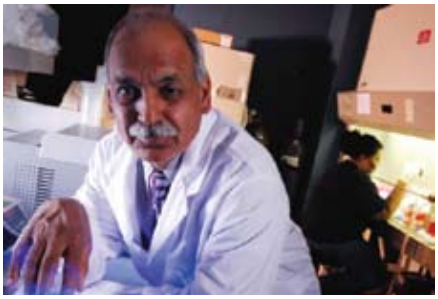
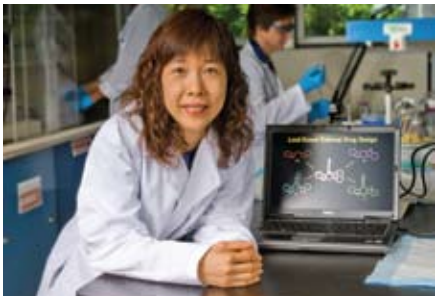
Department of Defense
Congressionally Directed Medical Research Programs

Prostate Cancer Research Program





Congressionally Directed Medical Research Programs

Prostate Cancer Research Program (PCRP)

PCRP Vision:

To conquer prostate cancer.

PCRP Mission:

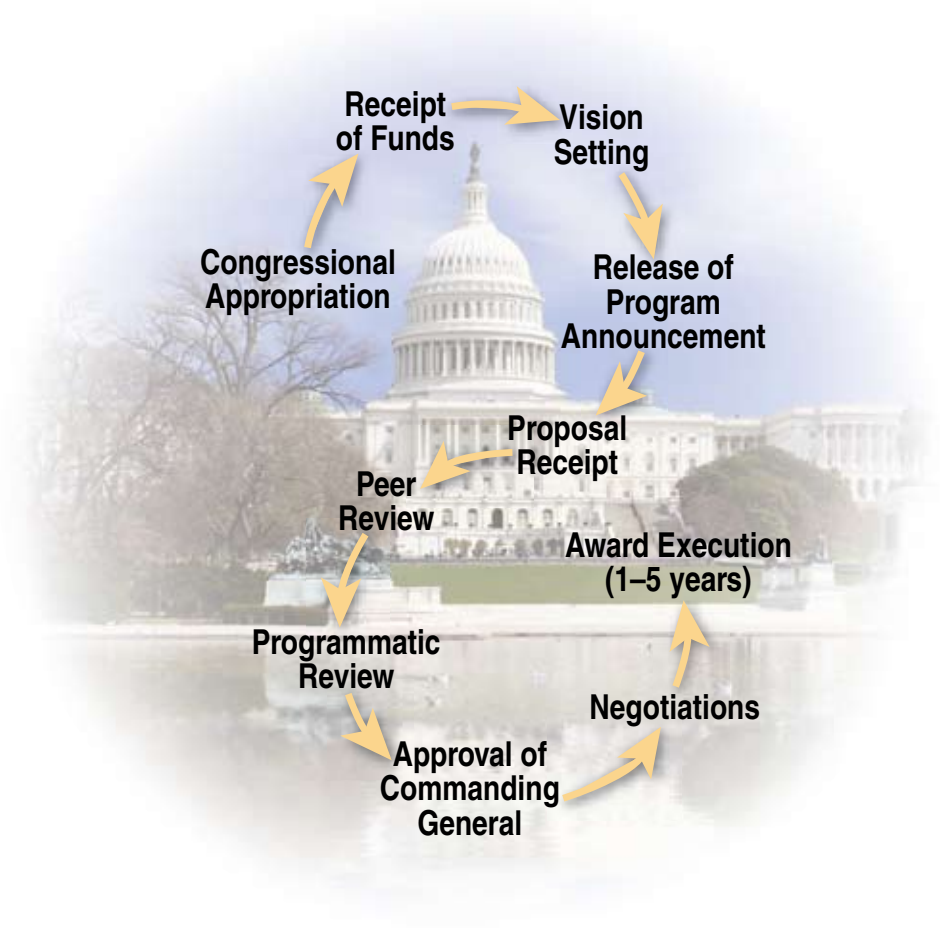
To support research that will eliminate prostate cancer.

Two-Tier Proposal Review Process

The PCRP, like all CDMRP programs, is conducted according to the two-tier review model recommended by the National Academy of Sciences Institute of Medicine. The first tier is a peer review of proposals to determine scientific and technical merit. The second tier is a programmatic review, conducted by members of the Integration Panel (IP) (an advisory board of leading scientists, clinicians, and consumer advocates), which compares proposals to each other and makes recommendations for funding based on scientific merit, relative innovation and impact, portfolio balance, and overall program goals. The two-tier model has received high praise from the scientific community, advocacy groups, and Congress.

Summary

In fiscal year 1997 (FY97), grassroots efforts by the prostate cancer advocacy community led to a congressional appropriation of $45 million (M) for prostate cancer research to be administered by the Department of Defense. Since then, the efforts of prostate cancer advocates have resulted in a total appropriation of $890M to the Prostate Cancer Research Program (PCRP), including $80M for FY08. This funding has energized the development of a unique partnership between Congress, the military, and prostate cancer survivors, clinicians, and scientists. The PCRP is part of the Congressionally Directed Medical Research Programs (CDMRP), within the U.S. Army Medical Research and Materiel Command. The CDMRP funds high-risk, high-gain research with particular emphasis on innovation and technologies that impact research as well as patient care. The work of hundreds of consumer advocates helps the CDMRP focus on finding and funding the best science that will have the widest impact on alleviating suffering due to disease.

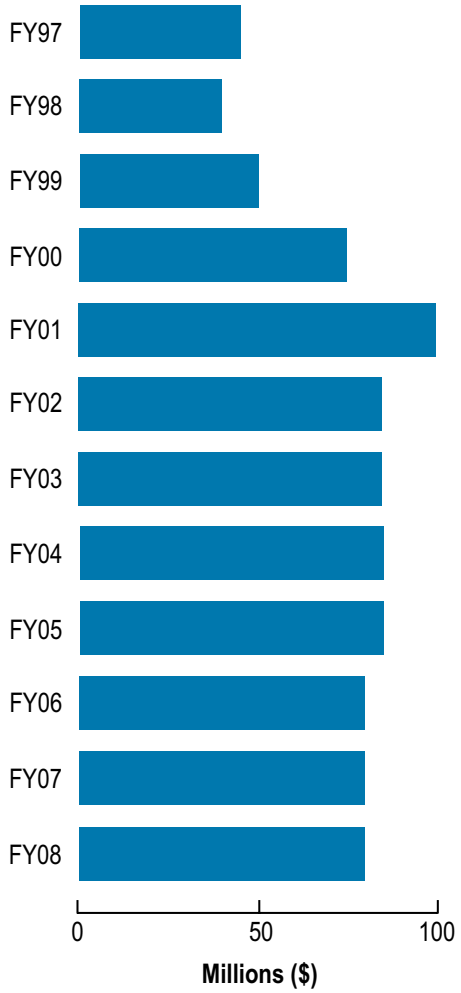


PCRP Investment

PCRP's Next Decade

Since its inception in 1997, enthusiasm for the PCRP has skyrocketed among researchers and consumer advocates. The PCRP has been forging new paths to conquer prostate cancer by emphasizing innovative and collaborative research; translating discoveries into clinical practice; focusing efforts to understand and resolve prostate cancer health disparities; developing new avenues to leverage resources and accelerate discoveries; training scientists in prostate cancer research; and identifying new methods to prevent, diagnose, and treat prostate cancer.

Today, the PCRP is the second-leading source of extramural prostate cancer research funding in the United States. In FY08, the program received an $80M congressional appropriation to invest in prostate cancer research. The research dollars will be invested across the PCRP's portfolio of basic, clinical, and population-based research through a variety of award mechanisms. These award mechanisms promote research in novel ideas or concepts, multidisciplinary and multi-institutional research, translation of early discoveries into agents for clinical trials, and training for the next generation of prostate cancer researchers.

