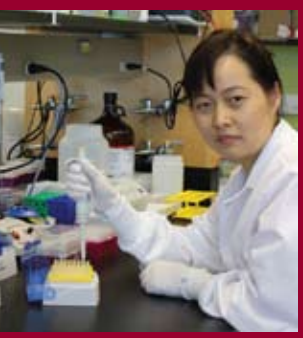
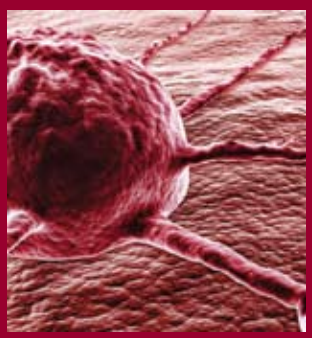
CDMRP

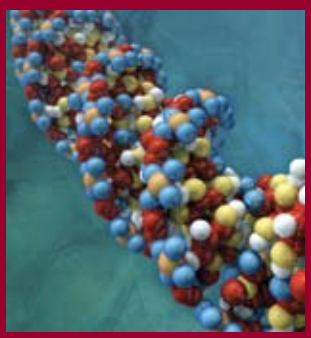
Department of Defense

Prostate Cancer Research Program

Innovative Minds in Prostate Cancer Today

IMPaCT

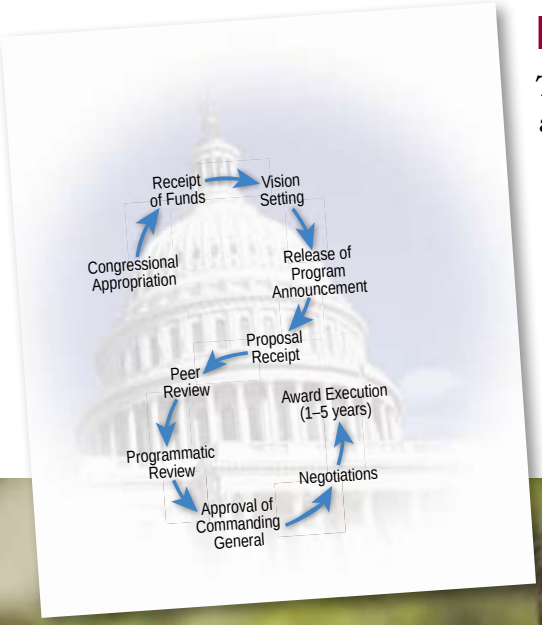






U.S. Army Medical Research and Materiel Command

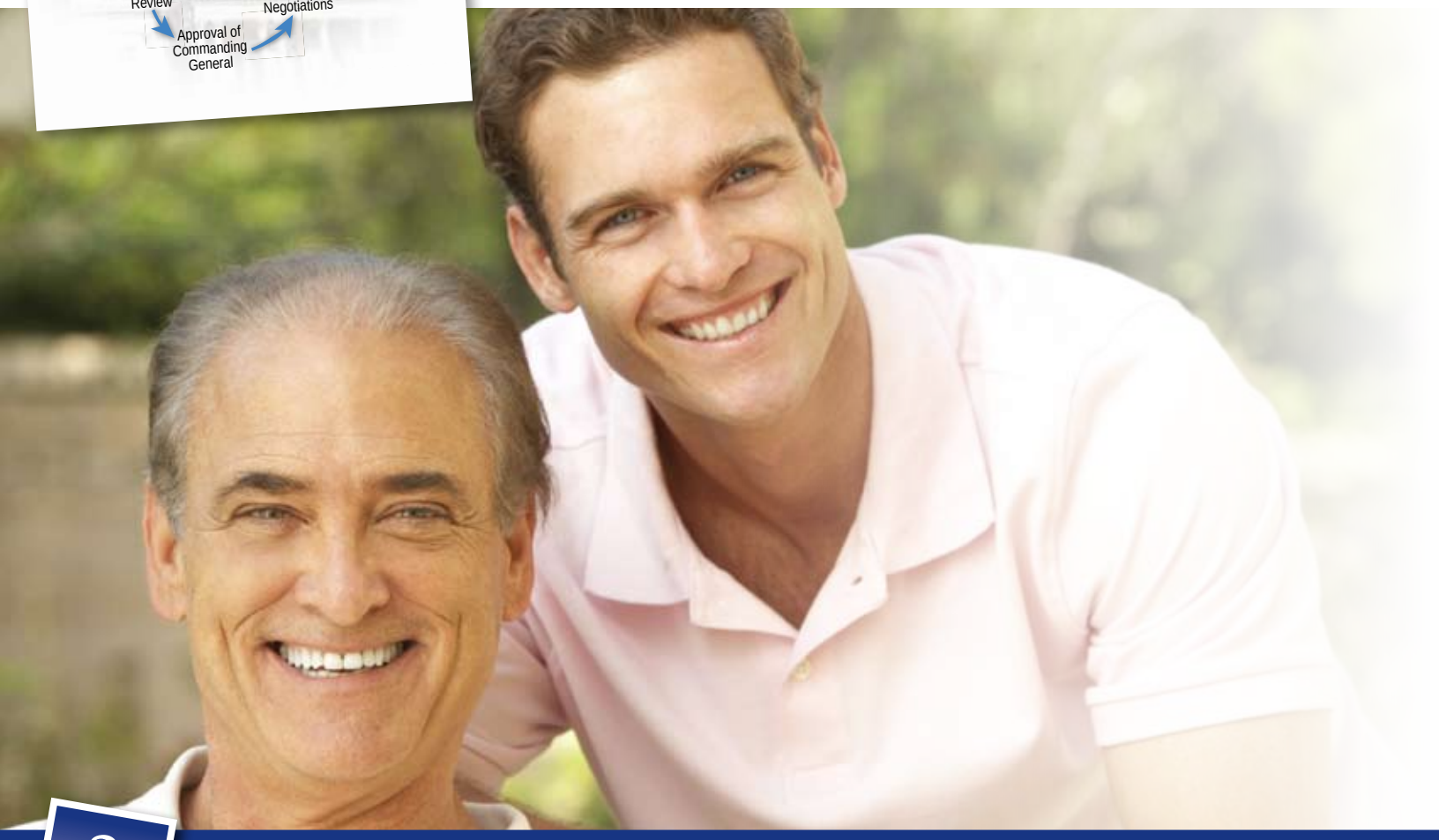
Congressionally Directed Medical Research Programs

The Office of the Congressionally Directed Medical Research Programs (CDMRP) was born in 1992 from a powerful grassroots effort 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 it has received almost $5.9 billion in appropriations from its inception in fiscal year 1993 (FY93) through FY10. 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 an Integration Panel, composed of leading scientists, clinicians, and consumer advocates, that compares proposals to each other and makes recommendations for funding based on scientific merit, portfolio balance, and relevance to overall program goals.



Summary of Our History

In 1997, the DOD received a congressional appropriation of $45 million (M) dollars to conduct research in prostate cancer (PCa). The funds were to be administered by the DOD PCRP to support meritorious scientific investigations toward the goal of eliminating PCa. This new research effort in PCa research was born out of grassroots efforts by dedicated and energized PCa advocates and supporters who worked to realize additional research funds for PCa. To date, this effort has resulted in a total appropriation of over $1.1 billion to the PCRP, including $80M in FY10. This unique partnership among Congress, the military, and PCa survivors, clinicians, and scientists has changed the landscape of biomedical research, energizing the research community in conducting high-risk research that is more collaborative, innovative, and impactful on PCa.

