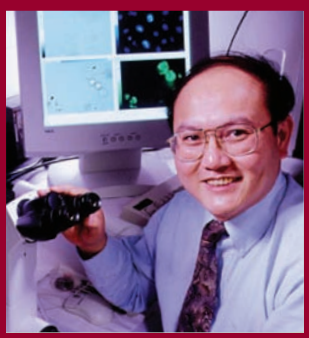
CDMRP

Department of Defense

Prostate Cancer Research Program


U.S. Army Medical Research and Materiel Command

Congressionally Directed Medical Research Programs

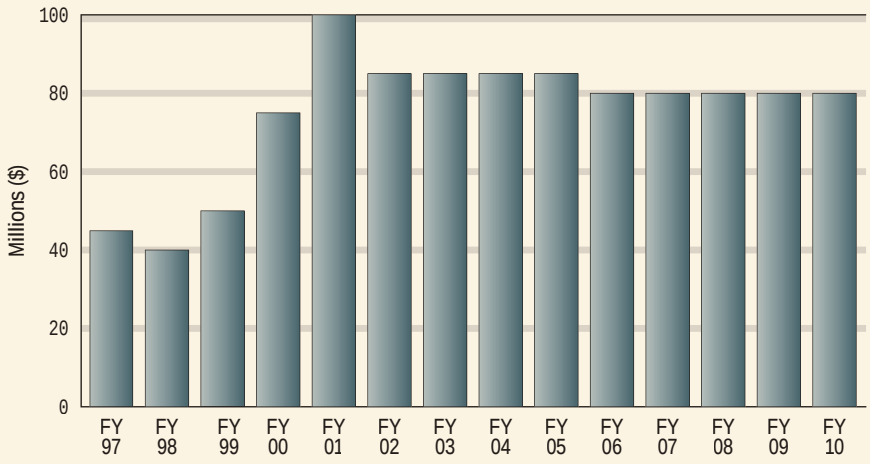
HISTORY

The Office of the Congressionally Directed Medical Research Programs (CDMRP) was born in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. Since then, the CDMRP has grown to encompass multiple targeted programs and has received almost $5.4 billion in appropriations from its inception in fiscal year 1993 (FY93) through FY09. Funds for the CDMRP are added to the Department of Defense (DOD) budget, in which support for individual programs, such as the Prostate Cancer Research Program (PCRP), is allocated via specific guidance from Congress.

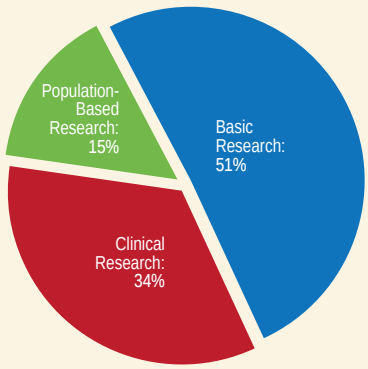
Proposal Review Process

The CDMRP uses a two-tier review process for proposal evaluation, with both tiers involving dynamic interaction among scientists and disease survivors. The first tier of evaluation is a scientific peer review of proposals measured against established criteria determining scientific merit. The second tier is a programmatic review, conducted by the Integration Panel (or IP, composed of leading scientists, clinicians, and consumer advocates), which compares proposals to each other and makes recommendations for funding based on scientific merit, portfolio balance, and relevance to program goals.

PCRP Funding History



PCRP Funding Portfolio FY97–FY08



Prostate Cancer Research Program

VISION

Conquer prostate cancer

MISSION

Fund research that will eliminate prostate cancer

SUMMARY OF OUR HISTORY

In 1997, Congress appropriated $45 million (M) to be administered by the DOD for prostate cancer research. Since then, the efforts of prostate cancer advocates have resulted in a total appropriation of nearly $1.1B to the PCRP, including $80M in FY10. This funding has energized the development of unique partnerships among Congress, the military, prostate cancer survivors, clinicians, and scientists. Through these partnerships, the PCRP is investing in high-risk research by emphasizing innovation and training. The impact of these research studies is being translated into clinical therapies and technologies, uncovering mechanisms and barriers that result in prostate cancer health disparities, and developing new methods and technologies to prevent, diagnose, and treat prostate cancer.

PCRP Goals

- Support innovative research by individual investigators in multiple disciplines
- Sponsor multidisciplinary team science to bring together diverse expertise and approaches that will accelerate the conquering of prostate cancer
- Fund translational research to promote the bench-to-bedside-to-bench transition between basic and clinical science
- Foster the next generation of prostate cancer investigators through mentored research and training
- Promote research into prostate cancer health disparities, including but not limited to race and ethnicity, socioeconomic status, access to health care, insurance status, age, geography, and cultural beliefs
- Promote research on patient survivorship, life extension, and quality of life

Consumer Participation

Since its inception more than 12 years ago, consumer advocates have been key players in helping to shape the PCRP's direction and goals, and in making funding recommendations. To date 301 consumer advocates have served on peer and programmatic review panels for the PCRP. Their firsthand experience with prostate cancer provides a unique perspective that inspires scientists and clinicians and enlightens them about the human side of the disease, such as the concerns and needs of patients, their families, and communities. Born from this partnership of consumer advocates, scientists, and clinicians are funding recommendations that reflect the collective wisdom of these partners after careful deliberations.

Fred Allen
Arkansas Prostate Cancer Foundation
"As a prostate cancer survivor, I found the peer review experience stimulating and life-changing. When I think of the long-term impact that PCRP grant awardees will have on the quality of life for cancer patients and, ultimately, on the eradication of this dreadful disease, I am humbled to play a role in the process."

Will Spurgeon
Alta Bates Summit Medical Center
"As a survivor of aggressive prostate cancer, diagnosed when I was 52, I have found a great way to 'give back' by participating in the CDMRP peer review. Here I have the opportunity to support the scientific community that is seeking a cure, expand my knowledge of the disease, and apply my energies in a way that could save lives—perhaps my own and my son's someday."

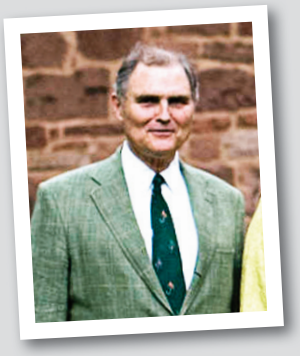
Kermit Heid
National Patient Advocate Foundation
"Why do I eagerly look forward to the next PCRP peer review panel? Maybe it's because I think that I will read the application that will describe the protocol to halt the progression of metastatic disease or to develop a vaccine that will prevent prostate cancer. There is knowledge gained from reading these applications for cutting-edge research. Satisfaction comes from taking part in a process that will ultimately save millions of men from a disease that affects entire families. The vision of the PCRP—'Conquer Prostate Cancer'—is reflected in its approach to this disease: Make careful use of the funding available in supporting 'high-risk, high-impact' research to bring an end to this disease."

Jim Kearns
Virginia Prostate Cancer Coalition
"A comparison of my experience with choroidal melanoma and my experience with prostate cancer is interesting, especially regarding the definitive treatment for one type of cancer and its lack in another type. I asked myself, 'How is it that medicine can solve my rare eye cancer and not my all-too-common prostate cancer?' As a PCRP consumer reviewer, I bring my story as a survivor to the table. I take part in the exchange of questions and ideas that fuel research that could eliminate this disease."

Earl Jones
California Prostate Cancer Coalition
"My experience as a PCRP Consumer Reviewer on a Health Disparity panel was both personally enlightening and rewarding. All aspects of the disease disparity were addressed in the range of proposals reviewed. A diverse group of scientific and consumer reviewers engaged in panel discussions that were thorough, spirited, and well organized, and gave me a much broader appreciation of the many facets of prostate cancer. Not only did I feel that my views were sought, respected, and appreciated, but I could also see that the mutual respect enjoyed among us facilitated a thoroughly effective exchange of ideas and opinions, allowing those proposals with the highest impact value to advance. I am confident that my input was influential and made a difference."

IN MEMORY

In Memory of John Willey



John Willey, a consumer member of the PCRP's IP since FY07, died on November 24, 2009, after battling prostate cancer for 17 years.

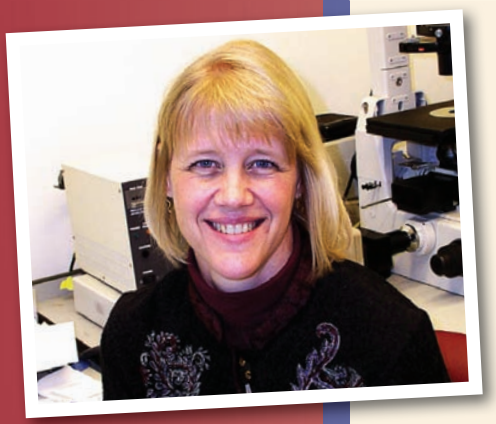
John brought firsthand experience of prostate cancer and a sense of urgency to the work of the IP. In doing so, he helped shape the program by contributing to the investment strategy, participating in programmatic review of proposals, and focusing attention on issues critical to patients, such as outcomes and quality of life. As a consumer member, he helped to keep the program's focus on innovation and risk taking when the potential payoff was high. John was a staunch advocate of the Prostate Cancer Clinical Trials Consortium—a multi-institutional clinical research endeavor consisting of a nationwide network of 13 leading institutions specializing in cutting-edge prostate cancer clinical research and therapies. John declared this effort to be "the best use of PCRP funds in support of collaborative partnerships between scientists/clinicians and institutions to advance clinical trials."

John advocated for more impactful research as a central part of the PCRP investment strategy. On behalf of the advocate community, he argued energetically for increased investment in early-stage research, effective prevention, minimally invasive screening, better treatment options for advanced prostate cancer, and methods to improve quality of life for patients. Tireless in his efforts to garner increased congressional support for prostate cancer research, this Navy veteran of the Vietnam War brought the determined spirit of the warfighter in his quest to find a cure for all those diagnosed with prostate cancer and those who lack access to screening.

The PCRP is indebted to John Willey for his gracious leadership, robust advocacy, and selfless generosity in the fight to conquer prostate cancer not only for himself but for the thousands of men who continue to hope for a cure.

Peer Reviewer Participation

Scientists and clinicians work in partnership with consumer advocates to identify research with high-risk, high-gain approaches and with groundbreaking ideas aimed at filling critical gaps, with the potential for an unprecedented impact on prostate cancer. The peer review panels, organized by scientific discipline, provide expert advice on the scientific and technical merit of research proposals.



Cindy Miranti, Ph.D.
Van Andel Research Institute
"It is a pleasure to review grants for an agency that is truly dedicated to improving the patient's quality of life as well as to curing disease. The ability to provide expert advice regarding the scientific and technical merits for promising innovative, high-impact, and quality research is rewarding. The dedication and integrity of the CDMRP to the task are admirable."

Steven J. Kridel, Ph.D.
Wake Forest University School of Medicine
"As a PCRP-funded investigator, it is always interesting to read grants on the cutting edge of science. Importantly, the consumer reviewers always provide a sense of reality to the peer review process by demonstrating why we do science."

Omar Bagasra, M.D., Ph.D.
South Carolina Center for Biotechnology, Claflin University
"I have been part of many grant reviews and study sections. I find the study panels managed by DOD-CDMRP to be the most fair and scientifically sound. Although there is always room for improvement, I believe that other federal agencies should adopt this peer review process."

Nagi B. Kumar, Ph.D., R.D., F.A.D.A.
Moffit Cancer Center, University of South Florida
"It was an honor and a privilege to serve as a scientist reviewer for the CDMRP Prostate Cancer Research Program. One of the most distinct aspects of the review that I truly appreciated was the attention paid to planning and executing all details of the review process. Each and every grant submitted received a fair and thorough scientific review. I hope to continue to be involved in this process in the future."

V. Diane Woods, Dr.P.H., M.S.N., R.N.
University of California, Riverside
"African American men continue to die almost 10 years earlier than other men; that age, in my county, is 56 years. This is too young, and prostate cancer is one of the foremost contributors to premature death of African American men. The CDMRP Prostate Cancer Research Program is on the cutting edge of understanding the complexity of this disparity and is supporting innovative interventions to eliminate the problems. Thank you."

Ivan Borrello, M.D.
The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University
"The review process provided a thorough, comprehensive discussion of each proposal. Overall, there was a very cordial, professional environment in which the true scientific merit as well as adherence to the overall mandate of the program was genuinely respected."

Integration Panel

Superb Visionaries and Exceptional Leaders: PCRP Integration Panel

Seventeen prominent and gifted individuals with deep and diverse expertise in prostate cancer constitute the PCRP Integration Panel. They include scientists, clinicians, and consumer advocates who collectively forge an annual vision and investment strategy for the PCRP that leads to breakthroughs in prostate cancer research. Key to their vision of conquering prostate cancer is the development of a broad research portfolio that is focused on scientific innovation, partnerships, multi-institutional collaboration, clinical experimentation, training, and resource and infrastructure development. These visionaries are working together to harness technological advances and human intellectual capital to provide substantial research support to conquer prostate cancer.