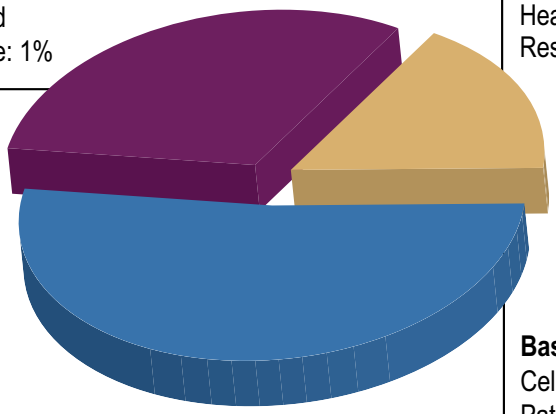


The Investment Portfolio

The PCRP has built a multidisciplinary portfolio by implementing research and training award mechanisms designed specifically to address critical gaps and move the field of prostate cancer research closer to finding a cure. At the same time, a balance is struck among the interconnected goals of advancing basic, clinical, and population-based research.

Clinical Research: 34%
Clinical and Experimental Therapeutics: 24%
Detection and Diagnosis: 7%
Primary Prevention: 2%
Complementary and Alternative Medicine: 1%

Population-Based Research: 15%
Epidemiology: 5%
Behavioral and Psychosocial Sciences: 3%
Healthcare Delivery: 1%
Research Resources: 6%



Basic Research: 51%
Cell Biology: 23%
Pathobiology: 11%
Genetics and Molecular Biology: 9%
Endocrinology: 6%
Immunology: 2%

Consumer Advocates…

Prostate Cancer by the Numbers

- It is the most common non-skin cancer in men
- It is the second-leading cause of death from cancer in men
- An estimated 186,320 new cases of prostate cancer will be reported in the United States in 2008
- An estimated 28,660 men are expected to die from prostate cancer in the United States in 2008
- 1 man in 6 will get prostate cancer during his lifetime

Source: American Cancer Society

FY08 PCRP Integration Panel Members

- Philip Arlen, M.D.
- Angelo De Marzo, M.D., Ph.D.
- Shuk-Mei Ho, Ph.D.
- Natasha Kyprianou, Ph.D.
- Cheryl Lee, M.D.
- Donald Miller, M.D., Ph.D.
- Timothy L. Ratliff, Ph.D.
- Howard Sandler, M.D.
- A. Oliver Sartor, M.D.
- Westley Sholes, M.P.A.
- Virgil Simons, B.B.A.
- Howard R. Soule, Ph.D.
- Donald Tindall, Ph.D.
- John Willey, B.A.

Consumer Participation

Consumer advocates actively participate in setting program priorities and making funding recommendations. More than 285 consumer advocates have served on peer and programmatic review panels for the PCRP. Their firsthand experience with prostate cancer provides a unique perspective that helps scientists understand the human side of the disease and allows for funding recommendations that reflect the concerns and needs of patients, their families, and clinicians.

"Participating in this program gives me hope and encouragement, which I share with other men and their families dealing with prostate cancer."

Jim Kiefert
Us TOO International

"I am privileged to have provided a human face and patient's point of view to the doctors and scientists whose charge is to evaluate research grants seeking to prevent, diagnose, or treat prostate cancer. Quality of life for the patient and his family is recognized as an invaluable element of the evaluation process."

Quince Fleming, Jr.
Southern Maryland Hospital

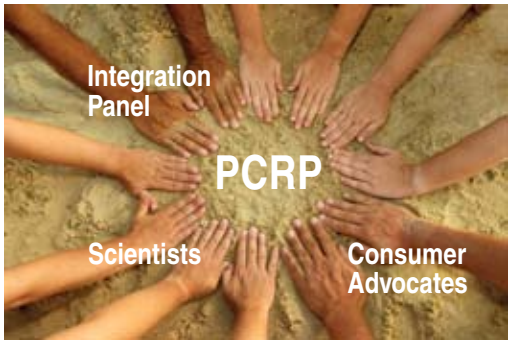
"CDMRP, a leader in addressing health disparities, has recognized the value of HBCU/MI [Historically Black Colleges and Universities/Minority Institutions] and has supported the building of infrastructure so that good scientific research can be conducted. It continues to support initiatives to build a pool of minority researchers and consumer participation."

Jim Williams
Pennsylvania Prostate Cancer Coalition

...Supporting the Search for a Cure

PCRP Partnerships

The success of the PCRP is critically dependent on successful partnerships among consumer advocates, the PCRP IP, and the scientists who participate in peer review and as funded researchers.



"The range and depth of proposals was eye-opening, more than I truly expected, and the scientist-judges gave each and every proposal a detailed examination that was very impressive."

Thomas Owen
Longwood Medical Area Prostate Cancer Support Group

"No one likes having cancer, and survivors may describe the experience in many ways, including strengthening or challenging. For me, the PCRP offers a way to help others going through this ordeal. Thus, the experience is not entirely negative—good can come out of it if we use it."

William Houston
American Cancer Society—Man to Man

"As a prostate cancer survivor participating in national organizations that address cancer education and research, I was honored to be selected to take part in the PCRP. It is a rare opportunity to have an open discussion with professional cancer research scientists and to express your opinion. Everyone has a vested interest to get it right."

Fred Blanchard
Us TOO, Walter Reed Army Medical Center

"Helping to select research projects for CDMRP funding for prostate cancer research has been one of the most satisfying things I have ever done."

David S. Most
The Annie Appleseed Project

Scientists and Clinicians…

Peer Reviewer Participation

Scientists and clinicians work in partnership with consumer advocates to identify high-risk, high-gain research with groundbreaking ideas aimed at filling critical gaps and having an unprecedented impact on prostate cancer.

"I am very honored to have served as a peer reviewer for the Prostate Cancer Research Program and have benefited greatly from my association with the program and the people involved. The PCRP is an extremely well-run funding program that is crucial for the advancement of prostate cancer research."

Edward M. Uchio, M.D., Fellow, American College of Surgeons
Yale University School of Medicine

"It is an honor to serve as an ad hoc member of the Integration Panel and participate in selecting the most promising research for prostate cancer cure and prevention. Particularly at a time when funds are difficult to obtain, the DoD [Department of Defense] PCRP support for young investigators and trainees is essential to insure continued progress in both clinical and basic science."

Diane Robins, Ph.D.
University of Michigan

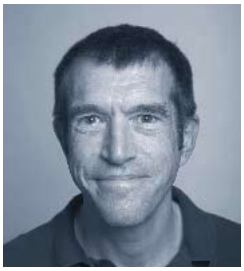
"The Prostate Cancer Research Program provides essential funding mechanisms to develop new areas of prostate cancer research and lays the foundation to explore new points of therapeutic intervention to impact the disease. Consumer advocate reviewers' input is highly regarded and influential to the review process."

Matthew Lorenzi, Ph.D.
Bristol-Myers Squibb

"All of us owe a great deal to the CDMRP Prostate Cancer Research Program. It is hard to believe, but before this program there were significantly less studies being carried out in prostate cancer research. This research is extremely relevant and has had a great impact—largely due to the unique input given by basic scientist, clinician, and consumer advocates."

James W. Lillard, Jr., Ph.D., M.B.A.
University of Louisville

...Partnering to Find the Best Research



"The most remarkable thing about the DoD Prostate Cancer Research Program review process is the involvement of the patient advocates. One may be skeptical at first, but quickly that doubt turns into respect and delight at how knowledgeable and focused these men are. I have learned so much by listening to their cogent and thoughtful comments. It is their presence on the panel that makes it really worth the time and energy."