VISION

Conquer prostate cancer

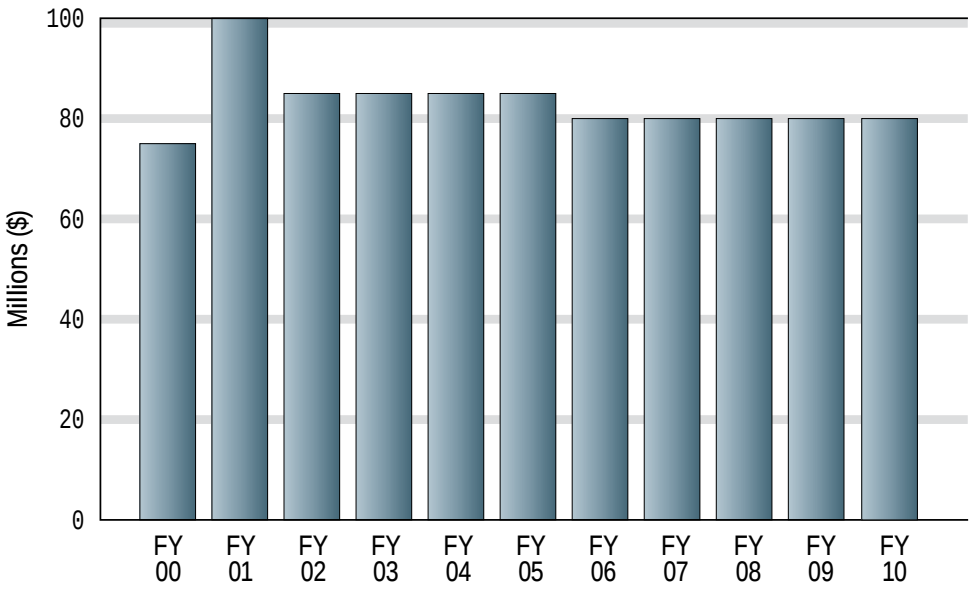
MISSION

Fund research that will eliminate death and suffering from prostate cancer

PCRP Goals

- Support innovative high-risk, high-gain research with potential near-term impact
- Sponsor multidisciplinary synergistic research
- Fund translational studies to promote the fluid transition of knowledge between bedside and bench
- Invest in research on patient survivorship (quality of life)
- Foster the next generation of PCa investigators through mentored research
- Promote research into PCa health disparities

Recent PCRP Funding History



Introduction to This Booklet:

PCRP's Challenges, Successes and a Look to the Horizon

More than a decade ago, the PCRP was initiated with the ambitious goal of defeating PCa by bringing together the best minds in research to find solutions for the most critical issues affecting patients. Propelling these efforts were grassroots advocates, who formed a powerful partnership with scientists and clinicians, all focused on fostering innovation in PCa research and bringing major discoveries to the clinic as quickly as possible. Over the years, investigators in this effort have faced many challenges in understanding PCa and preventing its effects. Some of these challenges have been overcome through the successes of PCRP-funded investigators, who have used their discoveries to develop better diagnostic tools, novel treatments, and methods to predict treatment response. However, still far from realizing our goal of a PCa-free society, the PCRP keeps its focus on the horizons for PCa research, namely the advances that are still needed to finally eliminate all death and suffering from this disease.

In 2007, the PCRP held its inaugural Innovative Minds in Prostate Cancer Today (IMPaCT) meeting in Atlanta, Georgia, bringing together nearly a thousand consumer advocates, scientists, and clinicians to listen, discuss, and problem-solve to move closer to achieving the PCRP mission. Since then, major discoveries have moved the field forward, and so PCRP-funded investigators are again coming together in 2011, in Orlando, Florida, for a second IMPaCT meeting to discuss their most recent findings, share exciting ideas, and form new collaborations to address the challenges that lie ahead. As the PCRP is poised to launch an ambitious program for FY11, a common theme has developed between the program's vision and the IMPaCT meeting. This unified theme of Challenges, Successes, and Horizons in PCa research underscores the progress since the first IMPaCT meeting while also demonstrating that the PCRP is primed to lead the next wave of innovative and impactful research in PCa. In light of this common theme, we have consolidated in this report the program's annual research highlights with information compiled for the second IMPaCT meeting, including input from thought leaders in the field. This report conveys the various challenges and successes of the PCa investigators and what could be on the horizon for PCa research.

PCRP Consumer Advocates

Thirteen years of involvement by consumer advocates (disease survivors) has helped to shape the direction, goals, and funding recommendations of the PCRP. Over 300 consumer advocates have participated in peer and programmatic reviews, bringing to the forefront their unique perspective of what it is like to be a PCa patient. Their involvement has inspired and enlightened PCa investigators and caregivers, causing both to seek innovative approaches to solve difficult challenges in PCa today. The collective wisdom and partnership between consumer advocates, scientists, and clinicians have forged a new decade of exciting advancements in clinical therapeutics and technology.

With each participation in the PCRP, two things happen: My knowledge of prostate cancer increases immensely, and I realize how little I know about this disease. When I return to my community and to the outreach programs of which I am a member, I internalize the value of not giving people answers but, instead, giving them questions to think about and to ask their medical team. I find the impact of this approach so much more beneficial in helping cancer patients to grow internally and to help themselves. This, for me, is the ultimate goal of a mentor—to teach others to teach.