Members

A. Oliver Sartor, M.D., Chair, Tulane University School of Medicine

Donald Tindall, Ph.D., Chair-Elect, Mayo Clinic, Rochester

Howard R. Soule, Ph.D., Chair-Emeritus, Prostate Cancer Foundation

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

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

Philip Arlen, M.D., Neogenix Oncology

Alvin Chin, J.D., Virginia Prostate Cancer Coalition

Leland Chung, Ph.D., Cedars-Sinai Medical Center

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

Natasha Kyprianou, Ph.D., University of Kentucky

Cheryl Lee, M.D., University of Michigan

Timothy McDonnell, M.D., Ph.D., University of Texas, M.D. Anderson Cancer Center

Timothy L. Ratliff, Ph.D., Purdue University

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

Howard Sandler, M.D., Cedars-Sinai Medical Center

Virgil Simons, The Prostate Net

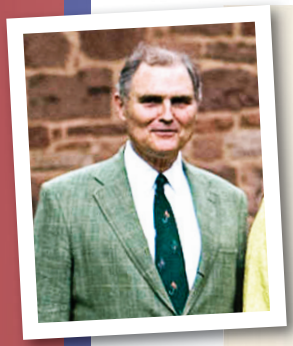
John Willey, Zero, The Project to End Prostate Cancer

"The DOD prostate cancer program is one of the most important strategic investments in medical research today. By focusing an array of new technologies and concepts on this disease, which will affect nearly one in six American men in their lifetime, this program has the potential to benefit men and their families for generations to come."

A. Oliver Sartor, M.D.
Tulane University
FY09 Integration Panel Chair

"In my opinion this program has made the single largest impact on the careers of young investigators who have made commitments to undertake research in prostate cancer."

Donald Tindall, Ph.D.
Mayo Clinic, Rochester
FY09 Integration Panel Chair-Elect

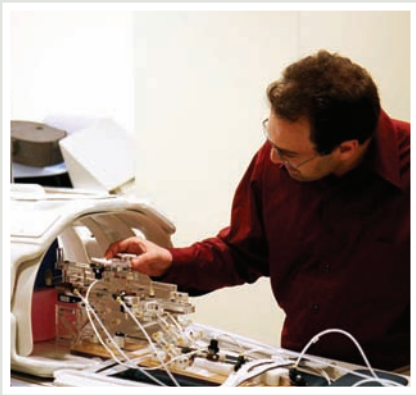


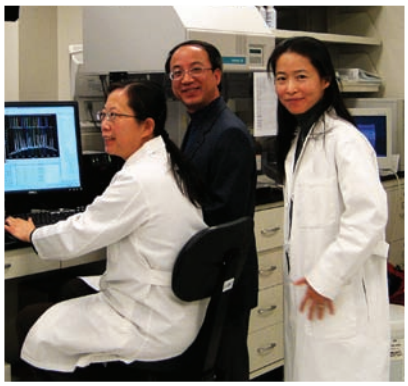
"The PCRP... is one of the best examples of direct action that is specifically dedicated to targeting prostate cancer and eliminating its tragic consequences. It is through the PCRP that research scientists and medical professionals are able to thoroughly and thoughtfully develop new ideas for the treatment of prostate cancer and translate the research into therapies for those affected with this disease. Because of its efficacy, the PCRP is highly respected and is the example that other research programs should be modeled after. It is the best there is in its field. It was an honor to serve on the Integration Panel and to have the final review of and vote for the very best therapies specifically targeted against prostate cancer."

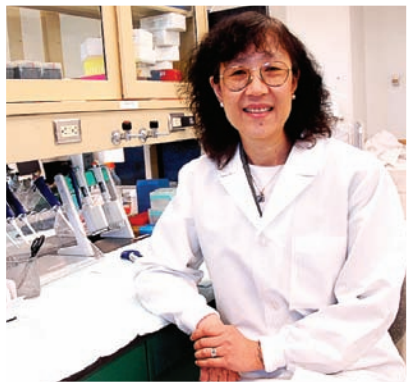
John L. Willey
FY09 Integration Panel Member (deceased)

The Scientific Community

The intellectual capital of PCRP investigators is matched by their passion and drive to use cutting-edge technology to unravel complex pathways and paradigms. More than 1,900 investigators have been funded by the PCRP to advance research and treatment options for prostate cancer patients. These investigators are working to improve methods in early detection and diagnosis, to develop effective therapies and prognostic tools, and to improve the quality of life for all affected persons.

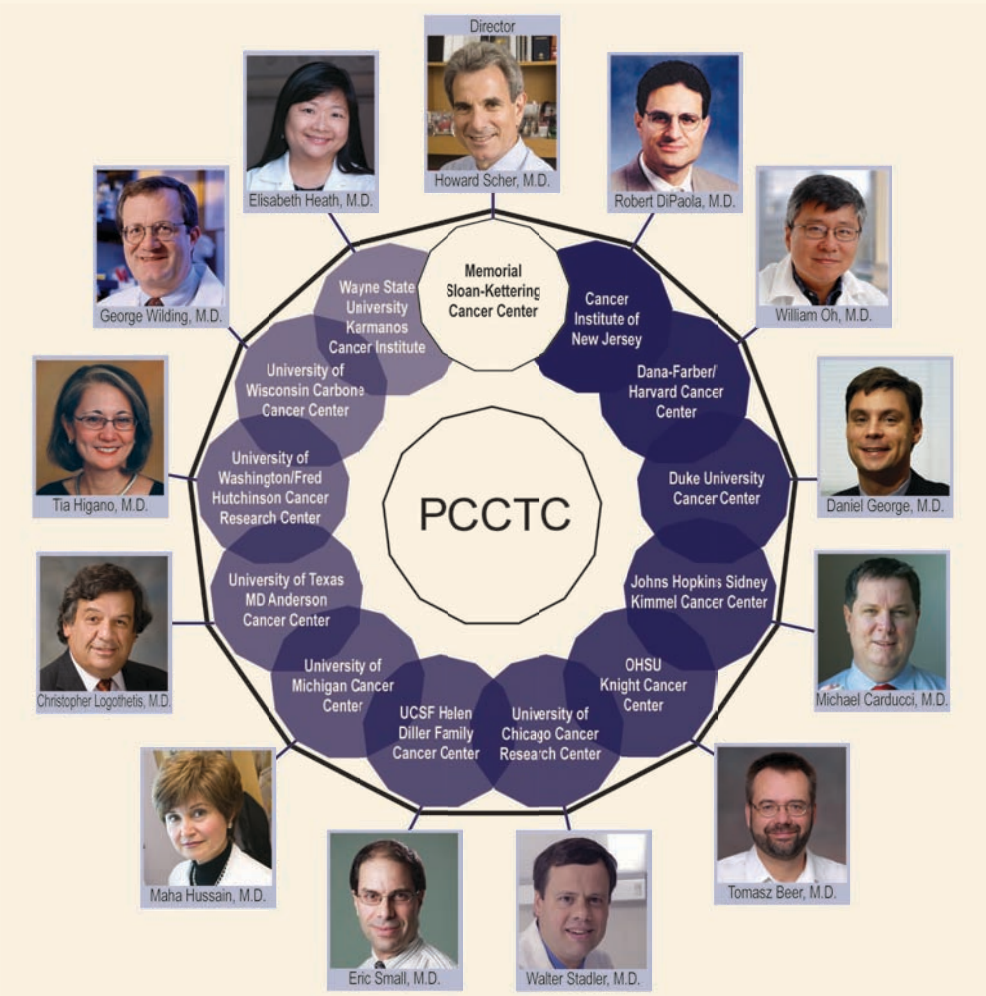






The PCRP Breaking Through to Major Advancements in Clinical Trials

In 2005, the PCRP supported the development of the Prostate Cancer Clinical Trials Consortium (PCCTC) through the Clinical Consortium Award in response to gaps identified by physician investigators and prostate cancer advocates. Capitalizing on scientific expertise and unique institutional resources, Consortium members from 13 Clinical Research Sites work together to design and execute more rapid, efficient, precise, and cost-effective Phase I/II and Phase II clinical trials. Additionally, Consortium members participate in several subcommittees, such as Scientific Working Groups, Clinical Review of Data Management, and Clinical Research Quality Assurance. These subcommittees assist the Coordinating Center in executing its coordination and management functions. Since its inception, the PCCTC has conducted 66 Phase I or II studies investigating approximately 51 different drugs, either alone or in combination, targeting five clinically defined stages of prostate cancer. More than 1,767 patients have been recruited to participate in these trials, with more than 10% representing minority patient populations. These efforts have recently moved five potential therapies into Phase III clinical trials. While the Consortium continues to develop new clinical trials to address unmet needs, it also is working to transform cancer treatment from a one-size-fits-all approach of today to a strategy of patient-specific care that will select the best treatments for each and every patient.



The PCCTC remains poised to make a significant impact on the lives of prostate cancer patients by ensuring the selection of promising drug candidates, designing informative clinical endpoints, executing clinical trials in a timely fashion, and determining which drugs should advance to larger Phase III clinical trials.

Memorial Sloan-Kettering Cancer Center (MSKCC)
Dr. Howard Scher

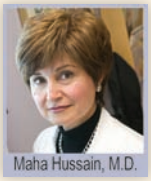
MSKCC serves as the Coordinating Center for the PCCTC. The Coordinating Center has capitalized on the scientific expertise and unique institutional resources of Consortium members by:

- Implementing an organizational structure that facilitates interactions between participating sites, regulatory agencies, trial sponsors, and internal and external advisory boards, and that ensures highly effective centralized management of PCCTC research activities.
- Harmonizing the diverse scientific, clinical, and administrative expertise of members to create unified scientific priorities, standardized protocol and contract language, and centralized data management.

In addition, as a Clinical Research Site MSKCC has influenced clinical trials and standard operating procedures by:

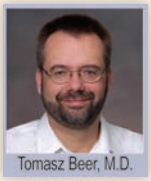
- Leading the Phase I/II development of novel drug targeting the androgen receptor (MDV3100) from concept to Phase III decision in 18 months, and accruing 64 patients to the trial.
- Establishing a centralized laboratory infrastructure to collect and evaluate CTCs obtained from PCCTC trials.

The Consortium's successful acceleration and streamlining of the clinical trial process are tributes to the collaborative nature and intellectual synergy of its members.



University of Michigan (UM)
Dr. Maha Hussain

The research conducted in UM laboratories identified several novel targets for the treatment of prostate cancer, including AT-101 and CNTO888. AT-101 is an antiapoptotic agent derived from cotton seed oil that was shown to enhance the efficacy of radiotherapy, chemotherapy, and hormonal therapy in experimental models and is moving into Phase III clinical trials. CNTO888 is a monoclonal antibody against CCL2 and works by inhibiting tumor angiogenesis.

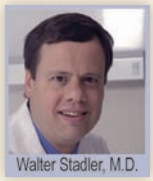


Oregon Health & Science University (OHSU)
Dr. Tomasz Beer

OHSU is dedicated to the development of comprehensive personalized medicine strategy to overcome treatment resistance through tumor assessment of individual patients. They have identified several novel tumor-promoting cytokines and enzymes that are induced by chemotherapy that allow cancer cells to survive after treatment. OHSU introduced clusterin (a prosurvival chaperone protein target) to the PCCTC, and it is the first clinical trial to specifically target this chemotherapy-inducible survival mechanism.

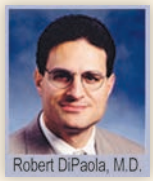
Dana-Farber/Harvard Cancer Center (DFHCC)
Dr. William Oh

The DFHCC has introduced novel clinical trials in several areas. The recent completion of a presurgical treatment of high-risk localized prostate cancer trial combining docetaxel therapy with the angiogenesis inhibitor bevacizumab revealed promising shrinkages of tumors. A trial of presurgical abiraterone acetate and hormone therapy is under way. Dana-Farber also is conducting the first PCCTC biomarker-only study to assess the accuracy of a six-gene whole blood test for predicting survival of men with advanced metastatic castration-resistant prostate cancer.



University of Chicago (UC)
Dr. Walter Stadler

As a new member of the PCCTC, UC boasts a diverse patient population, which facilitates a 13% accrual rate of African Americans to clinical trials. Additionally, UC brings experience and expertise in clinical biomarker development such as quantitative dynamic contrast-enhanced MRI parameters, quantitative fluorodeozyglucose-PET parameters, PSA, other serum diagnostic biomarkers, quality-of-life outcome biomarkers, and biomarkers of frailty.



Cancer Institute of New Jersey (CINJ)
Dr. Robert DiPaola

CINJ, a new member of the PCCTC, is focusing clinical trials on apoptotic and metabolic pathways. They are particularly interested in the Bcl-2 checkpoint and Bcl-2-mediated resistance, which they address by combining Bcl-2 inhibition using AT101 (a pan-Bcl-2 protein family inhibitor) and androgen ablation chemotherapy in patients with metastatic prostate cancer. CINJ is also seeking to overcome tumor cell resistance by inhibiting the catabolic process of autophagy, which is induced by metabolic stress and leads to tumor cell survival. CINJ is developing novel inhibitors of autophagy and is currently conducting trials to test the commercially available agent hydroxychloroquine, which overrides regulation of the gene beclin 1.


Christopher Logothetis, M.D.