James J. Manfredi, Ph.D.
Mount Sinai School of Medicine

"Participating in PCRP review brings the satisfaction that my involvement has contributed to the national science effort at combatting prostate cancer. On a personal level, I have regularly gained new insights into this disease by reviewing grant proposals submitted by our peers."

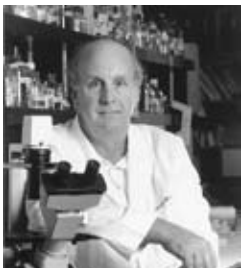
Khalil Ahmed, Ph.D.
University of Minnesota & VA Medical Center

"Peer review directed at new treatments for prostate cancer is an enjoyable aspect of my life in academic urology—the vigor of young investigators is appealing, their continued quest for new knowledge gratifying. The future for patients is bright when we select the best of biomedical research to improve the outcomes for men with this deadly disease."

Robert Bahnson, M.D.
The Ohio State University College of Medicine

"The emphasis on high-risk, innovative work is a welcome departure from the traditional approach and has generated very exciting proposals."

Rashid Fawwaz, M.D., Ph.D.
New York Presbyterian Hospital



"Using review criteria that select for potential high-risk, high-gain proposals also provides a mechanism for funding important ideas that might never see the light of day through other funding mechanisms."

Ross B. Mikkelsen, Ph.D.
Virginia Commonwealth University

Impacting Prostate Cancer…

Selected Clinical Therapeutics and Devices in Development

- Prostatic Acid Phosphatase DNA Vaccine (pTVG-HP DNA)
- Clusterin Antisense Oligonucleotide (OGX-011)
- Allogenic Prostate GVAX (GC1940 & GC8711) vaccine
- Chimeric immunoglobulin (Ig) T-cell receptor (TCR) (fusion of PMSA (prostate-specific membrane antigen) antibody binding domain and the zeta signal domain of the TCR)
- 3 Telsa Magnetic resonance spectroscopic imaging and perfluorocarbon compound endorectal coil
- Adenovirus prostate-specific antigen vaccine (Ad/PSA)
- Stereotactic body radiation therapy (SBRT)

PCRP-funded investigators are translating basic discoveries into clinical research. Clinical trials develop new avenues in patient care, therapeutic agents, and diagnostics. Here are a few examples of successful clinical trials being conducted by PCRP investigators and by the Prostate Cancer Clinical Trials Consortium (PCCTC).

Phase I/II clinical trial testing the immunological efficacy of a plasmid DNA vaccine encoding prostatic acid phosphatase (PAP) in patients with early, clinical-stage D0, prostate cancer. This vaccine has shown that it can elicit an IFNγ-secreting CD8+ T-cell immune response to PAP and PAP-specific CD4+ and CD8+ T-cells. These studies support the safety, immune reactivity, and clinical efficacy of the vaccine leading to a randomized Phase II clinical trial, currently under way and also funded by the PCRP.

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

Phase I/II clinical trial of OGX-011 in combination with neoadjuvant hormone therapy prior to radical prostatectomy in patients with localized prostate cancer. Completed Phase I trials show a dose-dependent 90% decrease in expression of the pro-survival protein clusterin in prostate cancer and lymph nodes. A Phase II neoadjuvant trial (funded externally to the PCRP) with the effective dose of OGX-011 has completed accrual, and correlative studies are in progress.

Kim Chi, M.D.
British Columbia Cancer Agency

Phase I/II clinical trial combining GVAX allogenic prostate vaccine, chemotherapy-induced lymphopenia, and reconstituted peripheral blood mononuclear cells (PBMCs) for advanced hormone refractory prostate cancer.

Bernard A. Fox, Ph.D.
Providence Portland Medical Center

…Through Clinical Trials

Phase I clinical trial of anti-PMSA designer T-cells in advanced prostate cancer following nonmyeloablative conditioning.

Richard Junghans, M.D., Ph.D.
Roger Williams Medical Center

Phase I/II clinical trial to determine whether 3 Tesla magnetic resonance spectroscopic imaging (MRSI) and a perfluorocarbon compound (PFC) endorectal coil can be used as a tool to improve accurate assessment of the grade and stage of an operable prostate tumor. The efficacy of identifying abnormal peaks of prostate metabolites (Cho, CR, Po, and Ci) in prostate tumors from 3T PFC-MRSI for tumor detection will also be determined.

Haesun Choi, M.D.
University of Texas, M. D. Anderson Cancer Center

Phase I/II clinical trial testing stereotactic body radiation therapy (SBRT) for low-risk, localized prostate tumors. Using unique beam arrangements and special immobilization equipment, SBRT will deliver very high doses of focused radiation.

Robert Timmerman, M.D.
University of Texas Southwestern Medical Center

Phase II clinical trial of an adenovirus/prostate-specific antigen (Ad/PSA) vaccine for the treatment of prostate cancer. The trial will encompass two protocols—one for men with recurrent prostate cancer following local therapy, and the other in men with hormone refractory disease.

David M. Lubaroff, Ph.D.
University of Iowa

Accelerating Discovery Through Consortia…

The Prostate Cancer Clinical Trial Consortium consists of a Coordinating Center and ten Clinical Research Sites:

- Memorial Sloan-Kettering Cancer Center (MSKCC)
- Dana-Farber/Harvard Cancer Center (DF/HCC)
- Oregon Health & Science University (OHSU)
- University of Texas M.D. Anderson Cancer Center (UTMDACC)
- Sidney Kimmel Clinical Cancer Center/ Johns Hopkins (SKCC/JHU)
- University of California, San Francisco Clinical Cancer Center (UCSFCCC)
- University of Michigan Clinical Cancer Center (UMCCC)
- University of Washington, Seattle (UWASH)
- Duke University Medical Center (DUKE)
- University of Wisconsin Clinical Cancer Center (UWCCC)

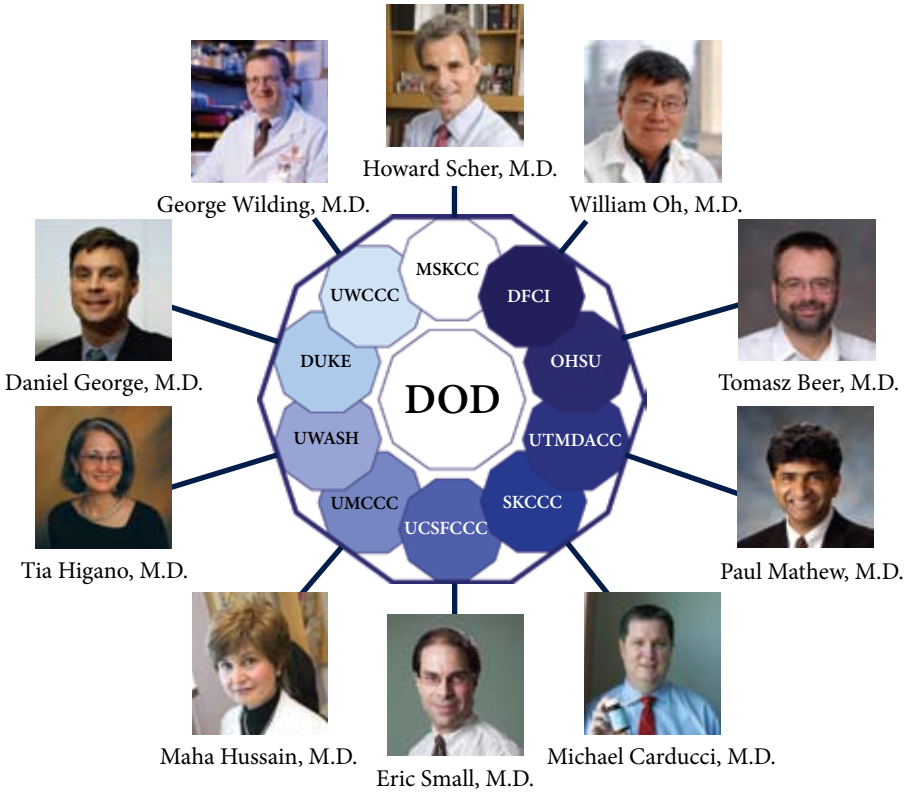
The Clinical Consortium Award

The PCCTC is a major multi-institutional research effort designed to rapidly develop and execute Phase I/II and Phase II clinical trials in prostate cancer. Initiated by the PCRP in 2005 through a Clinical Consortium Award, this network of ten medical centers across the U.S., coordinated by the MSKCC, is poised to expedite clinical trials with promising new therapeutic agents and chemopreventatives that will improve outcomes for prostate cancer patients. Through this award, the consortium supports collaborations among prostate cancer investigators and provides critical resources such as personnel and information technology infrastructure—gaps that are often difficult for a single institution to fill. Since January 2006, more than 1,061 patients have been enrolled in 43 trials completed or in progress across the Consortium, investigating a variety of anti-cancer therapies that could revolutionize prostate cancer treatment.