Pete Collins, Us TOO, Walter Reed Army Medical Center

My participation as a consumer reviewer in the PCRP was a very rewarding experience. As a prostate cancer survivor, I had an opportunity to see, firsthand, the ongoing research and scientific programs aimed at conquering this lethal disease that affects so many men and their families. Being afforded the opportunity to review research proposals and present my point of view, I saw the awareness, the progress made, and the new research proposed to deal with the disparity of prostate cancer affecting African Americans. The introduction of new research has provided me an insight on prostate cancer that someday there will be a means to identify and prevent suffering from this disease.

Dewey Helms, Siteman Cancer Center, Barnes-Jewish St. Peter's Hospital

As a retired research scientist who is a consumer reviewer, I can understand the research scientist's point of view while personally experiencing the consumer reviewers viewpoint. Research is a seductively addictive activity, as I well know from personal experience. The intellectual challenges in first-class research tend to absorb the mental and emotional energies of the researcher and, not infrequently, lead to a sort of tunnel vision focus on solving specific research problems while obscuring awareness of the bigger picture issues, such as the impacts of particular therapeutic regimens on patient quality of life. Consumer reviewers, by being focused, understandably, on the direct personal impacts of possible research outcomes, help ensure that research is more than a value-free game that addresses intellectual puzzles without attention to the living, breathing, often suffering humans who deal personally and intimately with the profoundly intimate, interpersonally disruptive, and soul-searing disease that prostate cancer can be.

Herbert Gerjuoy, Ph.D., Hartford Hospital Prostate Cancer Support

My participation has heightened my activism and patient advocacy with other men I have met or encountered. I find that I am more actively pursuing new scientific knowledge and how that translates into patient-related information. And I feel that representing other prostate cancer consumers makes me more acutely aware of the need to eliminate prostate cancer.

Scientific research has a goal to convert new knowledge learned from bench to bedside. The consumer reviewer brings in real-world experience from diagnosis, imaging tests, biopsies, surgeries, and radiotherapy to the discussion. The consumer is the first line of real-time experience. Therefore, the consumer has a personal stake in the success and outcome of the research. The viewpoint a consumer brings to the conversation will accelerate the high-risk, high-impact proposals being sought and funded.

James (Jim) Bailey, Man to Man, American Cancer Society, Indianapolis, Indiana

The most exciting developments are the possible improvements in early detection of prostate cancer and the possible elimination of biopsies for the detection of the disease. Although it does not appear that biopsies will totally go away, newer procedures may greatly reduce the need. This, in turn, may encourage more men to be tested.

As a PCRP consumer reviewer, I have been able to give a nonscientific perspective to researchers and advise them on what men are looking for in terms of research, prevention, and treatment. What I do as a consumer reviewer helps to remove some of the stigma of being screened, diagnosed, and treated. The consumer reviewers express opinions and concerns that would probably be overlooked by the scientific community.

Robert Young, ZERO – The Project to End Prostate Cancer

PCRP Partners for Peer Review

Scientists and clinicians partner with consumer advocates on peer review panels to provide expert advice on the scientific and technical merit of research proposals. Together they are tasked with measuring each proposal against a gold standard for innovation and impact, along with a well-reasoned scientific rationale and research strategy for addressing the hypothesis proposed. This assessment is a critical component in enabling the program to identify innovative, high-risk, high-impact approaches to PCa that will move the field toward accomplishing the PCRP mission.

Federally funded basic and translational prostate cancer research would be meager at best were it not for the wisdom and tremendous support of the PCRP. The unique process of peer review implemented by the PCRP has risen above that of other, more traditional, largely shortsighted, funding mechanisms. As such, the status quo is avoided, and truly innovative ideas are given the provisions necessary to develop the next generation of lifesaving interventions.

Robert Bright, Ph.D., Texas Tech University Health Sciences Center

As a reviewer and award recipient of the PCRP since its inception, I have seen the PCRP provide opportunities for research like no other entity. Research takes breathtaking leaps and turns these days, and the types of funding mechanisms provided by the PCRP allow researchers to quickly change direction and follow new leads. This type of flexibility is critical for keeping prostate cancer research state-of-the-art and moving innovative approaches into the clinic.

Donna Peehl, Ph.D., Stanford University

In my view, the PCRP will play a pivotal role in re-focusing the scientific community's attention to critical, unresolved problems in prostate cancer, such as distinguishing indolent from lethal disease. By releasing clearly defined program announcements with an eye toward high-reward potential, the PCRP provides investigators an opportunity to explore important issues via reframing first principles and addressing central questions.

