basis of prostate cancer has allowed the development of specific therapeutic strategies to target critical pathways and mechanisms that contribute to tumor development and metastases.

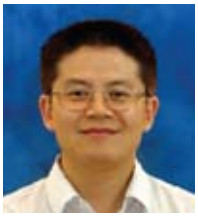
Novel Dietary Indole Analogs for Prostate Cancer Treatment: Managing Prostate Cancer with Quality of Life Considerations

Ling Jong, Ph.D.
SRI International

FY02 Idea Development Award recipient
Dr. Ling Jong, of SRI International, has evaluated the therapeutic efficacy of two analogs (developed from the dietary phytochemical and indole-3-carbinol found in cruciferous vegetables) against prostate cancer in both in vitro and in vivo models. In both androgen-sensitive and -insensitive prostate cancer cells, SR13654 inhibited survivin expression and induced apoptosis by altering src phosphorylation activation, resulting in epidermal growth factor receptor degradation. When administered orally, SR13654 in combination with paclitaxel potentiates antitumor activity. In vitro studies in PC-3 cells showed that SR13668 exerts its antitumor effect by blocking Akt activation and, consequently, its anti-apoptotic downstream effectors. SR13668 showed effective antitumor activity in a prostate tumor xenograft model, and this activity was further enhanced when combined with paclitaxel. These results suggest that development of the indole analogs for use both as single agents and in combination with paclitaxel may offer a promising strategy for the treatment of androgen-sensitive and -insensitive prostate cancer. Dr. Jong has begun preclinical testing of SR13654 and SR13668 as new therapies against prostate cancer.



SR13654 and SR13668 were developed from the naturally occurring anticancer agent indole-3 carbinol using rational drug design aimed at maximizing drug potency while minimizing structural changes to ensure that the analogs retain the safe and unique biological profiles of the dietary compounds.



Increasing the Effectiveness of Photodynamic Therapy

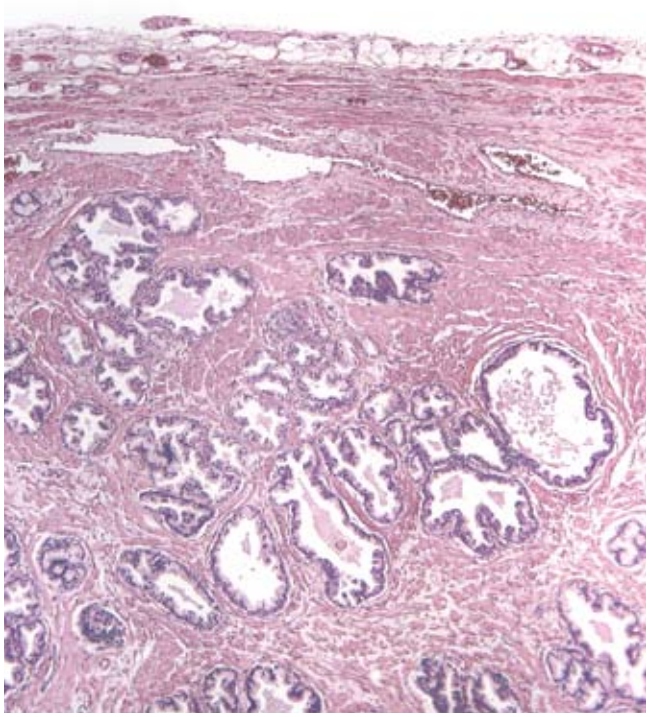
Bin Chen, Ph.D.
University of the Sciences in Philadelphia

Cancer therapies run the risk of inciting tissue morbidities in normal structures and can result in reduced quality of life for patients undergoing conventional treatments. To mitigate these effects, Dr. Bin Chen has been using an FY03 Postdoctoral Traineeship Award and an FY05 New Investigator Award to develop the next generation of photodynamic therapies (PDT) for localized prostate cancer. This therapy takes advantage of special molecules that respond to specific wavelengths of light to generate cytotoxic oxygen radicals that kill prostate cancer cells. As a postdoctoral researcher, Dr. Chen studied the established PDT agent verteporfin and discovered that its pharmacological properties could be modified to target either a localized tumor or its supporting vasculature. Rapid illumination following verteporfin treatment resulted in a preferential targeting of the tumor vasculature as compared to the tumor itself. Longer periods of drug circulation before irradiation resulted in targeting of the tumor directly. As a new investigator, Dr. Chen recently discovered that targeting the vasculature of tumors with verteporfin can be enhanced with the antineoplastic agent Avastin to synergistically treat localized prostate tumors.