Clinical Trials

Phase I/II clinical trial of Abiraterone, a 17.20 lyase inhibitor: Abiraterone was shown to be active in post-chemotherapy castration-resistant disease, leading to 50% reduction in PSA levels. Based on this efficacy, a Phase III post-chemotherapy trial is being conducted by members of the PCCTC: UCSFCCC, DF/HCC, MSKCC, MDACC, and JHU.

Phase I clinical trial of a small-molecule compound, MDV3100, an anti-androgen agent with activity in cells overexpressing the androgen receptor. The study is being conducted in castration-resistant prostate cancer patients, using five dose levels. PCCTC members participating include MSKCC, OHSU, UWASH, MDACC, UMCCC, and DF/HCC.



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

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

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

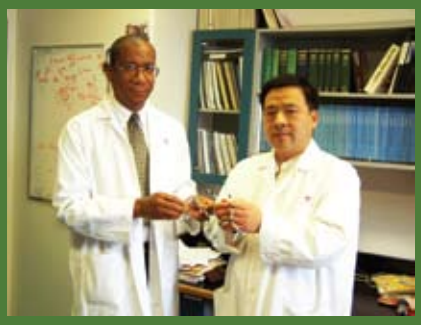
The PCaP team overcame almost insurmountable obstacles to resume the study, exceeding initial recruitment and in-home visit goals of 145 men over the first 6 months. Since then, UNC-CH has completed North Carolina recruitment, and Louisiana continues recruitment with a target completion date in mid-2009.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

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

James Mohler, M.D., RPCI (co-director)

Jeannette Bensen, Ph.D., UNC-CH (co-director)

Forging New Partnerships…



Betrand Jean-Claude, Ph.D., and Qiyu Qiu, M.D., Ph.D., McGill University

Drs. Bertrand Jean-Claude and Qiyu Qiu demonstrate a new type of cancer therapeutic called *combi-molecules,* which provide a "divide and conquer" approach to attacking tumor cells. These *combi-molecules* have proven to be more potent than the standard BCNU (bischloroethyl nitrosourea) treatment in prostate tumors. *Combi-molecules* offer a new therapeutic alternative with a complex multidrug combination in one molecule.

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

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

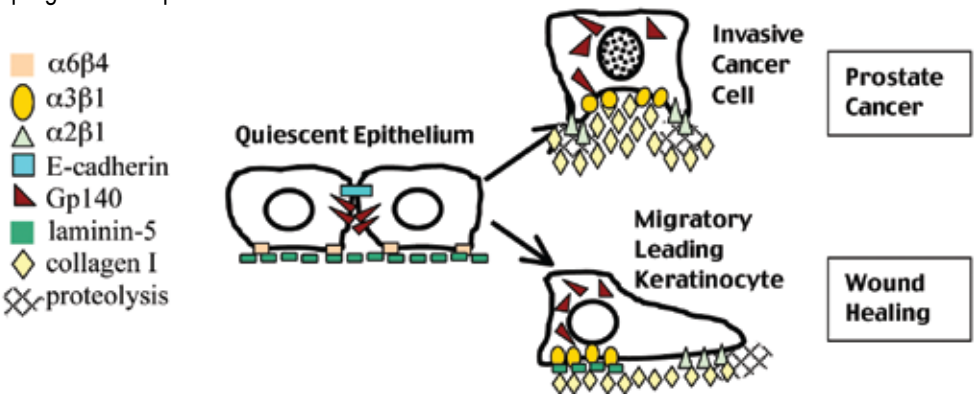
Funding from an FY07 Synergistic Idea Development Award is allowing Principal Investigators Thomas Conrads, Beth Pflug, and Uddhav Kelavkar to test the hypothesis that a diet rich in omega-3 polyunsaturated fatty acids (PUFAs) will slow prostate tumor growth. Tissues will be harvested from two groups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

Gp140/CDCPI in the Development of Prostate Cancer Metastasis

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

The transmembrane receptor Gp140 has been studied for years in wound healing. It has been shown that a wounded epidermis generates migratory keratinocytes that assume a phenotype resembling metastasizing tumor cells. Dr. William Carter, an expert in keratinocyte biology and wound healing, discovered the function of Gp140 as a regulator of the cross talk between cell-cell and cell-substratum adhesions in keratinocytes. This led Dr. Beatrice Knudsen, a molecular pathologist at the Fred Hutchinson Cancer Research Center, to team up with her colleague Dr. Carter to investigate the role of Gp140 in prostate cancer and the potential of Gp140 as a biomarker of prostate cancer metastasis. In particular, GP140 appears to promote cancer cell invasion and the survival of metastasizing cells. Therefore, inhibition or down-regulation of Gp140 with nontoxic pharmacologic agents may halt the development of prostate cancer metastasis. Bringing the epithelial biology discovered in keratinocytes to prostate cancer invasion and metastasis through the complementary experiences of these two researchers will potentially change our view of how cancer cells metastasize and provide fresh avenues to develop treatments against the development and progression of prostate cancer metastasis.

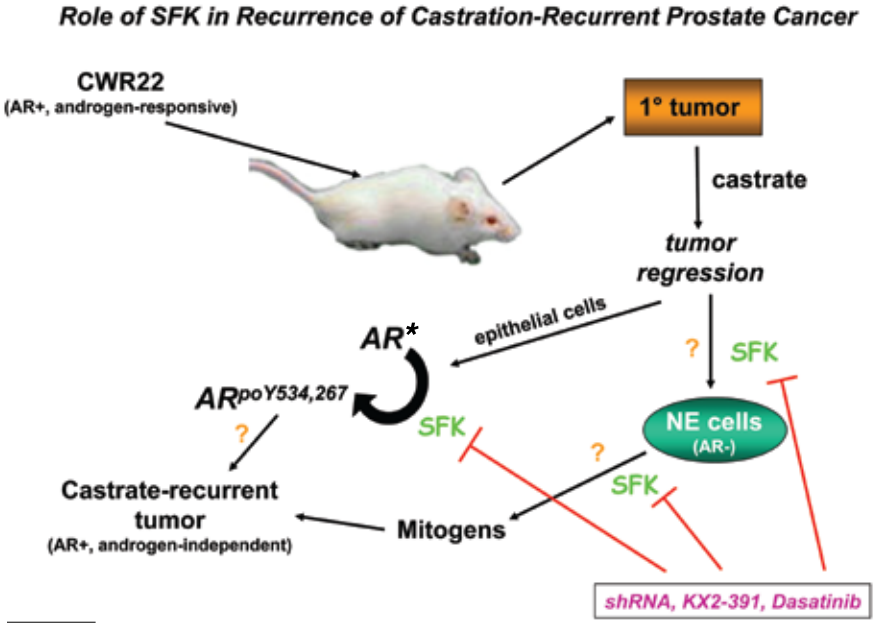
Gp140 is a regulator of the cross talk between cell-cell and cell-substratum adhesions in keratinocytes. It also appears to promote cancer cell invasion and the survival of metastasizing cells.