M.D. Anderson Cancer Center (MDACC)
Dr. Christopher Logothetis

MDACC has led several clinical trials that have yielded promising therapies, including Phase I and Phase II trials of the Src inhibitor, dasatinib, in combination with docetaxel, in patients with advanced prostatic carcinoma. This well-tolerated two-drug combination showed significant duration and decline in PSA levels, leading to an international Phase III trial that is accruing patients rapidly. MDACC also is conducting the first multidisciplinary combination trial of sunitinib (vascular endothelial growth factor and platelet-derived growth factor inhibitor) and radiation therapy, made feasible by the DOD-supported multicentered Consortium. This trial follows on earlier studies that demonstrated high rates of complete pathological remission of primary prostatic carcinoma following combination treatment of sunitinib and androgen ablation therapy. The use of nanotechnology to deliver cytotoxic therapies with improved therapeutic index is being tested in a trial using nab-docetaxel. Early indications support favorable efficacy relative to docetaxel with significant reduction in toxicity.


Tia Higano, M.D.

University of Washington (UWash)
Dr. Celestia (Tia) Higano

UWash introduced studies of A12, an antibody to the insulin growth factor I receptor (IGF-IR), to the PCCTC, based on preclinical studies showing that interference with the IGF pathway could enhance response to both androgen deprivation therapy (ADT) and chemotherapy in the lab. A Phase II trial of A12 as a single agent confirmed enhanced cytotoxic effects of docetaxel by IGF-IR inhibition, and a neoadjuvant combination trial of A12 and ADT was initiated to test whether ADT enhances A12 in the radical prostatectomy setting. Results from both the laboratory and clinical studies served as the impetus for a Phase III combination trial of A12 and docetaxel with correlative studies.


Michael Carducci, M.D.

Johns Hopkins University (JHU)
Dr. Michael Carducci

Johns Hopkins Sidney Kimmel Cancer Center brings to the consortium expertise in early phase drug development, and a patient population with diverse disease states, especially those prior to undergoing prostatectomy and those with biochemical recurrence after local therapy. Additionally, they have introduced a number of clinical trial sponsors to the Consortium (Kinex, KanaLaTe, Tiltan, POM Wonderful) with agents ready for first-in-human studies, initial Phase II prostate cancer studies, and /or preventative agents, including natural products for biomarker studies. More recently, previously known drugs such as itraconazole and disulfiram, which have been shown in Phase II trials to have anticancer activities, are being explored as possible prostate cancer therapeutic agents.


George Wilding, M.D.

University of Wisconsin (UW)
Dr. George Wilding

Investigators at UW lend to consortium trials their expertise in angiogenesis and early drug development, novel imaging, tumor vaccines, and biomarker development. UW is developing PET/MRI-based multimodality imaging to characterize response in bone metastasis while also testing the immunological efficacy of DNA vaccines for the treatment of prostate cancer. Additional efforts are being made in the development of functional circulating tumor cell (CTC) assays as a prognostic tool in advanced prostate cancer. The CTC counts from these assays will be correlated with other biomarkers to provide prognostic information and prediction of metastatic disease.


Elisabeth Heath, M.D.

Wayne State University (WSU)
Dr. Elisabeth Heath

As a new member of the Clinical Consortium, WSU intends to conduct prostate cancer clinical trials using compounds against angiogenesis and the PTEN/AKT/mTOR pathway, as either single agent or combination therapies. Importantly, WSU contributes a unique patient population that comprises 64% African Americans. The high percentage of disproportionately affected individuals to be enrolled in clinical trials at this institution is important in the PCRP's efforts to resolve prostate cancer health disparities.


Daniel George, M.D.

Duke University (DU)
Dr. Daniel George

DU brought to the PCCTC an expertise in the use of image-guided metastatic bone marrow biopsies, which has been used in genomic profiling for treatment selection (e.g., prediction of docetaxel sensitivity and resistance, predictive patterns of androgen receptor expression). Another first for the Consortium is a multimodality trial combining chemotherapy with radiation therapy in patients with rising PSA after prostatectomy (or salvage setting). A subsequent study combining docetaxel and sunitinib with radiation therapy in the salvage setting is currently under way in patients with advanced disease. Overall, DU has a 20% success rate of accruing minorities to clinical trials. This is the result of actively reaching out to traditional North Carolina community venues (e.g., churches and social groups) to engage leaders in communicating the importance of clinical research and addressing obstacles faced by minorities.

Health Disparity

With the goal of eliminating disparities in prostate cancer incidence and death, the PCRP places special emphasis on supporting research that will identify underlying factors that contribute to this critical issue. The PCRP has invested in a broad portfolio of behavioral, epidemiological, basic, and clinical studies focused on socioeconomic status, time to detection and treatment, differences in treatment, and differences in survival, diet, lifestyle, and molecular and genetic factors that will provide new knowledge to guide strategies in prevention, detection, and treatment.

The Influence of Metabolic Syndrome on Prostate Cancer Progression and Risk of Recurrence in African American and European American Men

Isaac Powell, M.D., Wayne State University

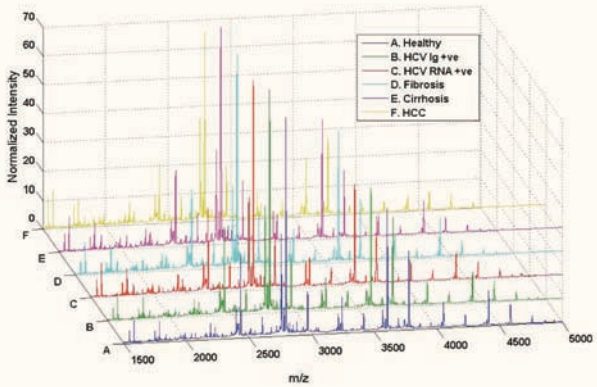
Metabolic syndrome includes insulin resistance, abdominal obesity, hypertension, and dyslipidemia (elevated triglycerides and low high-density lipoprotein). African Americans are known to be afflicted with a high incidence of several of these features, which also have been shown to be associated with prostate cancer. FY08 Health Disparity Award recipient Dr. Isaac Powell and colleagues plan to conduct a comprehensive study examining whether the components of metabolic syndrome are reliable predicting factors regarding aggressive versus nonaggressive prostate cancer and subsequent morbidity and mortality in African American compared to Caucasian males. This study is the first of its kind and, if successful, could reduce the incidence of prostate cancer recurrence by modifying patient diet and lifestyle while developing new therapeutics to treat components of metabolic syndrome.

Photo courtesy of Wayne State University School of Medicine

Glycomic Analysis of Prostate Cancer

Radoslav Goldman, Ph.D., Georgetown University, Washington, DC

The interaction of cancer cells with the microenvironment and the immune system relies on glycosylated proteins. Protein glycosylation (sugar molecules being added to proteins) is important for some cellular functions, host response to infections, and cancer cell migration. Dr. Radoslav Goldman, an FY08 Health Disparity Research Award recipient, is investigating the variability of protein glycosylation as a risk factor for prostate cancer in an age-matched case control study of African American and Caucasian men. The study will use mass spectrometry to measure the N-glycans in serum and urine samples from African American and Caucasian men with prostate cancer with the goal of identifying differences in the pattern in which sugars are attached to proteins within and between the two groups. The glycomic analysis will provide new information on the biological factors underlying prostate cancer health disparity and may identify novel biomarkers for prostate cancer diagnosis and lead to new strategies for prevention and intervention.

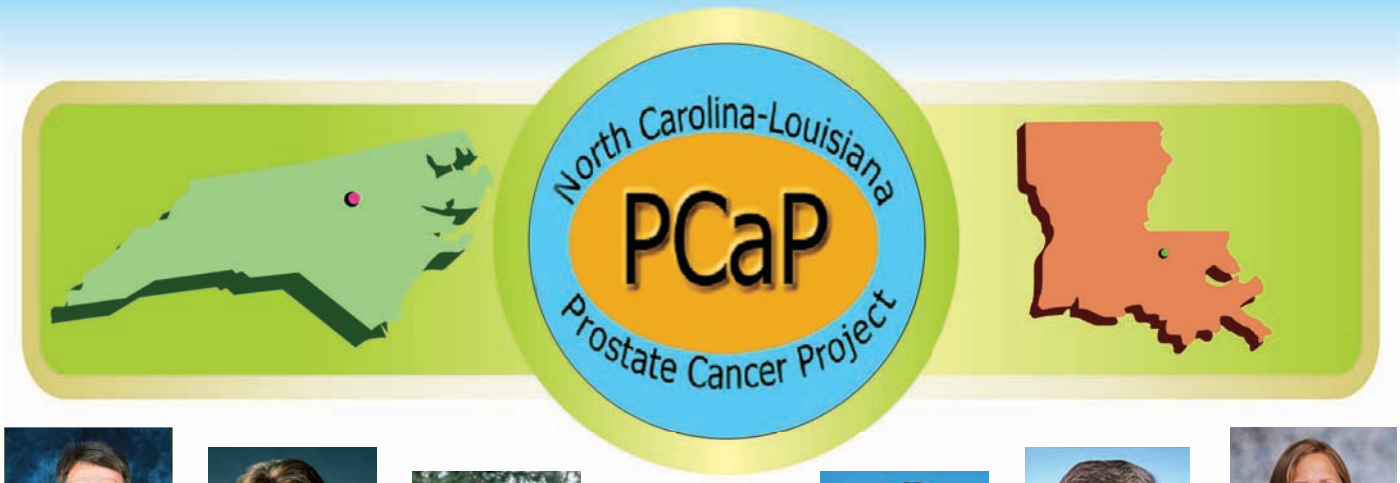


Mass spectrometric analysis of N-glycans in the progression of liver disease from hepatitis C viral infection to hepatocellular cancer. The PCRP award will support using this approach to compare protein glycosylation in prostate cancers from African American and Caucasian men.

Genetic Association Study of Ancestry-Matched African American Prostate Cancer Cases and Controls

William Isaacs, Ph.D., Johns Hopkins University

Social, economic, dietary factors, education about the disease, treatment delay, and genetic differences are often cited as factors that contribute to racial differences in incidence and severity of prostate cancer. Dr. William Isaacs, recipient of an FY06 Health Disparity Research Award, evaluated a set of 20 single nucleotide polymorphisms (SNPs) implicated in prostate cancer risk in patients of European descent to determine if these SNPs were also associated with prostate cancer in African American men. In total, 868 African American men with prostate cancer and 878 African American men without prostate cancer from four independent study populations were genotyped for the 20 SNPs. After adjusting for age, ancestry proportion, and population origin, the SNP rs16901979, located on chromosome 8q24, was identified as significantly associated with prostate cancer risk in African American men. Analysis of additional SNPs spanning 8q24 revealed three SNPs associated with prostate cancer risk (rs16901979, rs13254738, and rs10086908) in this region. The study suggests that fine mapping of regions containing African American prostate cancer risk variants are warranted, and that larger numbers of African American men from diverse backgrounds will be needed to detect prostate cancer risk variants with moderate effect.




James Mohler, M.D.
Co-director


Elizabeth Fontham, Dr.PH.


Joseph Su, Ph.D.


Merle Mishel, Ph.D.


Paul Godley, M.D.


Gary Smith, Ph.D.


Jeannette Bensen, Ph.D.
Co-director

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

The Prostate Cancer Project (PCaP) was initiated in FY02 to explore racial differences affecting prostate cancer aggressiveness with the goal of delineating the factors that contribute to the high incidences and disproportionate rates of prostate cancer morbidity and mortality in African American versus Caucasian men. PCaP represents the first comprehensive study of racial disparity in prostate cancer, facilitating the identification of factors that contribute to its severity in African American men. The project is a collaboration among three institutions, including the University of North Carolina at Chapel Hill (UNC-CH), the Louisiana State University Health Sciences Center (LSUHSC), and the Roswell Park Cancer Institute (RPCI). After 7 years of intensive work and despite significant loss of infrastructure and resources at LSU following Hurricane Katrina in 2005, accrual of more than 2,000 men with newly diagnosed prostate cancer was completed in August 2009: 1,032 from North Carolina and 1,018 from Louisiana. Half of the men in each state were African American and half were Caucasian. Study participants were 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.

PCaP has developed an Internet-accessible database, which serves as an open source to provide enhanced access to anonymized patient information, data derived from biorepository specimens, and to facilitate data sharing and communication with investigators in the prostate cancer research community. Portions of the website are secured by controlled access to safeguard information and maintain data integrity. Additionally, PCaP has developed user guides and data sharing policies to assist investigators in retrieving and depositing information, sharing their data, and facilitating standard operating procedures.