Combining Therapies to Inhibit Prostate Tumor Growth

Bruce M. Fenton, Ph.D.
University of Rochester

Radiotherapy is a common treatment used to kill solid tumor cancer cells, but its effectiveness has often proven to be limited. In addition, while anti-angiogenic agents offer immense therapeutic potential, clinical trials have demonstrated only limited success. Dr. Bruce Fenton, an FY04 Idea Development Award recipient from the University of Rochester, was recently the first to demonstrate that a combination of fractionated radiation and the receptor tyrosine kinase inhibitor AG-013736 could potentiate changes in tumor vascular maturity and function. Combination therapy studies in mice have revealed increased endothelial and tumor cell apoptosis, reduced tumor growth, and increased tumor hypoxia in PC-3 and DU145 human prostate xenografts compared to single therapy. Loosening of pericyte-vessel and pericyte-basement membrane attachments was also observed in these tumor models following combination therapy. Dr. Fenton is now focused on refining these observations by varying treatment schedules and by improving tumor models. Continued research will guide future combination therapy strategies for prostate cancer treatment.



Diet: Eat Your Way to a Healthier Prostate

Controlling and preventing prostate cancer through nutrition and a healthy lifestyle are the focus of several PCRP researchers. These investigators are exploring the risk of prostate cancer that may be associated with the foods we consume and certain health behaviors. Research in nutrition and lifestyle behaviors helps clinicians develop intervention strategies and helps in identifying new methods of detecting early prostate cancer. Additionally, various PCRP-funded scientists are identifying compounds in food that serve as anti-cancer agents that could ultimately translate into new areas of therapy.

Chemoprevention of Prostate Cancer by Phenethyl Isothiocyanate (PEITC)

J. W. Chiao, Ph.D.
New York Medical College

While it is well supported by research that eating cruciferous vegetables (i.e., broccoli, cauliflower, brussel sprouts, cabbage, and more) is a natural way to reduce your chances of getting prostate cancer, neither the dietary ingredient(s) nor the mechanism(s) by which they work have been identified. Dr. Chiao and colleagues at New York Medical College and Dr. L. G. Wang at New York University have used an FY02 Idea Development Award to study the role of PEITC, a compound found in large quantities in watercress and other cruciferous vegetables, to decipher how it acts as a chemopreventive agent. The investigators have determined that PEITC mediates regulation at the epigenetic level; it inhibits the growth of prostate cancer cells by upregulation of the cell cycle regulator p21 and downregulation of the transcription factor Sp1, a regulator of androgen receptor (AR) expression. Lower levels of AR expression reduce testosterone activity, leading to attenuation of prostate cancer cell growth. PEITC was also shown to be a dual inhibitor of the enzyme histone deacetylases and of abnormal CpG island methylation. The results of this study indicate the potential for isothiocyanates to be developed as novel prostate cancer therapeutics.

The Use of Omega-3 Fatty Acids to Slow Prostate Cancer Progression

Uddhav Kelavkar, Ph.D.
Beth Pflug, Ph.D.
Thomas Conrads, Ph.D.
University of Pittsburgh

Funding from an FY07 Synergistic Idea Development Award allowed Principal Investigators Thomas Conrads, Beth Pflug, and Uddhav Kelavkar, at the University of Pittsburgh, to test the hypothesis that a diet rich in omega-3 polyunsaturated fatty acids (PUFAs) will slow prostate tumor growth. Dietary sources high in PUFAs include cold-water fish, olive oil, and flaxseed. Tissues will be harvested from two groups of men, one consuming omega-3 fatty acids and the other consuming no PUFAs, prior to undergoing a radical prostatectomy. State-of-the-art molecular analysis technologies, including proteomic and metabolomics analyses of the tissue, along with metabolomic blood profiling and dietary record analysis, will be used to study the effect of omega–3 fatty acids on prostate tumor growth. If successful, this chemopreventive agent would be immediately available and targeted toward men who are unable to undergo surgery due to advanced age and/or poor health.