Dependency on Src-Family Kinases for Recurrence of Androgen-Independent Prostate Cancer

Irwin Gelman, Ph.D., James Mohler, M.D., Gary J. Smith, Ph.D., Roswell Park Cancer Institute

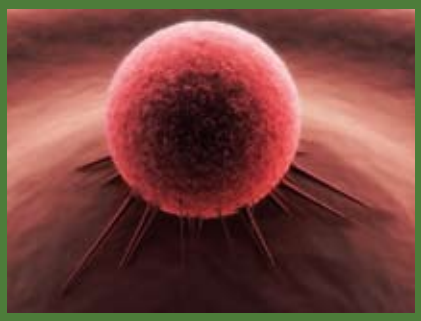
Prostate cancer recurrence following androgen-deprivation therapy continues to be a significant problem for men with prostate cancer. An increasing number of these prostate cancer recurrences involve aggressive tumors that are androgen independent (AI), invasive, and less likely to respond to therapy, and result in decreased patient survival. FY07 Synergistic Idea Development Awardee Dr. Irwin Gelman, in collaboration with Dr. James Mohler and Dr. Gary Smith, is investigating the role of Src-family tyrosine kinases (SFK) in AI prostate cancer recurrence following androgen deprivation therapy. These investigators will also examine whether tumor stromal neuroendocrine (NE) cells produce factors that drive the proliferation of AI prostate cancer cells. To accomplish this, the investigators will characterize the function of SFK using CWR22-SCID (Severely Combined Immunodeficient), TRAMP, and human prostate cancer SCID-xenograft models. In vitro experiments will be conducted to demonstrate SFK requirements, paracrine effects, and the role of NE on AI prostate cancer proliferation following androgen deprivation. Finally, these researchers will examine the effect of a novel targeted SFK inhibitor, KX2-391, on AI prostate cancer. These preliminary studies will serve as a foundation for establishing clinical trials for SFK inhibitors in combination with androgen-deprivation therapy for recurrent androgen-independent prostate cancer.



SFK may facilitate the proliferation NE cells and NE-mediated secretion of mitogens that induce androgen-independent growth. Mouse models of castration-recurrent prostate cancer (CR-CaP) such as CWR22 will test whether the antagonism of SFK via short-hairpin RNA (shRNA) or treatment with either the SFK inhibitor, KX2-391, or the multikinase inhibitor, Dasatinib, can prevent the generation of CR-CaP.

* androgen receptor

Forging New Paths Between Bench and Bedside…



Dr. Kridel and a research associate

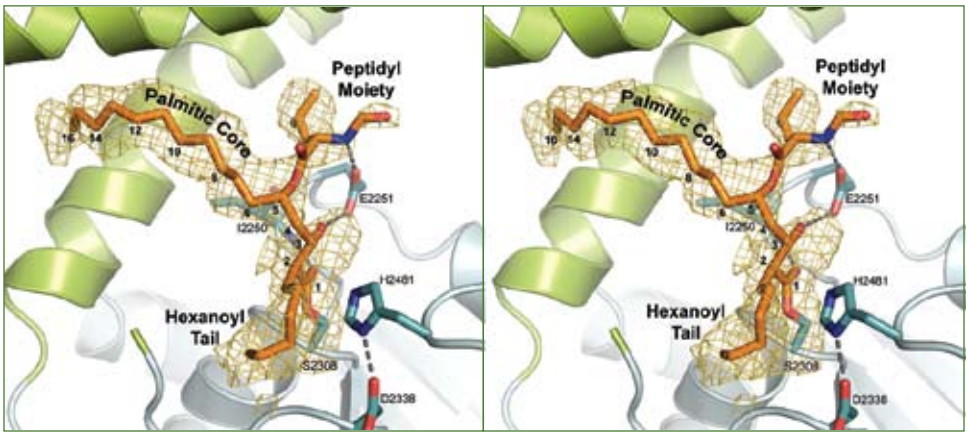
Inhibition of Fatty Acid Synthase in Prostate Cancer—A Novel Therapeutic Target

Steven J. Kridel, Ph.D., Wake Forest University School of Medicine

The fatty acid synthase (FAS) enzyme synthesizes palmitate, and it is expressed at high levels in prostate cancer cells compared to normal cells. By driving the synthesis of phospholipids, tumor cells become dependent on the high levels of FAS for survival. Phospholipids are shuttled through the endoplasmic reticulum (ER) for other processes downstream, thereby establishing a connection between FAS and the ER. Dr. Steven J. Kridel, recipient of an FY04 New Investigator Award (NIA) and an FY06 Idea Development Award, has investigated cell death caused by FAS inhibition via an ER stress-dependent pathway. Cell culture studies and mice xenografts showed that FAS inhibitors orlistat and C75 activate ER stress, leading to prostate cancer cell deaths.

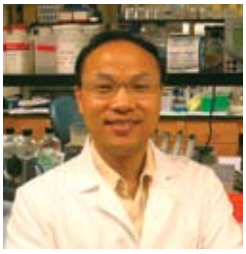
Further, FAS inhibition results in accumulation of ubiquitinated protein products while proteasome inhibitors increase FAS, suggesting cross talk between FAS and the proteasome pathway. Disruption of the cross talk between FAS and the proteasome pathway results in enhanced ER stress signaling.

Interestingly, combination treatment of the proteasome inhibitor Velcade® and FAS inhibitors synergize to enhance ER stress, increase the accumulation of ubiquitin-modified proteins, increase the levels of caspase-3 and cleaved poly ADP (adenine dinucleotide phosphate)-ribose polymerase, and potentiate androgen receptor-null prostate cancer cell death. Dr. Kridel has determined the crystal structure of the FAS domain bound to ligand as a first step in the development of novel FAS inhibitors. The use of FAS inhibitors in combination with other antitumor agents may be a promising strategy for the treatment of prostate cancer.



Orlistat (orange) bound in the active site domain of human thioesterase chain A. Orlistat extended conformation brings Ser2308 closer to Asp2338 in the Ser2308-His2481-Asp2338 catalytic triad.

…Transforming Basic Discoveries into Clinical Advances



Natural Product Derived from Cottonseed Oil May Help Fight Prostate Cancer

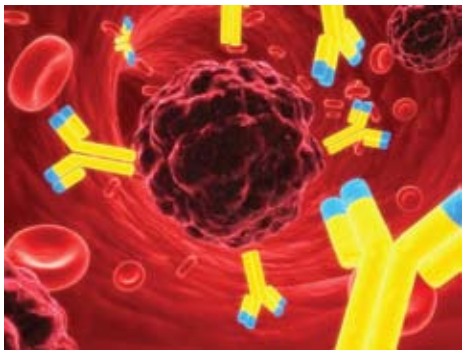
Liang Xu, M.D., Ph.D, University of Michigan Medical School

Chemotherapy and radiation are common therapeutic regimens for the treatment of localized prostate cancer. However, as prostate disease advances, these therapeutic strategies become less effective. The PC-3 hormone refractory human prostate cancer cell model is resistant to current chemotherapy and radiation therapies. PC-3 cells also have very high levels of Bcl-2 and Bcl-xL proteins, which may contribute to its chemo/radiotherapy resistance by inhibiting programmed cell death, or apoptosis. (-)-Gossypol, a natural polyphenolic compound derived from the cottonseed plant, was reported previously as an effective inhibitor of Bcl-2, Bcl-xL, and Mcl-1 that potently induces apoptosis in several other cancers that overexpress these proteins. Dr. Liang Xu, the recipient of an FY03 PCRP Idea Development Award, has recently shown that (-)-gossypol markedly enhanced radiation- and chemotherapy-induced apoptosis and growth inhibition of PC-3 cells. More importantly, (-)-gossypol significantly improved antitumor activity of X-ray irradiation and docetaxel chemotherapy in an established xenograft model of PC-3 tumors in nude mice, resulting in tumor regression even in large tumors. Based on the exciting data obtained partly from this PCRP project, the Investigational New Drug Application for (-)-gossypol was filed and approved by the FDA in 2005. (-)-Gossypol is now being tested in combination therapy with docetaxel and prednisone in Phase II clinical trials for human prostate cancer.