PCaP Data and Biologic Resources

PCaP Consortium has a central repository of clinical, biological, and research data on prostate cancer patients that will serve as a nexus for future studies of prostate cancer health disparity for the entire prostate cancer research community. This invaluable resource will help identify important factors that contribute to the high prostate cancer incidence and mortality rate in African Americans compared to Caucasians. Resources available through this repository include:

- *A characterized cohort of more than 2,000 men with newly diagnosed prostate cancer (PCaP Cohort): 1,000 African Americans and 1,000 Caucasian Americans.*
- *A comprehensive centralized database of clinical/medical, epidemiological, and interview data of each study participant.*
- *A high-quality biorepository of specimens collected from PCaP participants at the time of their in-home visit and linked to the PCaP Central Database: serum, plasma, red blood cells, immortalized lymphocytes, DNA, urine, abdominal adipose (fat) tissue, and toenails.*
- *A large population-based, high-quality, prostate cancer tissue repository (including paired normal prostate specimens) of diagnostic biopsy (slides available) and radical prostatectomy tissues (slides and tissue microarrays available) from PCaP participants that are linked to the clinical and research data in the PCaP central database.*

Major PCaP Project Analytical Studies

PCaP investigators are undertaking various major studies to determine the factors that contribute to the high prostate cancer incidence and death rates for African Americans. These studies are focused primarily on three areas: access to health care, biologic and genetic differences between African Americans and Caucasians, and factors contributing to disease aggressiveness. Investigators also are involved in several ancillary studies that address issues such as differences in lifestyle, health care and prostate cancer treatment, quality of life, and the relationship between prostate cancer aggressiveness and pesticide exposure. Major studies being undertaken by PCaP investigators are:

- *Racial Differences in Prostate Cancer Screening and Care-Seeking Behaviors – Paul A. Godley, M.D., Ph.D., University of North Carolina at Chapel Hill*
- *Cultural and Demographic Predictors of Interaction with the Health Care System and Prostate Cancer Aggressiveness – Merle H. Mishel, R.N., Ph.D., University of North Carolina at Chapel Hill*
- *Nutritional Modulation of Prostate Cancer Aggressiveness – Elizabeth T.H. Fontham, Dr.PH., Louisiana State University Health Sciences Center*
- *Genetic Determinants of Prostate Cancer Aggressiveness – Jack A. Taylor, M.D., Ph.D., National Institute of Environmental Health Sciences*
- *Familial Prostate Cancer Susceptibility Genes – William B. Isaacs, Ph.D., Johns Hopkins University*
- *Proteomic Analysis of the Prostate Cancer Host – Emanuel Petricoin, Ph.D., George Mason University*
- *The Androgen Axis in Prostate Cancer – James L. Mohler, M.D., Roswell Park Cancer Institute*
- *Androgen Receptor Regulated Genes and Nuclear Co-activators in Prostate Cancer – Elizabeth M. Wilson, Ph.D., University of North Carolina at Chapel Hill*
- *The Differential Role of Tissue Stem Cells in Prostate Cancer in African and Caucasian Americans – Gary J. Smith, Ph.D., Roswell Park Cancer Institute*

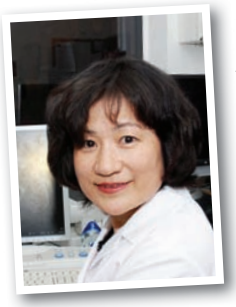
Published Manuscripts from PCaP Studies

PCaP investigators are utilizing the vast resources of clinical and research data and the combined expertise of its investigators to ask critical questions that will help us understand the underlying cause of prostate cancer health disparity and the biology of the disease. Early analyses have yielded important findings that will help focus public health resources and policies on prostate cancer health decisions. Here is a sampling of PCaP's most recent findings published in peer-reviewed journals:

- *The North Carolina-Louisiana Prostate Cancer Project (PCaP): Methods and design of a multidisciplinary population-based cohort study of racial differences in prostate cancer outcomes. Schroeder JC, Bensen JT, Su LJ, Mishel M, Ivanova A, Smith GJ, Godley PA, Fontham ET, Mohler JL.* Prostate. *2006 Aug 1; 66(11):1162–76.*
- *Feasibility of constructing tissue microarrays from diagnostic prostate biopsies. Singh SS, Mehedint DC, Ford OH III, Maygarden SJ, Ruiz B, Mohler JL.* Prostate. *2007 Jul 1; 67(10):1011–8.*
- *Trust, regular source of patient care, and screening and treatment utilization. Carpenter WR, Godley PA, Clark JA, Talcott JA, Finnegan T, Mishel M, Bensen JT, Rayford W, Su LJ, Fontham ET, Mohler JL.* Cancer. *In press.*
- *Comparison of acinus, caspase-3 and tunel as apoptotic markers in determination of tumor growth rates of clinically localized prostate cancer using image analysis. Singh SS, Mehedint DC, Ford OH III, Jeyaraj DA, Pop EA, Maygarden SJ, Ivanova A, Chandrasekhar R, Wilding GE, Mohler JL.* Prostate *(submitted May 17, 2009).*
- *Obesity and prostate cancer aggressiveness among African and Caucasian Americans. Su LJ, Arab L, Steck SE, Schroeder JC, Fontham ET, Bensen JT, Mohler JL.* Cancer *(submitted May 22, 2009).*
- *The relationship between admixture and self-reported race in African and European Americans in the PCaP study. Sucheston LE, Bensen JT, Mohler JL, Parker F, Su LJ, Schroeder JC, Fontham ET, Ruiz B, Xu Z, Taylor JA, Xu J, Smith GJ.* Cancer, Epidemiology, Biomarkers and Prevention *(submitted September 2009).*

Imaging

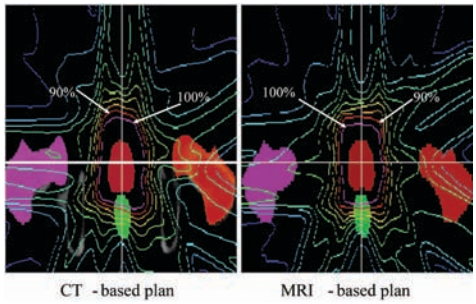
The PCRP recognizes that a lack of new imaging technology is a major barrier to prostate cancer detection, prognosis, and treatment. Although the heterogeneity of prostate cancer presents a challenge for its imaging, the use of molecular imaging may provide insights to help guide cancer detection in its earliest stages, monitor predictive molecular changes, allow assessment of therapeutic efficacy, predict prognosis, and facilitate the delivery of therapeutic agents directly to cancer cells, tissues, and the surrounding environment. Breakthroughs in this field have come from PCRP-funded investigators, who have combined previous diagnostic tools with cutting-edge advances in treatment. The following research studies are supported by the PCRP to develop new imaging agents and technologies for use in prostate cancer detection and treatment.



MRI-Based Treatment Planning for Radiotherapy of Prostate Cancer

Lili Chen, Ph.D., Fox Chase Cancer Center

Having a correct three-dimensional image of the patient's tumor and internal organs is essential during the planning phase of intensity modulated radiation therapy (IMRT) to specifically target tumor tissue and avoid damaging normal tissues and organs. Although this is usually accomplished by computed tomography (CT), Dr. Lili Chen, recipient of an FY03 New Investigator Award, aimed to replace CT with magnetic resonance imaging (MRI)-based treatment planning for IMRT of prostate cancer by improving MRI's accuracy and developing practical procedures for clinical implementation. Comparative analyses of MRI and CT digitally reconstructed radiographs from 20 prostate cancer patients showed only small positional differences, indicating that MRI-based IMRT plans can be used clinically. Furthermore, MRI-based treatment planning has several other benefits, including reduction in patient and staff time, savings in treatment costs, and decreased patient radiation exposure from CT scans. At the Fox Chase Cancer Center, MRI-based treatment planning for prostate cancer has become a standard technique for IMRT of prostate cancer.

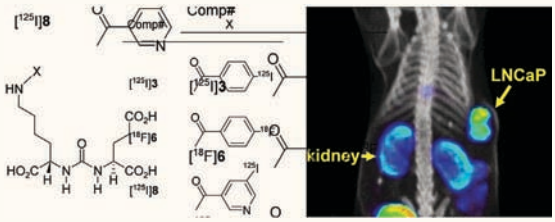


Comparison of IMRT treatment plans based on CT and MRI. The isodose distributions in both plans look similar and are acceptable according to the clinical acceptance criteria. The treatment target (prostate) is in red and the critical structure (rectum) is in green. The left and right femoral heads are in orange and pink, respectively.

PSMA-Based PET Ligands for Prostate Cancer Imaging

Martin Pomper, M.D., Ph.D., Johns Hopkins University

Dr. Martin Pomper, an FY05 PCRP Idea Development awardee, is focusing his studies on the development of positron emission tomography (PET) small-molecule tracers targeting prostate specific membrane antigen (PSMA), which is highly expressed in prostate cancer. The high affinity of the radiolabled small-molecule ligands for PMSA will facilitate rapid entry into tumors and detection of sites of prostate cancer recurrence via imaging. Nine new PET radiotracers were synthesized of varying hydrophobicity targeting PSMA, and these were tested in experimental prostate cancer models using a small animal PET imaging system. Analyses of biodistribution studies and in vivo imaging of tumor-bearing mice identified one compound, [18F]DCFBC, with a high signal-to-noise ratio. [18F]DCFBC is contained in a patent licensed to a pharmaceutical company that also has developed two closely related derivatives currently in Phase I clinical trials to evaluate their safety and utility in imaging prostate cancer in patients.



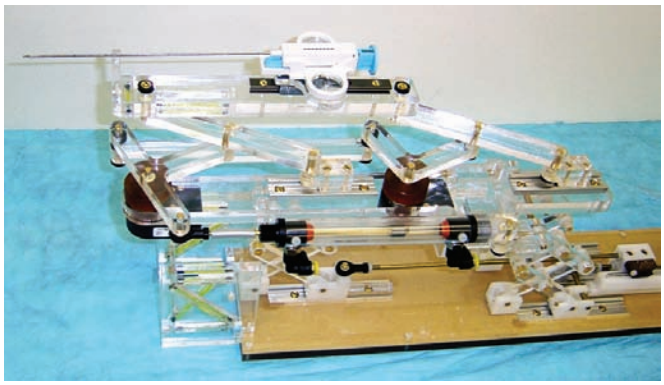
Imaging agents of the urea series that bind specifically to the PSMA

From Chen, Y et al. Radiohalogenated PSMA-based ureas as imaging agents for prostate cancer. J Med Chem *2008; 51:7933–7943*

Robotic Prostate Biopsy in Closed MRI Scanner

Gregory S. Fischer, Ph.D., Worcester Polytechnic Institute

The use of an MRI is well established as an imaging modality in monitoring organ function, tissue mechanics, therapy, and placement of surgical instruments. Despite its superior tissue contrast and volumetric imaging capabilities, high spatial resolution, and sensitivity in detection, its use in guiding prostate biopsy and brachytherapy interventional procedures is limited due to the strong magnetic fields, sensitivity to electronics, and accessibility in confined physical space. Dr. Gregory Fischer, recipient of an FY06 Prostate Cancer Training Award, developed an MRI-compatible robotic system that is capable of operating in a high-field (3 Tesla), closed-bore MRI scanner for interactive guidance of transperineal robotic prostate procedures. The integrated robotic system allows for precise image-guided transperineal prostate needle placement under real-time MRI and limits the effects of organ and patient movement while maintaining appropriate guidance for biopsy and brachytherapy in real time. Initial validation testing in phantom studies confirms MRI compatibility and shows accurate visualization and targeting.

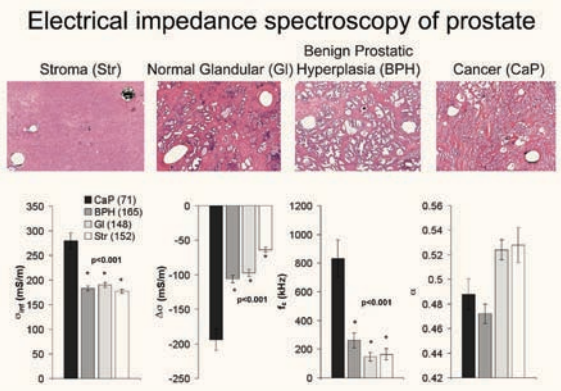


Dr. Fischer is also the recipient of an FY08 New Investigator Award that he is using to advance a clinical-grade version of the MRI-robotic system through further design enhancements and validation in preclinical trials in preparation for Phase I clinical trials in patients.

Electrical Impedance Spectroscopy of Prostate as an Alternative Tool for Cancer Detection

Ryan Halter, Ph.D., Dartmouth College

Dr. Ryan Halter, an FY06 Prostate Cancer Training Award recipient, has investigated the use of electrical impedance spectroscopy (EIS) as a tool for distinguishing benign from malignant prostate cancer by exploiting differences in electrical properties. Utilizing a cohort of 50 patients, Dr. Halter developed and tested an EIS four-point probe that identified differences in electrical properties between benign tissues (including benign prostatic hyperplasia) and prostate cancer, and showed that these differences are significant with respect to relative permittivity, resistivity increment, and relaxation frequency. Based on these observations, Dr. Halter now is using an FY08 New Investigator Award to develop an EIS sensor coupled to a standard clinical biopsy needle for use in transrectal ultrasound (TRUS)-guided biopsy procedures to provide real-time access to the pathological state of prostate tissue, and to more definitively assess the extent and aggressiveness of disease. Dr. Halter's findings and observations may lead to a major improvement in prostate cancer detection, as conventional TRUS-guided biopsy procedures only sample a small portion of the prostate and miss potentially clinically significant lesions. Employing EIS to detect electrical property contrasts in prostate tissues might provide a clear pathway to the clinic as a new modality for improving prostate cancer detection, diagnosis, and treatment.



*The morphological differences noted between the various prostatic tissue types (top) lead to significant contrasts between the spectral impedance parameters (bottom). Bar graphs represent mean spectral electrical impedance parameters for the various tissue types probed. Whiskers represent standard error. * denotes significant difference between CaP and benign tissue type with level of significance noted above.*

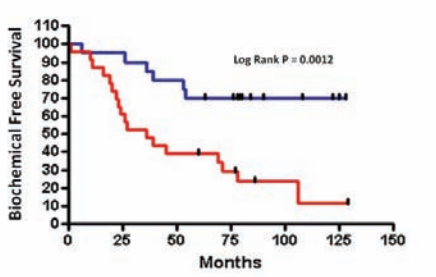
Biomarkers

With the goal of reducing prostate cancer morbidity and mortality, PCRP investigators are characterizing prostate cancer to identify biomarkers that have the potential to help guide therapeutic intervention. These biomarkers will require appropriate validation before they can be translated into clinical use to benefit patients. The following are some of the breakthrough studies that have identified potential new biomarkers for prostate cancer that are being characterized and validated to develop strategies for assessing risk, and for early detection, diagnosis, prognosis and/or therapeutic intervention.