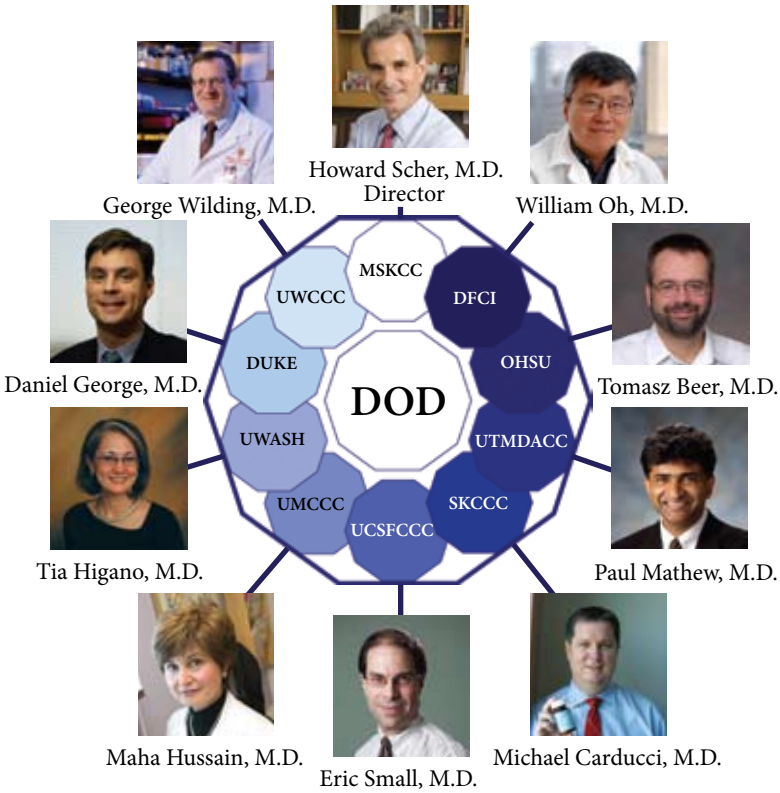
No-Carbohydrate Diet Delays Prostate Tumor Growth in Xenograft Mouse Model

Stephen J. Freedland, M.D.
Duke University

FY03 Health Disparity Training Prostate Scholar Award recipient Dr. Stephen Freedland of Duke University is investigating the association of obesity and cancer. Obesity is more common among black men and has been linked with increased risk of prostate cancer death. The underlying reasons that obesity may lead to more aggressive cancers remain unclear; however, Dr. Freedland hypothesized that a no-carbohydrate ketogenic diet (NCKD) would delay prostate cancer growth by preventing carbohydrate intake and thus lowering insulin levels. In vivo studies in SCID mice demonstrated that a NCKD diet lowers tumor burden compared to mice on a Western diet but is similar to mice on a low-fat diet. Mice fed the NCKD showed increased IGFBP-3 serum levels, prolonged survival, significantly reduced hepatic fatty infiltrate, and lower ratio of IGF-1:IGFBP-3. Further investigations into the mechanistic action of NCKD in prostate cancer cell growth and the relationship between obesity and aggressive prostate cancer are currently under way.

Partnerships That Forge New Paths Toward the Cure

The PCRP is committed to supporting the collaborations among investigators from multiple institutions and disciplines to accelerate the process of eradicating prostate cancer. Toward this effort, the PCRP has funded the work of several unique consortia to conduct research studies with a broad scope around central ideas or questions. Additionally, the PCRP is encouraging synergy among investigators of disparate disciplines focused on a single problem in prostate cancer that requires the unique expertise of each scientist. The findings from these collaborative investigations will be far-reaching and will significantly impact prostate cancer diagnosis and treatment outcomes.



MSKCC -	Memorial Sloan-Kettering Cancer Center
DFCI -	Dana-Farber Cancer Institute/Harvard Cancer Center
OHSU -	Oregon Health & Science University
UTMDACC -	University of Texas M.D. Anderson Cancer Center
SKCCC -	Sidney Kimmel Clinical Cancer Center/ Johns Hopkins
UCSFCCC -	University of California, San Francisco Clinical Cancer Center
UMCCC -	University of Michigan Clinical Cancer Center
UWASH -	University of Washington, Seattle
DUKE -	Duke University Medical Center
UWCCC -	University of Wisconsin Clinical Cancer Center
DOD -	Department of Defense

Clinical Consortium

Howard Scher, M.D.
Memorial Sloan-Kettering Cancer Center

The Prostate Cancer Clinical Trials Consortium is a major multi-institutional research effort designed to rapidly develop and execute Phase I/II and Phase II clinical trials in prostate cancer. Initiated by the PCRP in 2005 through a Clinical Consortium Award, this network of 10 medical centers across the United States, coordinated through the Memorial Sloan-Kettering Cancer Center, is expediting clinical trials with promising new therapeutic agents and chemopreventives that will improve outcomes for prostate cancer patients. Through this award, the Consortium supports a framework for drug development by establishing infrastructure to facilitate collaborations among prostate cancer investigators for clinical trials and provides critical resources such as personnel and information technology infrastructure—gaps often difficult for a single institution to fill. Currently, there are 35 trials in progress across the Consortium investigating a variety of anti-cancer therapies that could revolutionize prostate cancer treatment.