Development of PSCA-Targeted Minibodies for Imaging of Prostate Cancer

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

Dr. Robert Reiter, an FY06 Laboratory Clinical Transition Award–Stage I recipient, is investigating the use of radiolabeled prostate stem cell antigen (PSCA) antibody fragments to target prostate cancer cells for molecular imaging using single-photon emission computed tomography and positron emission tomography in animal models that better mimic prostate cancer initiation and progression. Dr. Reiter has shown that high levels of PSCA expressed on the surface of prostate cancer cells are an indication of loss of the tumor suppressor gene PTEN, and that antibodies against PSCA reduce cancer cell growth and metastasis without eliciting an immune response. Phase I clinical trials testing antibodies against PSCA as therapy in men with metastatic prostate cancer are ongoing. PSCA antibody fragments as a diagnostic tool to image prostate cancer will enter clinical trials pending successful studies in animal models.



Targeting Prostate Cancer Health Disparities…

African American men are disproportionately affected by prostate cancer compared to other ethnic groups (60% higher incidence compared to Caucasian men), and are 2.4 times more likely to die from the disease.

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

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

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

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

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

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

The Shaw UNC-CH Center for Prostate Cancer Research

Daniel Howard, Ph.D., Shaw University

The appropriate frequency of PSA testing following a diagnosis of prostate cancer is relatively undetermined in the clinical community. This lack of consensus in PSA surveillance may even contribute to the disparity in cancer burden for African American men. Dr. Daniel Howard, recipient of an FY04 HBCU Collaborative Partnership Award, is teaming up with investigators at UNC-CH to establish infrastructure support for junior faculty members at Shaw University to conduct research focused on racial disparities in prostate cancer. Dr. Howard and colleagues are investigating differences in disease-free survival outcomes among different ethnic groups following prostate cancer diagnosis, treatment, and cancer-free survival until death unrelated to prostate cancer. Dr. Howard will also examine whether variations in time interval between diagnosis, treatment option recommendations, and follow-through on recommendations for care are associated with race. Dr. Howard also received a FY06 HBCU Collaborative Partnership Award, to partner with the Johns Hopkins School of Medicine and Bloomberg School of Public Health to identify psychosocial factors contributing to racial differences in prostate cancer screening behavior, diagnosis, treatment, and quality of life.

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

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

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

Innovating…

Eat Your (Cruciferous) Vegetables

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

While it is widely known that eating cruciferous vegetables is a natural way to reduce your chances of getting prostate cancer, neither the dietary ingredient(s) nor the mechanism(s) by which they work have been identified. Dr. J.W. Chiao and colleagues at New York Medical College and Dr. L. G. Wang at New York University have used an FY02 Idea Development Award to study the role of phenethyl isothiocyanate (PEITC), a compound found in large quantities in watercress and other cruciferous vegetables, to decipher how it acts as a chemopreventive agent. The investigators have determined that PEITC mediates regulation at the epigenetic level; it inhibits the growth of prostate cancer cells by up-regulation of the cell cycle regulator p21 and down-regulation of the transcription factor Sp1, a regulator of androgen receptor (AR) expression. Lower levels of AR expression reduce testosterone activity, leading to attenuation of prostate cancer cell growth. PEITC was also shown to be a dual inhibitor of histone deacetylases and of abnormal CpG island methylation. PEITC reversed this hypermethylation and also reactivated the detoxifying enzyme GSTP1, known to be critically inactivated in most prostate tumor cells. Together, the data suggest that PEITC is able to target several key molecules that participate in the development of prostate cancer. Most importantly, the results of this study indicate the potential for isothiocyanates to be developed as novel prostate cancer therapeutics.

Pushing Cancer Cells to the Breaking Point

Robert S. DiPaola, M.D., University of Medicine and Dentistry of New Jersey

Scientists are uncovering potential new therapeutic strategies by targeting common metabolic features in cancer cells that could increase their vulnerability to cell death. Increased growth and proliferation and a reliance on glycolysis, an inefficient means of converting nutrients into energy, put cancer cells in a constant state of near starvation. Under such conditions, autophagy (self-eating) occurs, in which cells scavenge their own components and break them down to suit the needs of basic cell metabolism. In the short term this promotes cell survival, but under prolonged periods of nutrient deprivation, the autophagic pathway may ultimately lead to cell death. In a study funded by an FY04 Idea Development Award, Dr. Robert DiPaola and colleagues are exploring the utility of targeting this pathway for the treatment of hormone refractory prostate cancer. Using the molecule 2-deoxyglucose (2DG), an inhibitor of glycolysis, as a means of depleting cellular energy stores, Dr. DiPaola's research group has demonstrated the ability of 2DG to kill prostate cancer cells. In addition, they have shown that hyper-activation of the PI 3-kinase pathway, a key regulatory pathway that normally suppresses autophagy under conditions that favor growth, is correlated with increased cytotoxicity due to 2DG. Increased activity of the PI 3-kinase pathway is a common feature of various cancer cells, suggesting that they may be especially vulnerable to 2DG treatment.

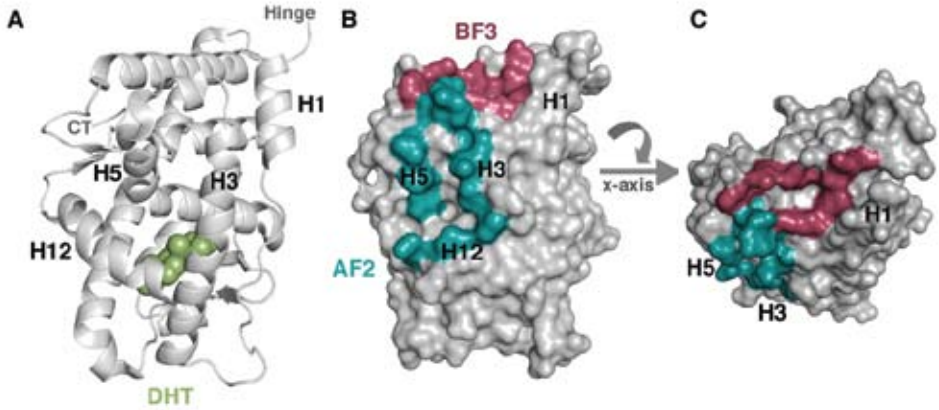
Dr. DiPaola and his research group have initiated a clinical trial, funded by the PCRP, to study the potential use of 2DG to treat hormone refractory prostate cancer.

…Toward New Paradigms Through Vision and Creativity

Inhibitors for Androgen Receptor Activation Surfaces

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

The androgen receptor is known to be a central factor in the development of prostate cancer and drives early disease progression with endogenous androgens. A chemical that blocks AR activity would prevent prostate cancer development irrespective of whether or not the receptor requires androgen activation. Dr. Robert Fletterick, recipient of an FY05 Idea Development Award, is using X ray crystallography to visualize receptor sites on the AR (androgen receptor), focusing on hormone-driven activation function 2 (AF-2), and as a result has found a novel allosteric site called BF-3. Dr. Fletterick is currently screening for compounds that show strong binding to these areas and antagonize coactivator binding, and he has found preliminary candidates in a thyroid hormone analog and aspirin-related compounds. Cellular assays show that these compounds inhibit transcription, and they could develop into promising prostate cancer therapeutics.