TGF-beta Signatures May Predict Prostate Cancer Recurrence

Phillip Febbo, M.D., Duke University

Dr. Phillip Febbo, recipient of an FY05 New Investigator Award, is exploring the role of TGF-beta signaling in prostate cancer in genetically engineered prostate epithelial cell lines (PrEC). His analysis shows that TGF-beta stimulation activates multiple pro-growth signaling pathways in PrEC, including insulin-like growth factor 1, interleukin 6, and platelet-derived growth factor pathways, and results in an expression-based "signature" of TGF-beta activity. Correlation of the TGF-beta expression "signature" with microarray data from a set of 102 radical prostatectomy samples shows that the TGF-beta signature is associated with biochemical recurrence after surgery. In addition, analysis of a larger dataset including 596 localized prostate tumors also found TGF-beta activity to be associated with recurrence after surgery and the development of metastatic disease. Together, these findings implicate TGF-beta as a potentially important therapeutic target in aggressive prostate cancer.



TGFbeta signature predicts poor prognosis. A signature of TGFbeta activity was developed and applied to prostate cancers from radical prostatectomy specimens. Patients with tumors having a high level of TGFbeta activity (Probability > 0.40, red line) had worse outcomes than patients with tumors having low levels of TGFbeta activity (probability ≤ 0.40, blue line).

Development of a Novel Protocol for Prostate Cancer Detection

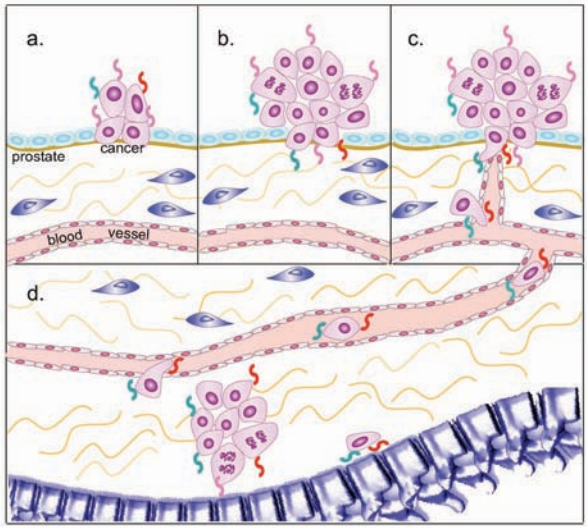
Shuk-Mei Ho, Ph.D., University of Cincinnati

Early diagnosis is vital for reducing death from prostate cancer, and the only approved, clinically relevant biomarker for detection is prostate-specific antigen (PSA). Although serum PSA levels usually correlate with prostate tumor stage and grade, PSA levels also have been found to be elevated in several noncancerous conditions, including benign prostatic hyperplasia (BPH) and prostatitis. An elevated PSA level can sometimes lead to painful and costly prostate gland biopsy for patients—only to find out the biopsy is negative. Dr. Shuk-Mei Ho, recipient of an FY05 Idea Development Award, combined recent advances in clinical and cancer biomarker research to develop a more reliable, cost-effective, and minimally invasive assay for the detection of prostate cancer. Dr. Ho and colleagues performed duplex quantitative real-time polymerase chain reaction assays for prostate cancer biomarkers AMACR (alpha-methylacyl-CoA racemase), prostate cancer antigen-3 (PCA3), and PSA using RNA isolated from urine sediments recovered after digital rectal examinations in 43 patients with prostate cancer and 49 patients without prostate cancer. Normalization of AMACR and PCA3 transcripts to PSA transcript expression and receiver operating characteristic analyses showed that the combination of AMACR and PCA3 in dual-marker tests together increased the level of sensitivity to 81% and improved the specificity to 84% for detection over the serum PSA test alone (sensitivity 77% and specificity 45%). These results show that the combined AMACR and PCA3 urinary test is superior to a serum PSA test for detecting prostate cancer and could be used along with the serum PSA test to improve diagnosis or for surveillance in patients with repeated negative biopsies.

New Markers of Prostate Cancer Progression

Neal Fedarko, Ph.D., Johns Hopkins University

The gene family of Small Integrin Binding Ligand N-linked Glycoproteins (SIBLINGs), comprising bone sialoprotein (BSP), osteopontin (OPN), dentin matrix protein-1 (DMP1), and dentin sialophosphoprotein (DSPP), are induced in some cancers and have been shown to bind and modulate matrix metalloproteinases, which are enzymes involved in tumor progression and angiogenesis. Recent studies conducted by Dr. Neal Fedarko, recipient of an FY04 Idea Development Award, compared the distribution and expression levels of SIBLINGs in the blood of normal individuals, patients with benign prostatic disease, and prostate cancer patients to determine whether SIBLINGs can be used as markers for prostate cancer progression, metastasis, and response to treatment. Serum-based measurements showed that there was a significant increase in BSP and OPN levels as tumors progress to late stage, whereas DSPP levels were significantly elevated in early stages of prostate cancer. OPN levels, but not BSP and DSPP, correlated with serum PSA and immune activation. Other analyses confirmed elevated levels of DSPP in serum from prostate cancer patients. These observations imply that both BSP and DSPP show potential for use as markers of prostate cancer disease progression.



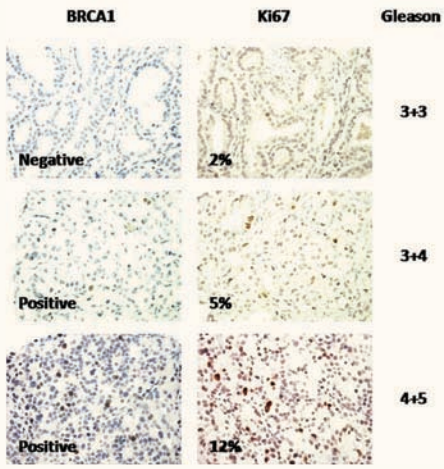
SIBLINGs (∿∿∿) are made by tumor cells (a); promote cell growth (b); new blood vessel formation (c); escape of cancer cells into circulation and distant metastases (d). The SIBLING DSPP (∿) appears to be a marker for early-stage disease while the SIBLINGs BSP (∿) and OPN (∿) are late-stage markers.

From Jain A et al. Small integrin-binding proteins as serum markers for prostate cancer detection. Clin. Cancer Res. *15(16): 5199-5207, 2009.*

Molecular and Clinical Predictors of Aggressive Prostate Cancer

Lorelei A. Mucci, Sc.D., Brigham and Women's Hospital, Harvard Medical School

An FY05 New Investigator Award recipient, Dr. Lorelei A. Mucci, has tested a set of molecular and clinical predictors at diagnosis to discriminate between lethal and indolent prostate cancer using two large, established cohorts: the Physicians' Health Study and the Health Professionals' Follow-up Study. A previously reported 12-gene model was used to predict prostate cancer outcome while a survival model will be developed by combining clinical and genetic markers to predict risk of developing aggressive or lethal disease. Immunohistochemical analyses were performed on tumor tissue microarrays, from a prostatectomy cohort of 950 men, and the results combined with clinical and pathologic data from medical records/reports showed that Gleason grade at the time of diagnosis is a significant predictor of lethal and indolent prostate cancer. At diagnosis, high PSA levels and older age were significantly associated with the development of lethal prostate cancer phenotype. Additionally, Dr. Mucci showed that several biomarkers (BRCA1, p63, cIAP1, and MTA1) were associated with increased prostate cancer-specific mortality 20 years after diagnosis. As result of Dr. Mucci's efforts, she was promoted to Assistant Professor of Medicine and Epidemiology at Brigham and Women's Hospital. The researcher also has received a Young Investigators Award from the Prostate Cancer Foundation.



Protein expression of BRCA1 in prostate tumors, according to Gleason grade and extent of cellular proliferation

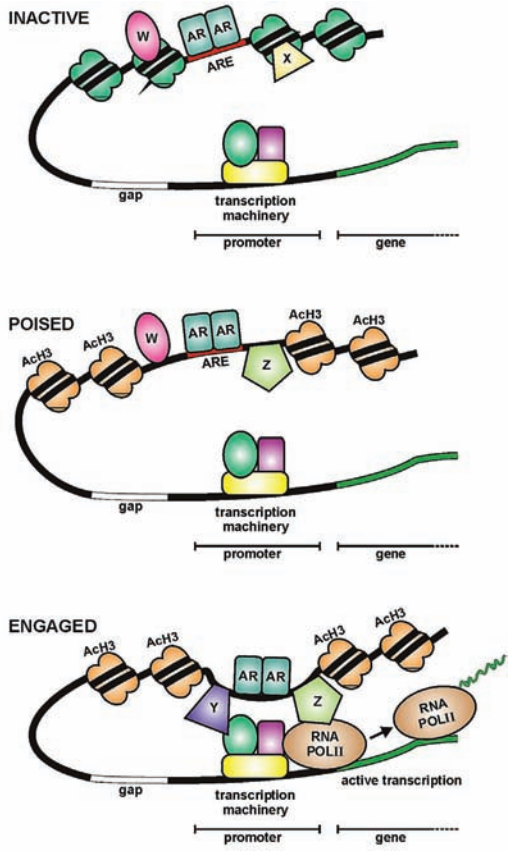
Metastasis

Exactly how prostate cancer spreads through the body is still unclear, and PCRP-funded scientists are working hard to decipher the processes that drive localized prostate cancer to invade, migrate, and become metastatic disease. While investigators have identified some of the key molecules in metastasis, many other elements that participate in cell-cell interactions, dysregulation of cell-matrix adhesion, breakdown of extracellular matrix, extravasations, distal migration, and attachment remain to be identified and functionally analyzed. Understanding the molecular mechanisms and interactions that are involved in the process is important to decrease the suffering and death from prostate cancer.

Androgen Receptor-Mediated Escape from Androgen Ablation Therapy in Prostate Cancer

Baruch Frenkel, D.M.D., Ph.D. (top) and Gerhard Coetzee, Ph.D. (bottom)
Keck School of Medicine, University of Southern California

The underlying reasons regarding why androgen-suppression therapy is initially effective, yet eventually fails to slow disease progression, are still largely unknown. Better understanding of this clinical problem may reside in high-throughput genomic technologies. Chromosomes 19 and 20 contain several androgen receptor (AR) target genes, including the PSA/Kallikrein gene family, which may point to some clues. FY04 Idea Development Award recipients Drs. Baruch Frenkel and Gerhard Coetzee used C4-2B prostate cancer cells to perform chromatin immunoprecipitation microarray analyses to uncover AR-occupied regions (ARORs) and markers of actively transcribed regions (histone H3 acetylation [AcH3]) on chromosomes 19 and 20. Sixty-two ARORs and 1388 AcH3 loci were mapped to both chromosomes, and 32 ARORs (52%) were associated with actively transcribed regions defining a subset of ARORs, which are likely to be androgen responsive. Microarray expression analyses in C4-2B cells showed that genes adjacent to ARORs and AcH3 loci, such as the PSA gene, were 10 times more likely to be androgen responsive compared to genes adjacent to ARORs without AcH3 loci. Further, nearly half of ARORs in prostate cancer cells are either inactive or awaiting activation as the cellular environment changes. This study illustrates the diversity of gene-specific functions of the AR. Identifying the myriad downstream effects of AR activation is critical to understanding how cells escape androgen suppression therapy.



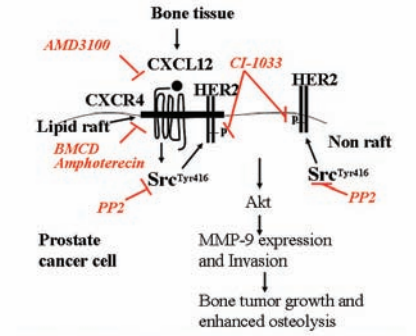
Schematic model of the functions of AR occupied region: Three types of AR/DNA engagements are envisioned. Inactive ARORs represent AR-occupying sites of relatively condensed chromatin along with coregulators W and X; these sites may represent a reservoir of AR to be used after dramatic changes in physiological conditions. Poised ARORs represent AR at AcH3-modified sites ready to engage the transcription initiation machinery, but held in check by coregulaters W and Z. Engaged ARORs represent AR in action; combinatorial control by the AR, along with coregulators Y and Z and other factors, result in looping of these ARORs across varying genomic distances to promote transcription of target genes.