Racial Differences in Prostate Cancer: Influence of Health Care and Host and Tumor Biology

James Mohler, M.D., RPCI (Co-Director)
Jeannette Bensen, Ph.D., UNC-CH (Co-Director)

One of the PCRP's largest joint efforts is exploring racial differences affecting prostate cancer aggressiveness through a collaboration between the University of North Carolina at Chapel Hill (UNC-CH), the Louisiana State University Health Science Center (LSUHSC), and the Roswell Park Cancer Institute (RPCI) funded under the FY02 Prostate Cancer Project (PCaP) Consortium Award. The PCaP Consortium is led by a team of researchers including Co-Directors Dr. James Mohler at RPCI and Dr. Jeannette Bensen at UNC-CH, as well as Co-Investigators Dr. Elizabeth Fontham and Dr. Joseph Su at LSUHSC; Dr. Jane Schroeder, Dr. Merle Mishel, and Dr. Paul Godley at UNC-CH; and Dr. Gary Smith at RPCI. PCaP is focused on determining the factors that contribute to disproportionately higher death rates from prostate cancer in African American versus Caucasian men. The study includes 2,000 men with newly diagnosed prostate cancer: 1,000 from North Carolina and 1,000 from Louisiana. Of the 1,000 men in each state, half are African American and half are Caucasian. Men participating in this study are assessed for various factors including (1) access to and interaction with the health care system, (2) diet and genetics, and (3) characteristics of the tumor. These various factors will be evaluated using information gathered from research questionnaires, medical records, and biological specimens provided by each study participant.

After LSU was ravaged by Hurricane Katrina in 2005, the team suffered significant losses, including homes, office space, study participants, and advisors. RPCI, UNC-CH, and LSUHSC investigators, with support from the PCRP, quickly developed a post-Katrina plan, providing a 1-year recovery period for the LSUHSC team. During this period, LSUHSC investigators contacted previous study participants, collected tumor blocks, and abstracted medical records. To facilitate recruitment, both Louisiana and North Carolina expanded their recruitment areas, with Louisiana adding a number of parishes to the north and west, including Baton Rouge.

The PCaP team overcame almost insurmountable obstacles to resume the study, exceeding initial recruitment and in-home visit goals of 145 men over the first 6 months. Since then, UNC-CH has completed North Carolina recruitment, and Louisiana continues recruitment with a target completion date in mid-2009. Because of the strong dedication of these scientists and the support of the PCRP, the PCaP Consortium is poised to become one of the first comprehensive studies of racial disparity in prostate cancer, facilitating the identification of factors that contribute to its severity in African American men.

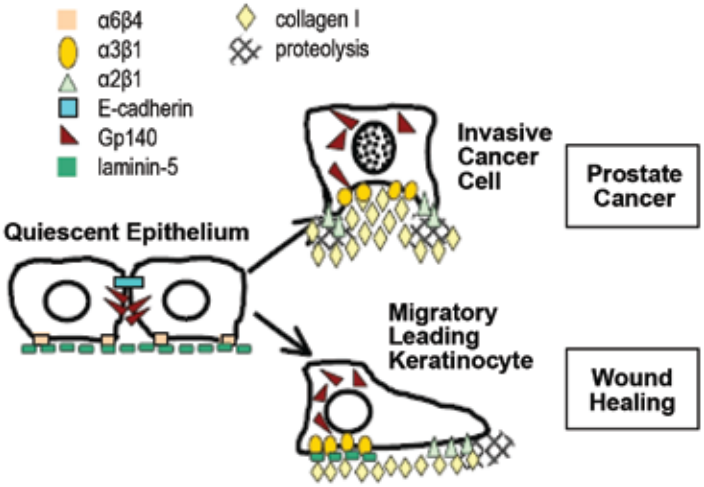
North Carolina-Louisiana PCaP Prostate Cancer Project