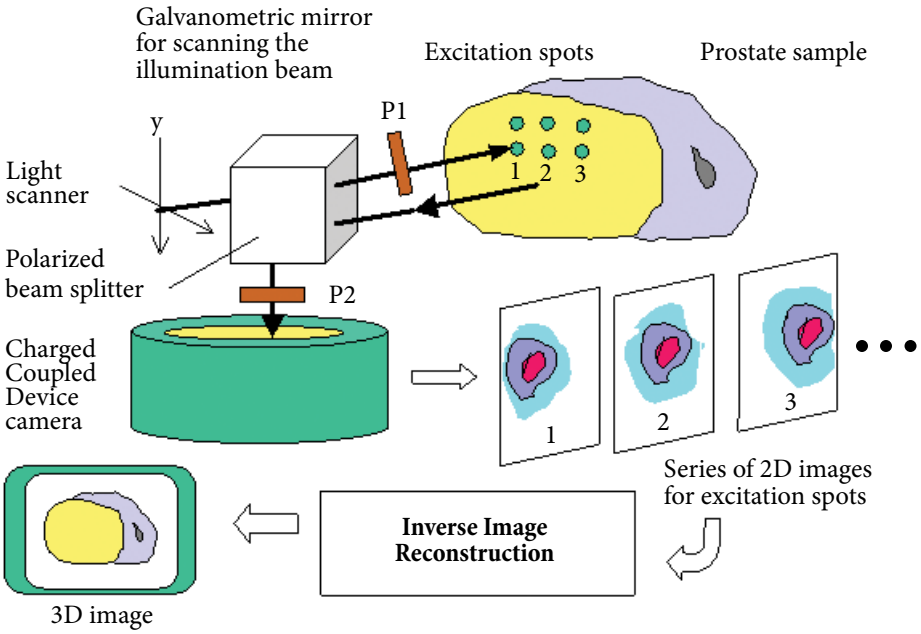
Location of AF-2 and BF-3. A. Schematic of AR ligand-binding domains (LBD) showing the location of the 5-alpha-dihydrotestosterone (DHT), key AF-2 helices (3,5, and 12), and H1. B. Space-filling model of AR LBD showing key residues in AF-2 (cyan) and BF-3 (red). C. As in B., but rotated 90° to reveal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

Developing New Tools…

New Near-Infrared Prostate Imaging Device Advances Cancer Screening

Wubao Wang, Ph.D., City College of New York

Dr. Wubao Wang of the City College of New York is leading a team of scientists developing a breakthrough imaging device for prostate cancer that uses a near-infrared (NIR) imager coupled with an image reconstruction algorithm to map the internal structure of the prostate and detect cancerous sites with three-dimensional (3D) imaging in a noninvasive procedure. This new device, supported by an FY07 PCRP Idea Development Award, will greatly improve upon current methods of PSA screening and digital rectal examination. The new device will scan the prostate transrectally with an NIR scanning unit that records images at fingerprint absorption peak wavelengths and generates a set of 2D images of the prostate. Software employing an inverse image reconstruction algorithm will then produce a 3D image of the interior of the prostate using the recorded 2D images. These results will be compared with ultrasound imaging and biopsy examination for improved predictive value and diagnosis of prostate cancer. Dr. Wang's out-of-campus collaborators are Dr. James Eastham of MSKCC and Professor Min Xu of Fairfield University.

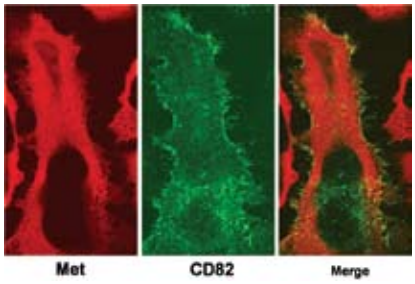


Schematic block diagram of a scanning NIR polarization imaging unit. The unit produces 3D images of the prostate sample with an inverse image reconstruction algorithm.

Loss of CD82 and Subsequent Increased Integrin Activity Contribute to Tumor Progression and Metastasis

Cynthia Miranti, Ph.D., Van Andel Research Institute

Dr. Cynthia Miranti, an FY03 New Investigator Award recipient, has investigated CD82, a putative metastasis suppressor that regulates the interplay between adhesion-mediated signaling and cell survival in prostate cancer. Loss of CD82 and up-regulation of c-Met, a receptor tyrosine kinase (RTK), is a frequent event in prostate cancer. Up-regulation of c-Met is associated with prostate cancer conversion to androgen independence and metastasis. Dr. Miranti has shown that CD82 suppresses c-Met signaling and inhibits the Src/FAK/p130Cas pathway downstream of integrins by an independent mechanism. In complementary studies, Dr. Miranti has elucidated the interplay between RTK and integrin signaling and mechanisms of prostate epithelial cell death in response to loss of adhesion. With an FY07 Idea Development Award, Dr. Miranti plans to identify the regions of CD82 protein that are responsible for the physical interaction of CD82 with integrins and for the suppression of c-Met tyrosine kinase activity. This will provide the basis for developing CD82 mutants that can be examined in vitro and in mouse models to establish the relationship between loss of CD82 expression, integrin-mediated c-Met activation, and the development of metastasis. Finally, a CD82 knockout mouse model will be developed to examine whether loss of CD82 is required for the development of metastasis.

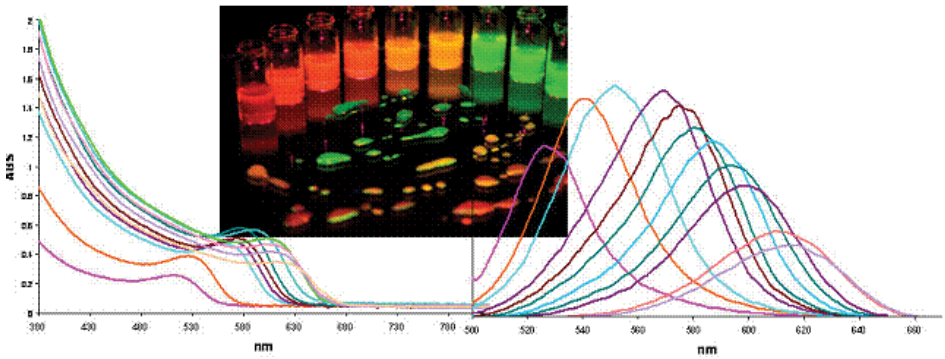


Immunostaining of CD82 and c-Met in PC3 cells re-expressing CD82. No co-localization was detected.

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

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

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



Ultraviolet-visible (left) and photoluminescence (right) spectra and color of different sized CdTe (cadmium telluride) quantum dots with silica shells in aqueous solution.

Preparing the Next Generation…

"My experiences during this program have been wonderful and rewarding. The outstanding staff and faculty were very resourceful. They assisted me with hands-on lab procedures and improved my acquired knowledge in several biological and chemical processes. I am truly honored to be a part of this summer program."