From Jia L et al. Genomic androgen receptor-occupied regions with different functions, defined by histone acetylation, coregulators and transcriptional capacity. PLoS ONE *3(11): e3645, 2008.*

The Role of SDF-1(Alpha)/CXCR4/MMP in Prostate Cancer Metastasis to Bone

Sreenivasa R. Chinni, Ph.D., Wayne State University School of Medicine and the Barbara Ann Karmanos Cancer Institute

Prostate cancer metastasis is the primary cause of mortality in patients. Chemokines and their receptors play a role in tumor cell migration and homing of metastatic cells to target tissues. Dr. Sreenivasa Chinni, recipient of an FY02 New Investigator Award, has been studying the role of chemoattractive mechanisms in prostate cancer bone metastasis. He hypothesized that the interaction of chemokine ligand stromal cell-derived factor-1 alpha (SDF-1α, also known as CXCL12) to its receptor, CXCR4, plays a crucial role in metastasis to bone. Studies by Dr. Chinni and colleagues showed that the expression of both CXCR4 and SDF-1α were detectable in prostate cancer cells and human fetal bone stromal cells. They found that migration of PC-3 prostate cancer cells in bone cocultures was dependent on SDF-1α/CXCR4 signaling, and SDF-1α induced the expression of matrix metallopeptidase 9 (MMP-9) protease in prostate cancer cells. Metalloproteases promote tumor progression and metastasis by degrading the extracellular matrix and promoting angiogenesis, a process required for tumor growth. Finally, gene expression profiles revealed that several members of the protease and chemokine families were upregulated in CXCR4-overexpressing PC-3 cells. These data suggest that chemoattractive mechanisms are involved in migration of prostate cancer cells toward bone tissue, and that cell signaling induced by binding of the chemokine to its receptor leads to the activation of multiple signaling pathways, including release of metalloproteases providing a link between chemoattractive mechanisms, growth of tumor cells in bone, and tumor-enhanced bone matrix turnover.

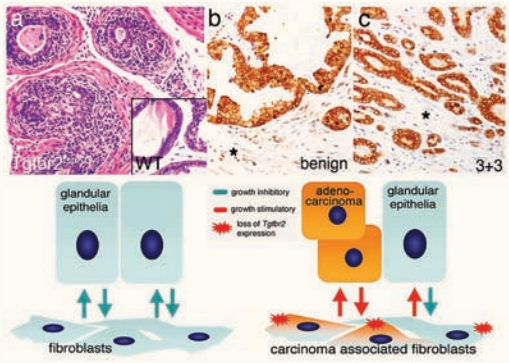


A model showing CXCL12/CXCR4 signaling in lipid raft membrane microdomains of prostate cancer cells.

Stromal Signaling Molecules as Potential Biomarkers of Metastatic Prostate Cancer

Neil A. Bhowmick, Ph.D., Vanderbilt University

In the normal human prostate gland, the epithelial compartment (composed of basal, luminal, and rare neuroendocrine cells) forms ducts that are in close contact with an underlying stromal compartment (composed of smooth muscle, myofibroblasts, blood vessels, and occasional fibroblasts). Dr. Neil Bhowmick, a recipient of FY01 and FY03 New Investigator Awards, developed a mouse model lacking the TGF-beta type II receptor (TGFBR2) in stromal cells. At 5 to 7 weeks of age, these mice developed spontaneous prostatic intraepithelial neoplasia (PIN) lesions showing that loss of TGFBR2 expression in the stroma induces early signs of tumorigenesis. The role of TGF-beta in prostate cancer was further investigated by mixing human prostate cancer cells with mouse prostatic stromal cells and transplanting them into mice. These mice developed tumors, but tumors containing stroma derived from conditional TGFBR2 knockout mice were 5 times larger than those with stromal cells derived from normal (wild-type) mice, suggesting that loss of TGFBR2 expression in the stroma enhanced tumor progression. To relate these observations to human prostate cancer, TGFBR2 protein expression was assessed in benign tissue and tumors from patients who had undergone radical prostatectomy. The cancer samples were 10 times less likely to show expression of stromal TGFBR2 than the benign prostate samples. Since recurrent disease following prostatectomy is indicative of metastatic cancer spread and poor outcome, stromal-derived signaling molecules represent both potential biomarkers for diagnosis of patients at risk of developing metastatic prostate cancer and potential therapeutic targets.

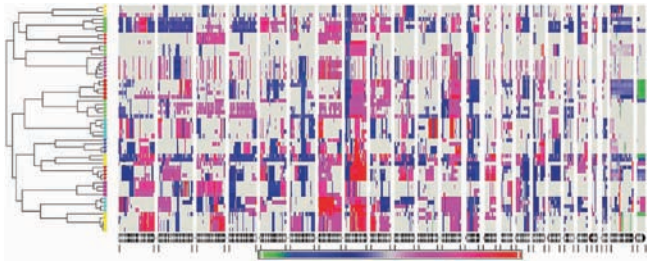


(a) The loss of TGF-beta responsiveness in the prostate stroma leads to prostate cancer initiation in the stromal conditional knockout mouse model (Tgfbr2fspKO). (b) Benign human prostate tissue expresses TGF-beta type II receptor in both epithelial and stromal compartments. (c) Analogous to the conditional mouse knockout model, stromal loss of TGF-beta receptor type II expression is observed in human prostate cancer.

Genome-Wide Copy Number Analysis Indicates Monoclonal Origin of Lethal Metastatic Prostate Cancer

G. Steven Bova, M.D. (top) and Srinivasan Yegnasubramanian, M.D., Ph.D. (bottom), Johns Hopkins University

With funds from their PCRP awards, investigators Drs. G. Steven Bova (FY04 Exploration-Resource Development Awardee) and Srinivasan Yegnasubramanian (FY07 New Investigator Awardee), along with colleagues, studied whether metastatic prostate cancer originates from single or multiple primary cancer cell clones using genomic technologies. DNA from two or more anatomically separate metastatic cancer sites, as well as from normal tissues taken at autopsy from 29 men who died from metastatic prostate cancer, were analyzed by comparative genomic hybridization and high-resolution genome-wide SNP analysis to assess the loss or gain of chromosome copy number and to determine on a genome-wide scale if the metastases share a common origin. The investigators found that metastatic prostate cancer cells contain a common defined set of copy number defects that can be traced to a parent cancer cell arising in the prostate while also acquiring a subset of variable copy number changes not shared between metastatic sites. These findings show that most metastatic cancer sites have their beginnings in a single precursor cell and furthermore suggest that integration of genetic, epigenetic, and expression data from primary tumors and metastatic sites may be a powerful approach toward the identification of effective new diagnostics and targeted therapeutics.



Unsupervised hierarchical clustering of Affy6 copy number data from 58 anatomically separate metastatic prostate cancer sites in 14 patients. All samples from each of 14 patients cluster together. From Liu W et al. Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer. Nature Medicine *15 (5): 559-565, 2009.*

Therapeutics

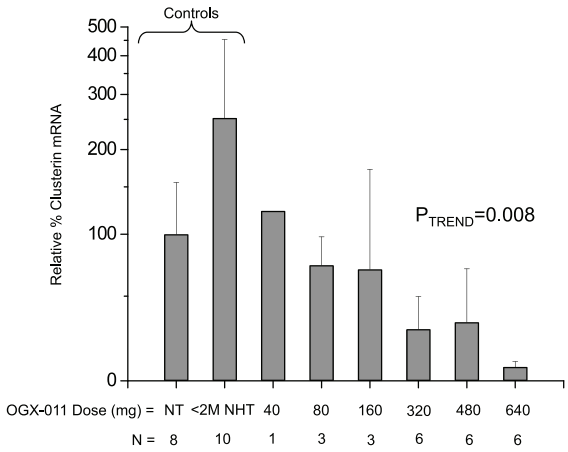
Advanced Therapeutics on the Edge of a Breakthrough

Translating basic discoveries into clinical trials to advance cancer treatment for prostate cancer patients is a high priority for PCRP-funded investigators. Developing new therapeutics and diagnostics for patient care requires collaboration among many scientists to design innovative clinical trials that extend from potential therapeutics developed and tested extensively at the laboratory bench. Evaluating the safety and effectiveness of novel therapeutics and diagnostics relies entirely on patients who participate in the trials. The following highlights are a few of the major contributions by PCRP investigators in the fight against prostate cancer.

Clusterin Antisense Oligonucleotide (OGX-011): A Major Advance?

Kim Chi, M.D., British Columbia Cancer Agency, Vancouver

Clusterin is a prosurvival protein that serves a protective function in cells. It inhibits apoptosis, is overexpressed in prostate cancer, and is associated with cancer progression. OGX-011 is a potential new therapeutic that targets clusterin and reduces its expression in prostate cancer cells. Dr. Kim Chi, recipient of an FY01 Clinical Trial Award, conducted Phase I and II clinical trials of OGX-011 in combination with neoadjuvant hormone therapy prior to radical prostatectomy in patients with high-risk localized prostate cancer. These studies, now completed, have provided evidence demonstrating that OGX-011 causes a dose-dependent decrease in clusterin expression in prostate cancer and lymph nodes of affected patients, establishing a biologically effective dose of 640 mg with only low-grade toxicities observed. The efficacy of OGX-011 in decreasing clusterin expression in prostate cancer patients has led to additional Phase II trials, including one with docetaxel in hormone refractory prostate cancer that was supported by additional funding from other sources. The results of the combination trial showed an increase in median survival time in patients receiving docetaxel plus OGX-011 compared to those patients that had received docetaxel alone. Consequently, OGX-011 will soon enter a Phase III clinical trial and, if successful, would represent the first antisense therapeutic to demonstrate clinical benefit for cancer patients, marking a major advance in cancer therapeutics.

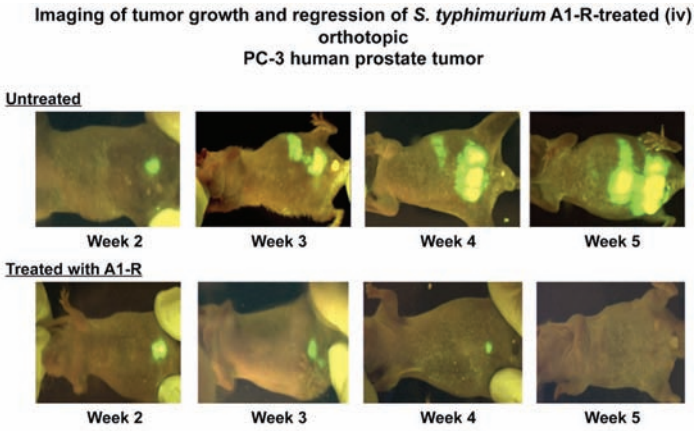


Clusterin mRNA by quantitative RT-PCR in laser-captured microdissected prostate cancer cells demonstrating a dose-dependent inhibition of clusterin expression by OGX-011. Abbreviations: NT, no prior treatment; <2M NHT, less than 2 months of neoadjuvant hormone therapy. Columns represent mean score, and error bars represent standard deviation. Chi KN et al. A phase I pharmacokinetic and pharmacodynamic study of OGX-011, a 2 ' -methoxyethyl antisense oligonucleotide to clusterin, in patients with localized prostate cancer. Journal of the National Cancer Institute, *97(17) 1287-1296, 2005.*

Salmonella Mutant A1-R Slows Prostate Cancer in Metastatic Mouse Model

Ming Zhao, M.D., Ph.D., AntiCancer Incorporated

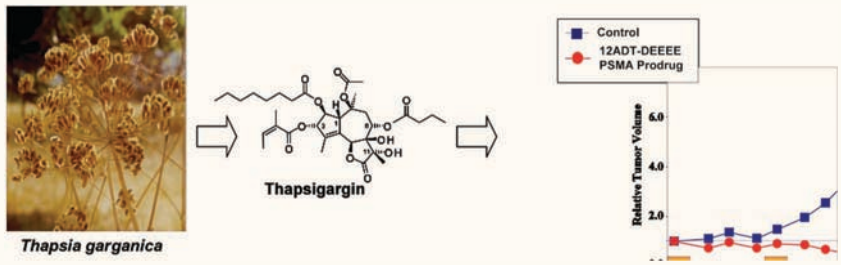
Dr. Ming Zhao, recipient of an FY05 Idea Development Award, has developed a strain of *Salmonella typhimurium (S. typhimurium)* that can target and kill metastatic prostate cancer cells in mice. It has long been known that anaerobic bacteria, such as *S. typhimurium*, can grow selectively in hypoxic and necrotic regions of tumors. Dr. Zhao's *S. typhimurium* strain, termed A1-R, helps restrict growth in normal tissues and favors growth in necrotic areas of tumors. To test antitumor efficacy of A1-R, mice with implanted PC-3 human prostate tumors received weekly intravenous injections of A1-R bacteria. The biodistribution ratio of A1-R in tumor to normal tissue was approximately 10^6, indicating a high degree of tumor targeting by A1-R. Thirty days after tumor implantation, tumor size in the treated group was approximately 75% smaller than the untreated mice. In addition, the untreated group showed metastases to other organs, and all untreated mice died within 6 weeks of tumor implantation. In contrast, metastatic tumors in mice treated with A1-R grew slowly or disappeared completely. Seventy percent of these mice were alive on day 40 when the last untreated mouse died. A1-R treatment resulted in a doubling of the 50% survival time compared to untreated mice. In addition, 40% of the A1-R treated mice remained alive 6 months after tumor implantation and were essentially cured of prostate cancer. These interesting findings may pave the way toward the development of a novel and powerful form of targeted therapy.