The PCaP Consortium consists of the University of North Carolina Chapel Hill and Louisiana State University

Gp140/CDCPI in the Development of Prostate Cancer Metastasis

William Carter, Ph.D.
Beatrice Knudsen, M.D., Ph.D.
Fred Hutchinson Cancer Research Center

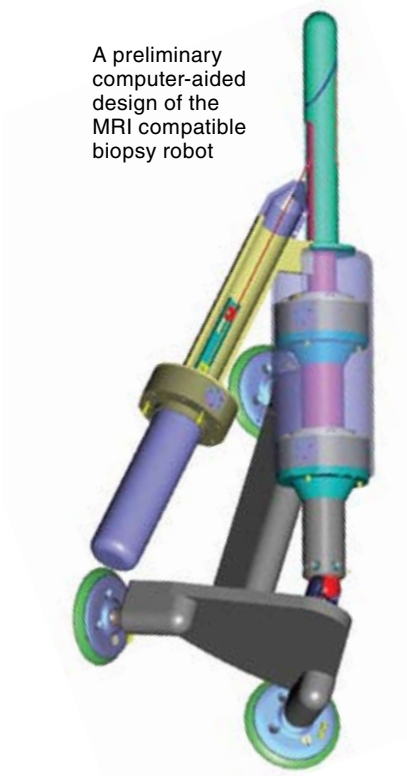
Dr. William Carter, an expert in keratinocyte biology and wound healing, discovered the function of transmembrane receptor, Gp140, as a regulator of the crosstalk between cell-cell and cell-substratum adhesions in keratinocytes. FY07 Synergistic Idea Development Award recipient Dr. Beatrice Knudsen, a molecular pathologist at the Fred Hutchinson Cancer Research Center, teamed up with colleague Dr. Carter to investigate the role of Gp140 in prostate cancer and the potential of Gp140 as a biomarker of prostate cancer metastasis. In particular, Gp140 appears to promote cancer cell invasion and the survival of metastasizing cells. Therefore, inhibition or downregulation of Gp140 with nontoxic, pharmacologic agents may halt the development of prostate cancer metastasis. Bringing the epithelial biology discovered in keratinocytes to prostate cancer invasion and metastasis through the complementary experiences of these two researchers will potentially change our view of how cancer cells metastasize and provide fresh avenues to develop treatments against the development and progression of prostate cancer metastasis.



Robot for Image-Targeted Prostate Cancer Biopsy

Dan Stoianovici, Ph.D.
Johns Hopkins University
Hedvig Hricak, Ph.D.
Memorial Sloan-Kettering Cancer Center

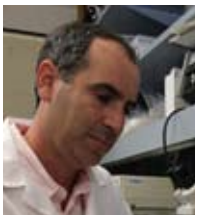
Prostate cancer recurrence is often the result of failed therapeutic outcomes due to the complex methods used to determine disease aggressiveness, extent of tumor, and accurate tumor biopsy. Targeting the tumor using more accurate methods may help in early detection and diagnosis of prostate cancer, leading to improved management outcomes. Drs. Dan Stoianovici and Hedvig Hricak, FY07 PCRP Synergistic Idea Development Award recipients, are developing a robotic instrument for image-guided biopsy of prostate cancer. A combination of magnetic resonance imaging (MRI) and new robotic technology will be used to target prostate cancer biopsy, thereby allowing accurate tissue sampling throughout the gland to better characterize the state of the disease.



A preliminary computer-aided design of the MRI compatible biopsy robot

Translational Research to Better Forge the Path from Bench to Bedside

The transition of promising lead agents (a biological or chemical therapeutic, imaging agent, or preventive agent that has potential clinical application) from the laboratory bench to the patient is a large hurdle in the path toward a cure for prostate cancer. The Laboratory Clinical Transition Award: Stage I was developed as the first step in a three-stage process toward the development of an agent that is ready for human clinical trials.



Development of PSCA-Targeted Minibodies for Imaging of Prostate Cancer

Robert Reiter, M.D.
University of California, Los Angeles

Dr. Robert Reiter, an FY07 Laboratory-Clinical Transition Award: Stage I recipient, is investigating the use of radiolabeled prostate stem cell antigen (PSCA) antibody fragment to target prostate cancer cells for molecular imaging using single photon computed tomography and positron emission tomography in animal models. Dr. Reiter has shown that high levels of PSCA expressed on the surface of prostate cancer cells are an indication of loss of the tumor suppressor gene PTEN and that antibodies against PSCA reduce cancer cell growth and metastasis without eliciting an immune response. The high specificity and sensitivity of PSCA antibody is also important in developing new imaging techniques for detecting metastatic prostate cancer. Ultimately, if successful, the PSCA antibody fragments will undergo clinical evaluation in Phase I trials.