James Barnett
Tuskegee University

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

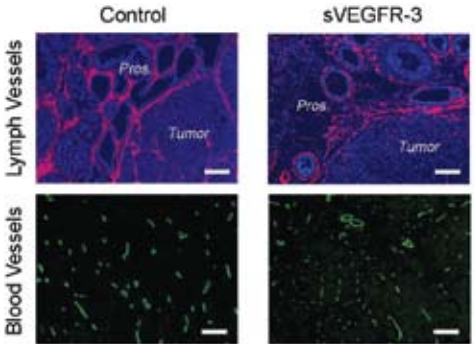
The PCRP's Collaborative Undergraduate Historically Black Colleges and Universities (HBCU) Student Summer Training Program Award (STPA), introduced in 2004, was created to encourage HBCU students to pursue careers in prostate cancer research. So far, more than 60 HBCU students have received hands-on,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

…To Forge Ahead in Prostate Cancer Research

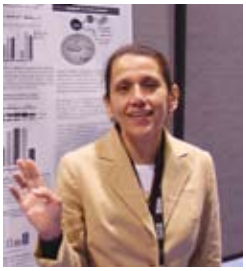
The Role of Lymphangiogenesis in Orthotopic Prostatic Tumor Environment on Regional Lymph Node and Systemic Metastasis

Jeremy Burton, M.S., University of California, Los Angeles

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



Tumors were sectioned and the interface of the tumor margin and mouse prostate tissue was examined by histological staining of lymphatics (Lyve-1). Soluble receptor reduced lymphangio-genesis in comparison to control tumors while blood vessel density remained unchanged.

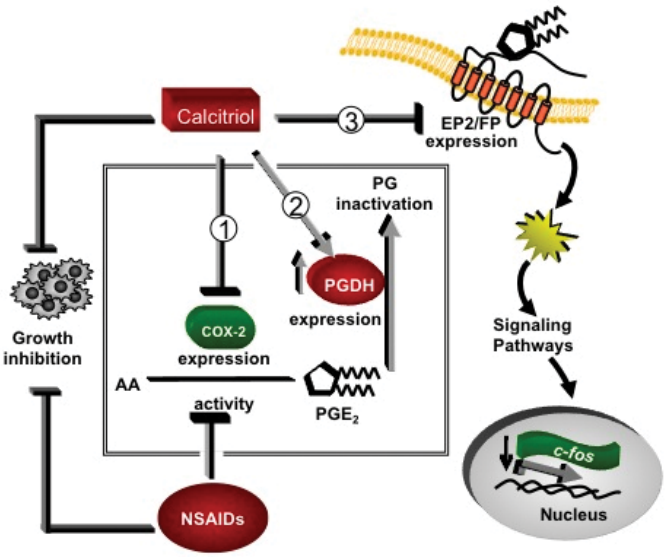


Delivering a One-Two Punch to Prostate Cancer

Jacqueline Moreno, Ph.D., Stanford University School of Medicine

Combination therapy for cancer treatment may offer enhanced efficacy at lower doses while minimizing side effects. In the laboratory of Dr. David Feldman at Stanford, Dr. Jacqueline Moreno and colleagues have demonstrated the promise of this approach for prostate cancer treatment. Through funding from an FY04 Postdoctoral Traineeship Award, Dr. Moreno examined the combined effects of two agents on prostate cancer proliferation. The first agent investigated was 1, 25-dihydroxyvitamin D3 (calcitriol), which is a well-established inhibitor of human prostate cancer cell growth. Dr. Moreno discovered that calcitriol blocked the synthesis and growth-stimulatory activities of prostaglandins (PGs) in prostate cancer cells by reducing the expression of cyclooxygenase (COX)-2, a key enzyme of PG synthesis. Calcitriol also enhanced the expression of a putative tumor suppressor that converts PGs into inactive metabolites, 15-prostaglandin dehydrogenase. Dr. Moreno then assessed the antiproliferative effects of calcitriol in conjunction with various COX-1 and -2 inhibitors known as nonsteroidal anti-inflammatory drugs (NSAIDs). The combination of calcitriol with ibuprofen, naproxen, or other NSAIDs synergistically inhibited prostate cancer cell growth at 2- to 10-fold lower concentrations than the individual drugs. Based on these results, a Phase II clinical trial (funded external to the PCRP) was initiated to examine the efficacy of calcitriol and naproxen in men with advanced, relapsing prostate cancer. Such combined treatment strategies may offer new hope to prostate cancer patients for whom other therapies have not been successful.

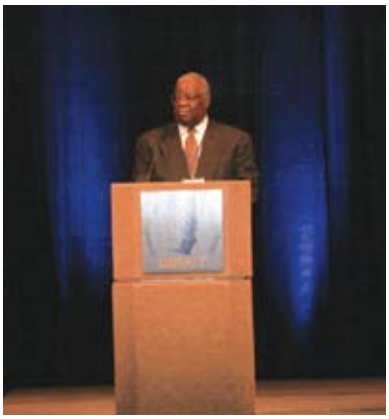
Three mechanisms through which calcitriol alters prostaglandin actions in prostate cancer cells: 1. decrease the expression of COX-2; 2. stimulate 15-PG dehydrogenase (PGDH); and 3. inhibit E-series prostanoid-2 (EP2) and PG-F (FP) receptor expression.



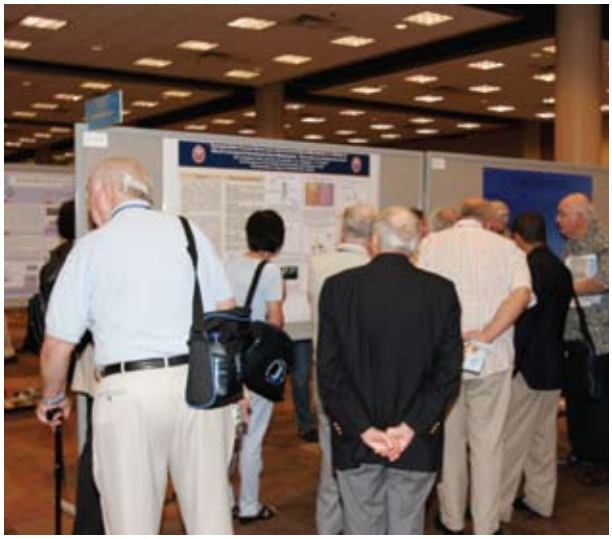
IMPaCT Meeting

In September 2007, the PCRP convened a landmark meeting called Innovative Minds in Prostate Cancer Today (IMPaCT), which brought together prostate cancer researchers and consumer advocates for an exchange of research progress and inspiration. Over the course of three days at the Hyatt Regency Hotel in Atlanta, 850 attendees shared research achievements and stories of perseverance in coping with prostate cancer. It was a celebration of how far the program has come over the past 10 years and a great way to reinforce our vision and mission to conquer prostate cancer!

Colonel Janet Harris and Captain Melissa Kaime, CDMRP



Innovative Minds in Prostate Cancer Research



2008 PCRP Award Mechanisms by Research Area

FOCUS

Clinical Research and Resources

Innovative Research

Training/Recruitment

AWARD MECHANISM

Clinical Consortium Award: Provides resources to facilitate the rapid execution of *collaborative* Phase II or Phase II-linked Phase I clinical studies

Clinical Trial Award: Funds the rapid execution of novel Phase 0/I, Phase I, Phase I/II, or Phase II clinical trials

Laboratory-Clinical Translational Award: Stage I: Supports preclinical studies of promising lead agents that have the potential to revolutionize prostate cancer clinical care

Idea Development Award: Supports innovative ideas and technology across all areas of laboratory, clinical, behavioral, and epidemiological research

Synergistic Idea Development Award: Encourages innovative and synergistic approaches from two to three investigators with the goal of accelerating prostate cancer research

New Investigator Award: Funds innovative research from newly independent investigators working in collaboration with experienced prostate cancer researchers

Health Disparity Research Award: Supports research from investigators at specific career stages who study the disparate burden of prostate cancer within disproportionately affected populations and communities

Physician Research Training Award: Prepares physicians for careers in prostate cancer research through a mentored training experience in a laboratory or clinical setting

Prostate Cancer Training Award: Provides prostate cancer research training opportunities to investigators early in their careers

Health Disparity Training Award: Provides training opportunities to investigators early in their careers to study the disparate burden of prostate cancer within disproportionately affected populations and communities

Collaborative Undergraduate HBCU Student Summer Training Program Award: Provides educational and training opportunities in prostate cancer research for undergraduate students at historically black colleges and universities

IMPaCT

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