Enzymatic Activation of Peptide Prodrugs by PSMA as Targeted Therapy for Prostate Cancer

Samuel Denmeade, M.D., Johns Hopkins University

The limited efficacy of many chemotherapeutic agents lies in their inability to effectively destroy nonproliferating cells. Thapsigargin (TG) is a plant toxin that is capable of inducing apoptosis in cells irrespective of their ability to proliferate. Dr. Samuel Denmeade, a recipient of multiple PCRP Idea Development Awards, has coupled inactive amine-containing TG analogs (prodrug) to the substrate for PSMA to target prostate cancer cells where PSMA is highly expressed. Activation of the TG prodrug by PSMA induces prostate cancer cell death in proliferating and nonproliferating prostate cancer cells. The PSMA-activated prodrugs are stable and 15- to 57-fold more toxic to PSMA-producing prostate cancer cells. Analyses in mice bearing human PSMA-producing prostate cancer tumors identified one lead prodrug that demonstrated complete and sustained inhibition of prostate cancer tumor growth with minimal toxicity. The effectiveness of the TG prodrug in killing PSMA-producing prostate cancer cells supports its development as a therapeutic for prostate cancer entering into Phase I clinical trials.

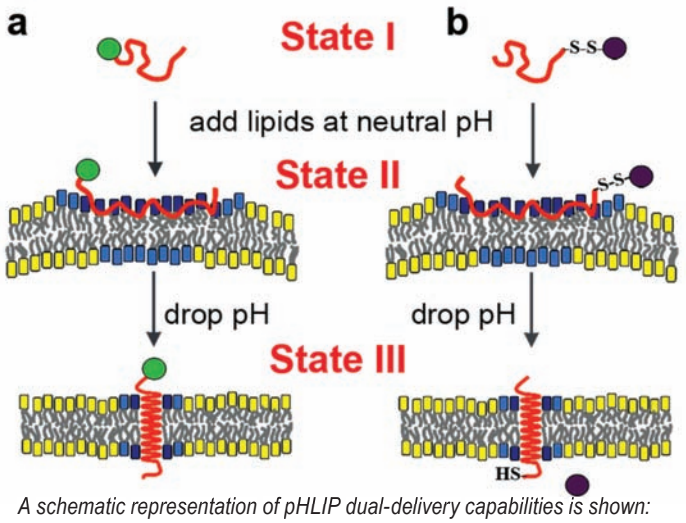


Thapsigargin is isolated from the seeds of Thapsia garganica and is converted to a prodrug by coupling to the PSMA-specific peptide Asp-Glu-Glu-Glu-Glu (DEEEE). Prodrug treatment of PSMA-producing prostate cancer xenografts results in regression and sustained growth inhibition.

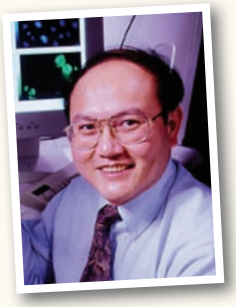
Development of Peptide Conjugates Specifically Targeting Metastatic Prostate Cancer

Yana Reshetnyak, Ph.D., University of Rhode Island

Dr. Yana Reshetnyak, an FY05 New Investigator Award recipient, is developing a novel strategy to attack metastatic prostate cancer cells by taking advantage of the Warburg effect (i.e., cancer cells maintain lower extracellular pH than normal cells due to lactic acid production and elevated CO_2 levels). Dr. Reshetnyak is using a short peptide (pH Low Insertion Peptide [pHLIP]) derived from bacteriorhodopsin, which acts as a microscopic syringe to selectively deliver drugs/agents to cancer cells. pHLIP exists in a water-soluble form that binds to cell membranes with no insertion and drug translocation at pH (7.4), but at acidic pH, pHLIP inserts across the cell membrane and translocates drugs/agents attached to its C-terminus to the cytoplasm of cancer cells. By tethering pHLIP to fluorescence dyes or 64Cu-DOTA chelate and applying whole-body fluorescent and PET imaging, Dr. Reshetnyak has shown that pHLIP can target human prostate tumors in mice with high accuracy. The accumulation of pHLIP in tumors directly depends on the extracellular acidity of the tumor environment, which correlates with the aggressiveness of tumors. The success of these studies involving pHLIP paves the way for the development of a novel delivery system for targeting prostate cancer cells to enhance efficacy of treatment and significantly reduce side effects.



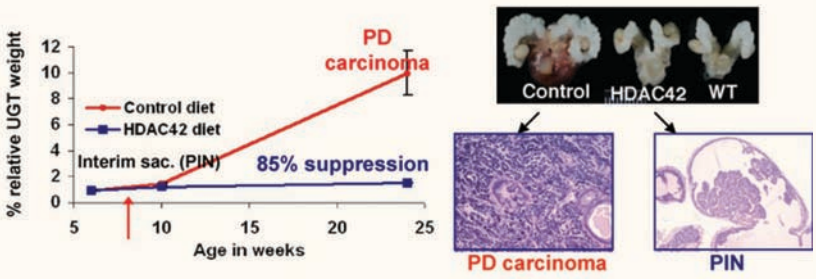
A schematic representation of pHLIP dual-delivery capabilities is shown: (a) tethering of cargo molecules to the surface of cells with low extracellular pH and (b) translocation of cell-impermeable polar cargo molecules across the membrane lipid bilayer. Andreev OA, Engelman DM, and Reshetnyak YK. Targeting acidic diseased tissue. Chemistry Today *27: 34–37, 2009.*



Novel Molecularly Targeted Agents for Prostate Cancer Treatment

Ching-Shih Chen, Ohio State University

Heterogeneity in the genetic and cellular defects associated with prostate cancer progression to a hormone-independent state represents a major challenge to the development of effective treatments for advanced disease. Dr. Ching-Shih Chen, recipient of FY04 and FY07 Idea Development Awards, has developed two oral agents that target signaling pathways underlying prostate cancer tumorigenesis and progression. The agents include OSU-HDAC42, a novel histone deacetylase (HDAC) inhibitor, and OSU-03012, derived from cruciferous vegetables, which targets the PDK-1/Akt signaling pathway. In prostate cancer cell lines, both agents were shown to be potent inhibitors of prostate cancer cell growth and survival. While OSU-HDAC42 showed greater potency compared to SAHA (vironostat), OSU-03012 was shown to be significantly more potent. In prostate cancer xenograft models, both drugs were shown to suppress tumor growth without any signs of toxicity. These drugs have been licensed for Phase I clinical trials. Based on the effectiveness of these compounds in blocking prostate cancer growth and survival, Dr. Chen is investigating their efficacy in chemoprevention of prostate cancer.



OSU-HDAC42 decreased the severity of prostatic intraepithelial neoplasia (PIN), prevented progression to poorly differentiated (PD) carcinoma, and suppressed urogenital tract (UGT) weights by 24 weeks of age in the TRAMP mouse model (Sargeant M et al. OSU-HDAC42, a histone deacetylase inhibitor, blocks prostate tumor progression in the transgenic adeno-carcinoma of the mouse prostate model. Cancer Res. *68: 3999-4009,2008).*

Training

The PCRP supports hundreds of outstanding prostate cancer research trainees in laboratories around the world who are involved in breakthrough discoveries in basic, clinical, and epidemiological research aimed at eliminating prostate cancer. The program supports predoctoral, postdoctoral, and summer trainees under the guidance of experienced prostate cancer researchers. The active involvement of these mentors in the context of a training program and research environment significantly contributes to their development as prostate cancer investigators. Here we highlight some of the outstanding accomplishments of our trainees as they prepare to assume new roles of scientific leadership in the prostate cancer research community.

Forging a Path from Trainee to Investigator

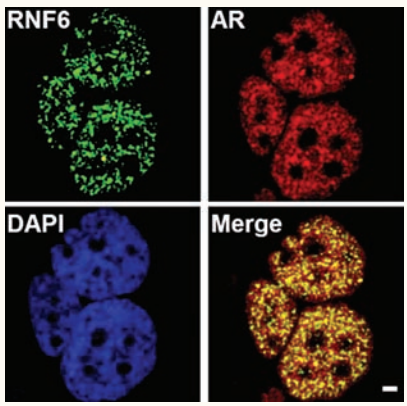
Arun Sreekumar, Ph.D., University of Michigan

The PCRP aims to support research that will one day lead to the eradication of prostate cancer, with the understanding that success relies heavily on the training of new investigators in this field. As an FY02 Postdoctoral Training Award recipient, Dr. Arun Sreekumar studied prostate cancer profiles using protein microarrays, hoping to discover novel biomarkers and develop new, noninvasive methods to detect prostate cancer. He created microarrays specific to prostate cancer proteins and used these to examine the sera from prostate cancer patients. After developing an "epitomic profile" of prostate cancer by identifying autoantibodies generated by the body against prostate cancer proteins, Dr. Sreekumar identified multiple prostate cancer biomarkers detectable with high sensitivity and specificity in urine and serum that may lead to more robust methods for early detection of prostate cancer utilizing multiple prostate cancer biomarkers, including AMACR. Dr. Sreekumar's research has led to four publications and two patents that will advance prostate cancer diagnostics. Recently, Dr. Sreekumar received his first R01 award from the National Cancer Institute to research cellular metabolism during prostate cancer progression, marking his successful transition, with the support of the PCRP, from trainee to independent investigator. This accomplishment underscores the PCRP's emphasis on the training of young investigators in prostate cancer research to expand scientific knowledge and find new therapies to conquer this disease.

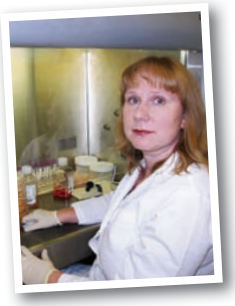
Regulation of Androgen Receptor Transcriptional Activity and Specificity

Kexin Xu, Ph.D., University of Maryland School of Medicine

Dr. Kexin Xu, recipient of an FY05 Predoctoral Traineeship Award, examined the role of androgen receptor (AR) interacting proteins that are important in castration-resistant prostate cancer. Dr. Xu and colleagues identified RNF6 as an AR-associated protein in CWR-R1 hormone refractory prostate cancer cells. RNF6 is an ubiquitin E3 ligase that modifies proteins by adding ubiquitin, an event generally thought to induce protein degradation. Experiments using short hairpin RNA to specifically inhibit RNF6 protein expression in LNCaP prostate cancer cells demonstrated that RNF6 selectively alters the expression of a subset of AR-responsive genes. Immunohistochemical analyses of human prostate cancer tissues showed that RNF6 is upregulated in hormone-refractory prostate cancer and may be important in prostate cancer growth under androgen-depleted conditions. Therapeutic intervention targeting RNF6 in hormone-refractory prostate cancer might be an effective treatment for advanced prostate cancer.



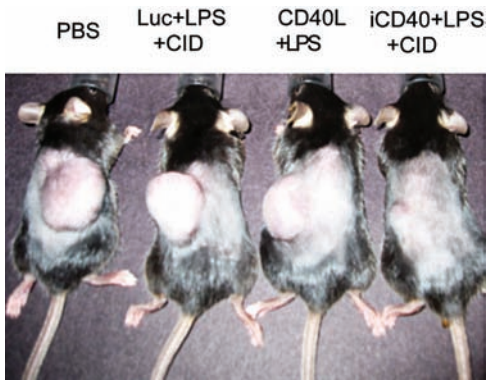
*Interaction between RNF6 and AR in hormone-refractory prostate cancer cell line CWR-R1. Confocal immunofluorescence microscopy was carried out by costaining in CWR-R1 cells with anti-AR (red) and anti-RNF6 (green) antibodies. Nuclei were counterstained with DAPI (blue). Scale bar = 1 μm. (*Cancer Cell, *Volume 15, Issue 4, pp. 270–282, 2009)*



Preclinical Evaluation of Novel Dendritic Cell-Based Prostate Cancer Vaccine

Natalia Lapteva, Ph.D., Baylor College of Medicine

Dendritic cell (DC)-based vaccination is a promising strategy for prostate cancer immunotherapy. However, the clinical efficacy of DC vaccines in cancer patients has been unsatisfactory, probably because of a number of key deficiencies, including suboptimal and transient DC activation leading to subsequently impaired T cell responses and limited migration to draining lymph nodes. Postdoctoral Trainee Dr. Natalia Lapteva has investigated a novel DC-based prostate tumor vaccine developed by Drs. Kevin Slawin and David Spencer. Their approach involves expressing the intracellular signal transduction domain of CD40, a DC activation molecule, which is fused to a synthetic drug binding dimerization domain. This prostate cancer vaccine has been rendered tumor cell-specific by incubation of DC with recombinant PSMA.



Mouse DC vaccine expressing drug-inducible CD40 eradicates pre-existing tumors. Mice-bearing E.G7 tumors (n=5/group) were treated by a single DC vaccine followed by AP1903 (CID) administration. Mice of control groups were treated with phosphate buffer solution (or saline), DC activated with Ad-luciferase or DC activated with CD40L and LPS.

Dr. Lapteva demonstrated that the DC-based vaccine could significantly enhance survival and pro-inflammatory cytokines production in DCs in vitro when activated with the dimerization-inducing drug and lipopolysaccharides (LPS). In vivo studies in a tumor mouse model showed that the vaccine potently inhibited tumor growth in a dose-dependent manner, suggesting the vaccine has immunotherapeutic efficacy. Based on these preclinical observations, an Investigational New Drug application was filed with the FDA, and this vaccine will be tested in castration-resistant prostate cancer patients in a standard dose escalation Phase I/II clinical trial at Memorial Herman Hospital, Houston, Texas.