Production and Characterization of a Novel OX40 Ligand for Clinical Use

Andrew Weinberg, Ph.D.
Providence Portland Medical Center

Prostate cancer cells have evolved ways to avoid destruction by the immune system resulting in cancer progression. Targeting cancer cell death by the immune system continues to be a goal of many investigators. Dr. Andrew Weinberg, an FY07 Laboratory-Clinical Transition Award: Stage I recipient, has developed a human OX40 agonist, OX40L:ILZ:Ig (monoclonal antibody), which has been shown in vitro to bind human OX40 protein on white blood cells and activate the cells. Activation of the white blood cells elicits an immune response, which leads to the destruction of cancer cells. Dr. Weinberg will optimize production of a humanized OX40 antibody and test its safety and efficacy in animals prior to beginning Phase I/II study in men with prostate cancer with the goal of developing a molecule for therapeutic use in the clinic.

Overcoming Health Disparity… Addressing the Barriers

Since its inception, the PCRP has been committed to supporting the best research focused on prostate cancer disparity across various populations and demographic characteristics. Since African American men are disproportionately affected by prostate cancer, with higher incidences of morbidity and mortality compared to all other ethnic groups, special emphasis has been placed on studying this community. PCRP researchers from all disciplines have been investigating the underlying factors that contribute to this health disparity to develop new ways of preventing, detecting, and treating prostate cancer.

Differential Expression of Zinc Transporters in Prostate Cancer Epithelia of Racial Groups

Omar Bagasra, M.D., Ph.D.
Claflin University
Andre Kajdacsy-Balla, M.D., Ph.D.
University of Illinois

Drs. Omar Bagasra and Andre Kajdacsy-Balla, through funding from an FY07 Synergistic Idea Development Award, will use their combined expertise in molecular biology and pathology to investigate expression levels of four zinc transporters and intracellular zinc levels of African American and European men. The investigators hypothesize that the low expression levels of zinc transporters in African Americans is the result of a compensatory mechanism developed to offset the high toxic levels of the mineral-rich environment present on the African continent. Drs. Bagasra and Kajdacsy-Balla will use prostate tissue samples, gene profile analysis, polymerase chain reactions, and immunohistochemistry to identify genes that are differentially expressed between the African American and European men.

Prostate Cancer in African American Men: Serum Biomarkers for Early Detection Using Nanoparticles

Catherine Phelan, M.D., Ph.D.
Moffitt Cancer Center

Dr. Catherine Phelan, recipient of an FY05 New Investigator Award, plans to use quantum dots—photoluminescent nanoparticles conjugated to specific antibodies—to detect biomarkers at extremely low levels in blood serum of African Americans with prostate cancer. To achieve this goal, a prostate cancer case control study of blood samples from 100 African American men and 200 ethnically matched healthy men (control) will be examined. As these differences may be subtle, Dr. Phelan will engineer a multi-biomarker panel (including PSA [total], Kallikrein 2, Kallikrein 14, Osteoprotegerin, p53, Caveolin-1, and Interleukin-6) that will provide high sensitivity and specificity so that it can be applied as a screening test. It is hoped that this screening will be rapidly translated into public benefit by improving early detection of prostate cancer, thereby decreasing morbidity and mortality among African American men.

Admixture Mapping for Prostate Cancer-Related Genes in African Americans

Rick Kittles, Ph.D.
The University of Chicago

The African American community has the highest incidence and mortality of prostate cancer of any population in the United States. Dr. Rick Kittles at The University of Chicago, recipient of an FY06 Idea Development Award, is investigating the potential for a relationship between genetic ancestry and susceptibility to prostate cancer among African American men. Dr. Kittles will employ a genetic mapping approach called admixture mapping to map genes linked to prostate cancer. Admixture mapping takes advantage of the genetic modifications created when previously isolated populations (i.e., Africans and Europeans) exchange genes over time. Over 1,500 ancestry informative markers (single nucleotide mutations) have been made available from the recently published admixture map for African Americans, and Dr. Kittles will scan a sample of 1,600 African American men with prostate cancer and those who are cancer-free. The results of the scans will be analyzed with advanced statistical software to correlate the markers to the incidence and progression of prostate cancer. This study will be important to better understand the underlying genetic profile of prostate cancer and will be useful for the optimization of prevention and treatment programs for the at-risk population of African American men.

Training the Next Generation of Prostate Cancer Investigators

The PCRP recognizes that future advancement in prostate cancer research requires a cadre of highly trained knowledgeable basic and clinical investigators. These investigators must be grounded in the biology of prostate cancer and must possess skill sets that enable them to address any question in prostate cancer research. The PCRP has invested in the training of some of the most promising young researchers and programs to ensure future generations of scientists will be available to address emerging needs of the prostate cancer community.

Increasing Minority Biomedical Researchers in Prostate Cancer Research Through Academic Partnerships

Jamboor K. Vishwanatha, Ph.D.
University of North Texas Health Science Center

The PCRP's Collaborative Undergraduate Historically Black Colleges and Universities (HBCU) Student Summer Training Program Award, introduced in 2004, encourages HBCU students to pursue careers in prostate cancer research. So far more than 60 HBCU students have received hands-on mentored training and education not possible at their home institution. One such successful program is being conducted by Dr. Jamboor K. Vishwanatha at the University of North Texas Health Science Center (students from his program are pictured above). Five students participated in this 10-week summer program in 2007 and had the opportunity to work in the laboratory with a prostate cancer scientist. The students also attended weekly seminars, including sessions on stem cells, cancer, and forensic genetics. At the end of the summer, each student prepared an abstract of his or her work and presented it at a student research symposium. Students have been so inspired by their summer training experiences that many have expressed their commitment to pursue studies in prostate cancer research.

The Role of Lymphangiogenesis in Orthotopic Prostatic Tumor Environment on Regional Lymph Node and Systemic Metastasis

Jeremy Burton, Ph.D.
University of California-Los Angeles

Dissemination of tumor cells through lymphatic vessels to regional lymph nodes leads to metastasis. The presence of pelvic lymph node metastases is used clinically as a predictor of poor patient prognosis and survival. Yet, little is known about how tumor cells access lymphatic vessels and carry out this process. Dr. Jeremy Burton, an FY06 Prostate Cancer Training Award recipient, is investigating the role of lymphangiogenesis in metastatic prostate cancer under the guidance of Dr. Lily Wu, an established prostate cancer scientist and PCRP awardee. Dr. Burton will limit lymphangiogenesis by reducing expression of the vascular endothelial growth factor C (VEGF-C) gene and use molecular imaging to evaluate whether metastatic progression is prevented in a murine model that mimics the disease. This investigation could result in the development of new therapies that lead to improved long-term prognosis and a better standard of care for prostate cancer patients.

The Program Today

FY07 Summary

FY07 marked the 10th anniversary of the PCRP, and the program received a congressional appropriation of $80M. To direct these funds toward the best prostate cancer research, the program offered 8 award mechanisms to emphasize its commitment to innovative, collaborative, and translational research and training. Of note, the program launched 2 new award mechanisms, one to emphasize translational research and the other to support collaborations. The Laboratory-Clinical Transition Award: Stage I focuses on the validation of novel therapeutics for prostate cancer identified from a lead agent. The Synergistic Idea Development Award supports scientific partnerships on innovative, high-impact studies. A total of 904 proposals were received across the 8 award mechanisms, and 193 awards were made as shown in Table III-1. The research portfolio developed by the FY07 PCRP cuts across several disciplines spanning basic, clinical, and population-based research, as illustrated in Figure III-2.