Inspiring Students Through Mentorship in Prostate Cancer Research

The PCRP Collaborative Undergraduate Historically Black Colleges and Universities (HBCU) Student Summer Training Program Award (STPA) was created to encourage HBCU students to pursue careers in prostate cancer research. Since the creation of this mechanism in FY04, training program awards have been granted to 14 laboratories with expertise in prostate cancer research. Following a competitive selection process, students receive training in prostate cancer research and are provided with opportunities to interact with other scientists and clinicians by attending workshops, weekly seminars, lab meetings, journal clubs, and national conferences. Examples of two successful training programs are those being conducted by Dr. Timothy McDonnell at the University of Texas M.D. Anderson Cancer Center and by Dr. Yu-Dong Yao at the Stevens Institute of Technology.

Dr. McDonnell is the recipient of an FY04 STPA award to train students from Texas Southern University (TSU). The awardee designed a unique training program in which students participate in a didactic curriculum (e.g., short courses and speaker seminars), obtain hands-on training and mentorship in the laboratories of national experts in biology, medical oncology, radiation oncology, molecular pathology, and epidemiology cancer research, and receive ongoing training in scientific ethics, laboratory safety, scientific literature, and scientific presentations at the Graduate School of Biomedical Sciences. Additionally, Dr. McDonnell has provided for the prostate cancer training of a faculty mentor from TSU to ensure the students continue to develop their knowledge and understanding of prostate cancer biology and to sustain the development of the training program at TSU. Sixteen students have successfully completed the training program, and five students have gone on to pursue graduate degrees in biomedical science and medicine. The success of Dr. McDonnell's training program resulted in a new award in FY08 to train a new cadre of students in prostate cancer research.

As an FY04 STPA awardee, Dr. Yao developed a collaboration between the Stevens Institute of Technology and Jackson State University, an HBCU institution. Additionally, the Moffitt Cancer Center at the University of Florida also has contributed its expertise to this training program. Dr. Yao designed a training program organized into 12 units that involved weekly group meetings, seminars, and laboratory work in telemedicine focused on using broadband technology to provide access to prostate cancer screening and diagnosis, particularly in rural areas. The students received training under the guidance of their mentors in the use of a wireless information system and applications in telehealth and telepathology to develop multimedia platform software packages for communication between screening sites and a central prostate cancer network office. The software package includes audio, video streaming, text, and whiteboard applications for teleconsultation and telediagnosis. Students worked on developing a comblock-based wireless test bed for use in detection and diagnosis of prostate cancer via a wireless network. Based on the summer training experience, the excited students expressed increased interest in pursuing careers in prostate cancer research and bioengineering for medical systems and applications. Dr. Yao has trained 21 students thus far, and 5 students have gone on to pursue graduate degrees in biomedical science and bioengineering. He plans to continue the summer research program with the hope of capturing the interest and imagination of a new group of HBCU undergraduate students interested in research careers in prostate cancer.

Dr. Yao's Laboratory, Summer Students in Training

Innovative Minds in Prostate Cancer Today

IMPaCT

The PCRP Innovative Minds in Prostate Cancer Today (IMPaCT) scientific meeting will take place in 2011 in Orlando, Florida.

The IMPaCT meeting will bring together PCRP-supported investigators and consumer advocates from across the country for 3 days of intensive learning to forge a new path in scientific discovery and to accelerate the elimination of death and suffering from prostate cancer.

The Vision for FY08 and FY09

In both FY08 and FY09, the PCRP received a congressional appropriation of $80M. The program's investment portfolio in FY08 included clinical research and resources, innovative research, and training and recruitment. Eleven unique award mechanisms were developed to forge new pathways in prostate cancer. A total of 1,344 applications were received, and 188 awards were made.

In FY09, an investment strategy was developed that emphasized development of new resources for prostate cancer, innovation in population-based studies, novel ideas, technology, and training and recruitment of a new cadre of prostate cancer investigators. The program offered 10 award mechanisms that provided multiple levels of support to address priorities and obstacles in prostate cancer research. In FY09, the program received 848 applications following preproposal screening, and 163 awards were recommended for funding.

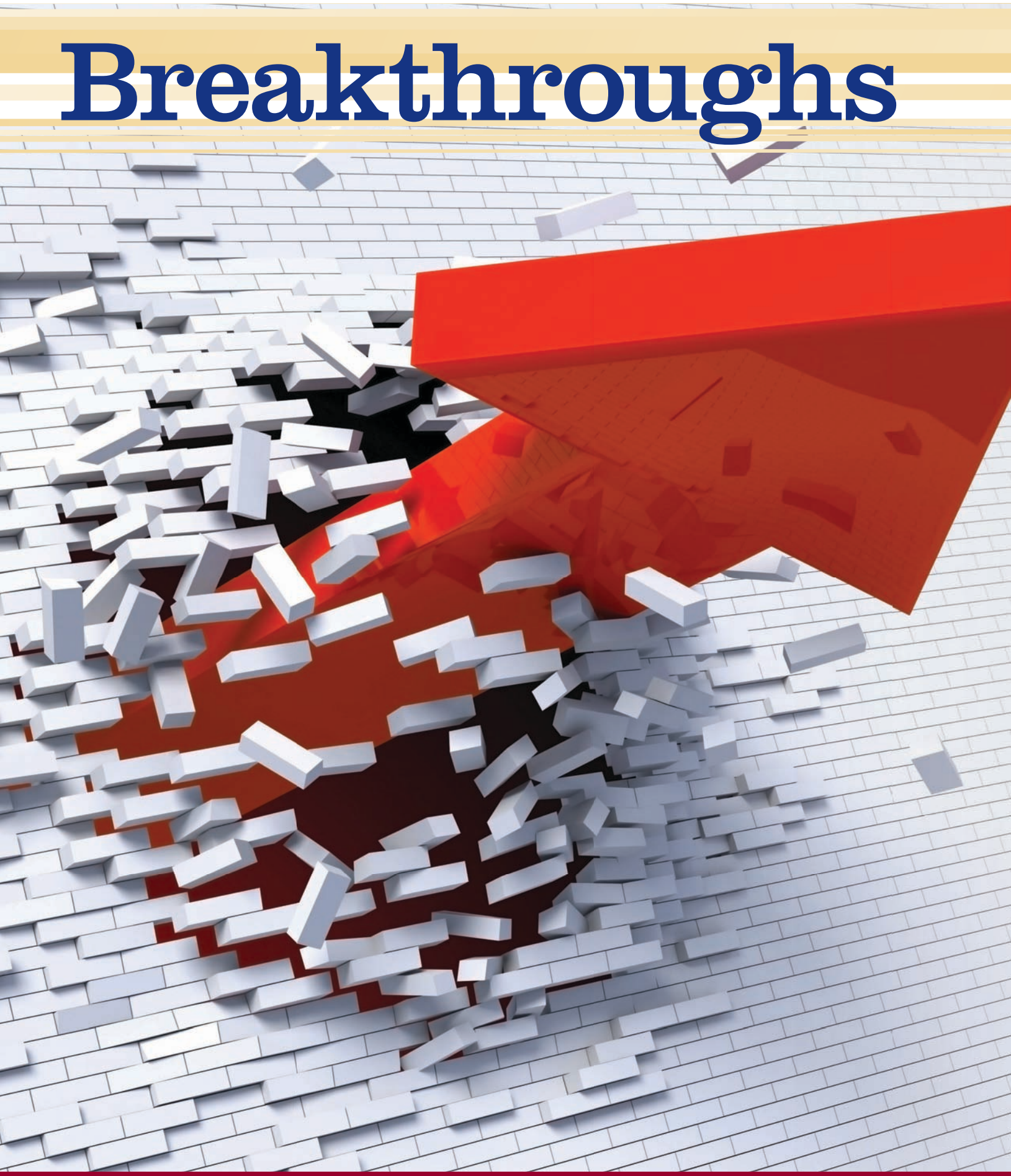
Categories and Award Mechanisms	FY08		FY09	
	Proposals Received	Awards Made	Proposals Received	Awards Recommended for Funding
Resource				
Pathology Resource Network	not offered	not offered	19	2
Clinical Research				
Clinical Consortium	19	13	not offered	not offered
Clinical Trial	27	2	not offered	not offered
Laboratory-Clinical Translational Award: Stage I	19	3	not offered	not offered
Innovative Research				
Idea Development	636	51	291	38
Population-Based Idea Development	not offered	not offered	31	0
Health Disparity Research	50	9	39	6
New Investigator	149	25	148	28
Synergistic Idea Development	213	12	90	14
Training/Recruitment				
Collaborative Undergraduate HBCU Student Summer Training Program	14	8	6	4
Health Disparity Training	4	3	3	1
Physician Research Training	13	8	13	8
Prostate Cancer Training	200	54	208	62
Totals	1,344	188	848	163

The Vision for FY10

The congressional appropriation for the PCRP FY10 program is $80M. The program developed an ambitious investment strategy to address major priorities in the field of prostate cancer. With two overarching challenges to the research community, (1) the development of effective treatments for advanced disease and (2) the ability to distinguish lethal from indolent disease, the PCRP released 10 program announcements for FY10. The award mechanism categories focus on **impact, innovation, translational research, and training/recruitment**. To specifically address the major issue of overtreatment of primary prostate cancer, the program is for the first time offering the **Impact Award**.

Focus	Award Mechanism
Impact Research 	Population-Based Idea Development Award: Supports high-impact approaches to prostate cancer research from the perspective of population-based studies that will, if successful, significantly accelerate the elimination of death and suffering from prostate cancer.
	Impact Award: Supports high-impact studies toward reducing or eliminating the problem of overtreatment of primary prostate cancer.
Innovative Research 	Idea Development Award: Supports new ideas that represent innovative, high-risk/high-gain approaches to prostate cancer research and have the potential to make an important contribution to eliminating death and suffering from prostate cancer.
	Exploration-Hypothesis Development Award: Supports highly innovative, untested, potentially groundbreaking concepts in prostate cancer.
	Synergistic Idea Development Award: Supports new or existing partnerships between two or three independent investigators to address a central question in prostate cancer that may include high risk, provided there is a potential for significant impact.
	Health Disparity Research Award: Supports new ideas that represent innovative, high-risk/high-gain approaches to prostate cancer health disparity research.
Translational Research	Laboratory-Clinical Transition Award: Supports goal- and product-driven preclinical studies of promising lead agents or targets that may revolutionize prostate cancer clinical care.
Training/Recruitment 	Physician Research Training Award: Supports training of physicians with clinical duties for careers in prostate cancer research.
	Prostate Cancer Training Award: Supports prostate cancer research training for individuals in the early stages of their careers.
	Health Disparity Training Award: Supports training in prostate cancer health disparity research for individuals in the early stages of their careers.

Breakthroughs



in Prostate Cancer Research Supported by the PCRP

The PCRP's focus on funding innovative ideas, high-impact, high-risk research has resulted in breakthroughs that will improve lives and advance research into the next frontier. Examples of successes are:

- **Magnetic resonance imaging-based treatment planning for radiotherapy of prostate cancer:** MRI-based treatment was shown to be advantageous over standard computed tomography imaging with decreased radiation exposure duration and cost for prostate cancer treatment. MRI-based treatment planning for Intensity-Modulated Radiation Therapy of prostate cancer is now the standard of care at Fox Chase Cancer Center.
  New Investigator Awardee, Dr. Lily Chen, Fox Chase Cancer Center

- **Development of hypoxia-inducible factor-1 alpha (HIF-1 alpha) antibody:** Antibody developed to HIF-1 alpha signaling molecule, which is induced by hypoxic conditions in prostate tumor cells and leads to the induction of tumor angiogenesis. The anti-HIF-1 alpha antibody is commercially available as a reagent for research laboratories around the world.
  Idea Development Awardee, Dr. Robert Abraham, Burnham Institute

- **Sunitinib advancing to Phase III clinical trial:** This multitarget inhibitor of receptor tyrosine kinases was studied in a Phase II clinical trial of 34 men with advanced prostate cancer (17 chemotherapy-naïve and 17-docetaxel refractory androgen-independent prostate cancer subjects). Favorable radiographic and clinical responses have resulted in the initiation of a Phase III trial of sunitinib with prednisone in men with docetaxel-resistant metastatic prostate cancer.
  Clinical Trial Awardee, Dr. Dror Michaelson, Massachusetts General Hospital

- **Denosumab currently in Phase III clinical trials:** Preclinical studies funded by the PCRP demonstrated that blocking receptor activator of nuclear factor kappa B ligand (RANKL) activity is an effective strategy to diminish progression of prostate cancer in bone. Denosumab, a monoclonal antibody to RANKL, was subsequently developed by Amgen and is being tested in 26 Phase III (six in prostate cancer) clinical trials. A U.S. Food and Drug Administration (FDA) license is filed for treatment and prevention of bone loss in patients undergoing hormone ablation therapy for prostate or breast cancer.
  Idea Development Awardee, Dr. Evan Keller, University of Michigan

- **Prostate-specific membrane antigen (PSMA)-based positron emission tomograpy (PET) ligand for prostate cancer imaging:** The PET radiotracer, [18F]DCFBC, was synthesized and found to successfully target PSMA in animal models in a PCRP-funded study. Molecular Insight Pharmaceuticals, Inc., purchased the patent for [18F]DCFBC and synthesized two closely related compounds, 123-I-MIP-1072 and 123-I-MIP-1095, which have progressed to Phase I clinical trials.
  Idea Development Awardee, Dr. Martin Pomper, Johns Hopkins University

For more information, visit
http://cdmrp.army.mil
or contact us at:
CDMRP.PublicAffairs@amedd.army.mil
(301) 619-7071

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