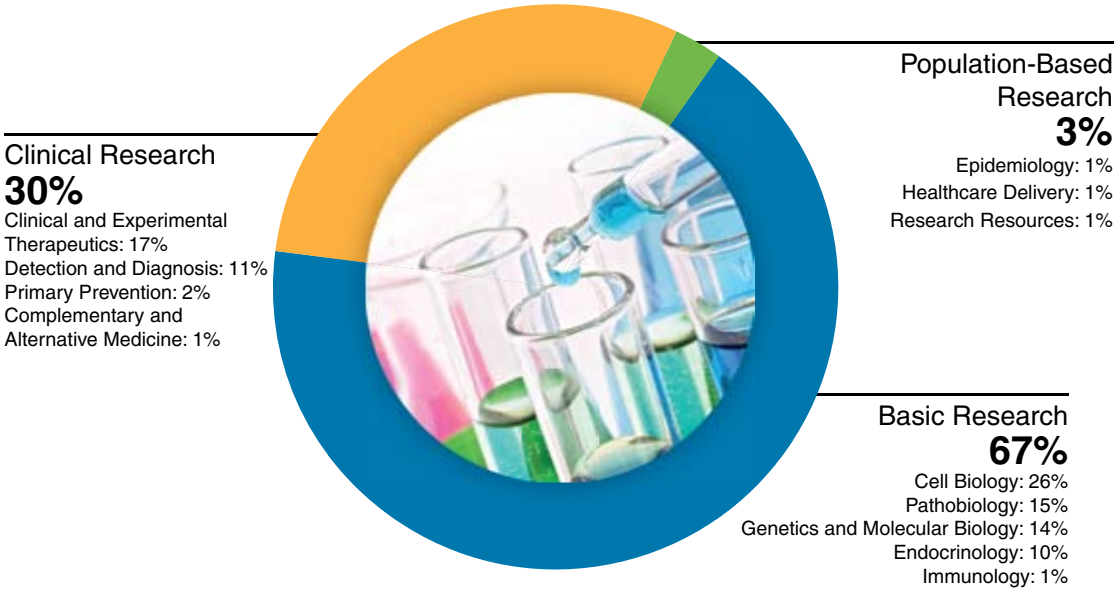


Figure III-2. FY07 PCRP Portfolio by Research Area

The PCRP Team

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Table III-1. Funding Summary for the FY07 PCRP

Categories and Award Mechanisms	Proposals Received	Awards	Investment
Clinical Research			
Clinical Trial	22	2	$2.3M
Laboratory-Clinical Transition Award: Stage I	17	3	$3.1M
Innovative Research			
Idea Development	511	64	$35.7M
New Investigator	143	31	$10.5M
Synergistic Idea Development	176	18	$9.3M
Training/Recruitment			
Collaborative Undergraduate HBCU Student Summer Training Program	3	2	$0.4M
Physician Research Training	13	6	$3.5M
Prostate Cancer Training	133	63	$6.4M
TOTAL	**1,018**	**189**	**$71.2M**

1,018 Proposals Received

189 Awards

$71.2M Investment

The Vision for FY08

For FY08, the PCRP was provided with a new congressional appropriation of $80M. The program's focus areas include clinical research and resources, innovative research, and training/recruitment. These focus areas were developed into 11 unique award mechanisms to forge new pathways in prostate cancer research. A total of 1,342 proposals were received as shown in Table III-2 and approximately 160 awards are predicted. Appendix B, Table B-2, summarizes the congressional appropriations and the investment strategy executed by the PCRP for FY07 and FY08.

Table III-2. Award Mechanisms Offered and Proposals Received for the FY08 PCRP

Focus	Award Mechanism	Proposals Received
Clinical Research and Resources	**Clinical Consortium Award:** Provides resources to facilitate the rapid execution of collaborative Phase II or Phase II-linked Phase I clinical studies	19
	Clinical Trial Award: Funds the rapid execution of novel Phase 0/I, Phase I, Phase I/II, or Phase II clinical trials	27
	Laboratory-Clinical Translational Award: Stage I: Supports preclinical studies of promising lead agents that have the potential to revolutionize prostate cancer clinical care	19
Innovative Research	**Idea Development Award:** Supports innovative ideas and technology across all areas of laboratory, clinical, behavioral, and epidemiological research	634
	Synergistic Idea Development Award: Encourages innovative and synergistic approaches from two to three investigators with the goal of accelerating prostate cancer research	213
	New Investigator Award: Funds innovative research from newly independent investigators working in collaboration with experienced prostate cancer researchers	149
	Health Disparity Research Award: Supports research from investigators at specific career stages who study the disparate burden of prostate cancer within disproportionately affected populations and communities	50
Training/Recruitment	**Physician Research Training Award:** Prepares physicians for careers in prostate cancer research through a mentored training experience in a laboratory or clinical setting	13
	Prostate Cancer Training Award: Provides prostate cancer research training opportunities to investigators early in their careers	200
	Health Disparity Training Award: Provides training opportunities to investigators early in their careers to study the disparate burden of prostate cancer within disproportionately affected populations and communities	4
	Collaborative Undergraduate HBCU Student Summer Training Program Award: Provides educational and training opportunities in prostate cancer research for undergraduate students at historically black colleges and universities	14
	TOTAL	**1,342**