Ganesh Palapattu, M.D., The Methodist Hospital

The most significant impact the PCRP will have on prostate cancer in the future is establishing the best treatment option for a man with newly diagnosed, low-risk prostate cancer based on the characteristics of his cancer. Such an accomplishment would be huge! It would minimize overtreatment and, more importantly, it would remove the uncertainty regarding treatment decisions that these men and their providers currently face.

Karla Ballman, Ph.D., Mayo Clinic

For almost a decade, my cancer research career has been shaped by the CDMRP PCRP, beginning with a New Investigator's Award to develop and validate a model of prostate cancer screening in African American men. Since then, I've been funded on several grant mechanisms, served as a reviewer on different review panels, and chaired four review panels. I am truly amazed and delighted by the significant impact the PCRP has made in the last decade on understanding prostate cancer disparities, especially in African American men. I anticipate that the PCRP will continue to lead in cutting-edge research on the biobehavioral etiology of prostate cancer disparities to end the disproportionate burden of prostate cancer experienced by African Americans. The high-risk, high-impact research approach taken by the PCRP continues to accelerate the advancements for prostate cancer research.

Folakemi Odedina, Ph.D., University of Florida

Members

Donald Tindall, Ph.D., FY10 Chair, Mayo Clinic, Rochester

Natasha Kyprianou, Ph.D., FY11 Chair, University of Kentucky

Philip Arlen, M.D., Neogenix Oncology Inc.

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

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

Maha Hussain, M.D., University of Michigan

Massimo Loda, M.D., Dana-Farber Cancer Institute

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

Timothy Ratliff, Ph.D., Purdue Cancer Center

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

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

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

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

Virgil Simons, The Prostate Net

Howard Soule, Ph.D., Prostate Cancer Foundation

Jianfeng Xu Dr.P.H., M.D., Wake Forest University School of Medicine

Integration Panel

Each year, the PCRP Integration Panel outlines a vision for the program that focuses on innovation and impact, clinical, multidisciplinary, and multi-institutional research and training, and resource and infrastructure development. The broad portfolio developed by the Integration Panel reflects the vision of conquering PCa by bringing together the brightest minds in science and technology and providing funding opportunities to develop new therapies, diagnostics, and technologies. Integration Panel members are prominent leaders in PCa research, drawn from the nation's leading research institutions, foundations, and PCa advocacy groups. Diverse in expertise, the 16-member panel includes highly knowledgeable scientists, clinicians, and consumer advocates.

Each year the PCRP re-emphasizes its vision to "conquer prostate cancer" and its mission to "fund research that will eliminate prostate cancer." The efforts of the PCRP are supported by annual congressional appropriations and realized through the steadfast and painstaking work of scientists—and consumer advocates—who boldly challenge current paradigms and push the boundaries of science with novel innovations. The quality of the science presented at the 2007 IMPaCT meeting was extraordinary. I am looking forward to hearing about the groundbreaking achievements of PCRP-funded investigators at the 2011 IMPaCT meeting.

Donald Tindall, Ph.D., Professor, Director and Vice Chair of Urologic Research, Carl Rosen Professorship in Urology, Departments of Urology, Biochemistry, and Molecular Biology, Mayo Clinic College of Medicine, FY10 Integration Panel Chair

What a tremendous investment the PCRP has been for patients, scientists, clinicians, and the American people. The unique structure of this dynamic program is unparalleled—in engaging the best scientific minds across the nation (and beyond) to embrace the challenges and opportunities of research; in supporting the development of brilliant young scientists in cancer research; and, above all, in delivering solutions to prostate cancer patients and saving lives. The unfolding impact of this effort is reflected in the phenomenal scientific achievements of PCRP-funded investigators across different aspects of prostate cancer research (clinical, epidemiological, genetic, mentoring). It is an honor to serve a cause so worthy of pursuit with a magnificent group of individuals sharing the same passion for finding the cure for prostate cancer, implementing discoveries swiftly from the lab to the clinic, and giving millions of patients hope. It is all about making a difference, conquering the disease, and creating a legacy for the next generation.

Natasha Kyprianou, Ph.D., James F. Hardymon Chair in Urology Research, Professor of Urology, Molecular Biochemistry, Pathology and Toxicology, University of Kentucky Medical Center, FY11 Integration Panel Chair

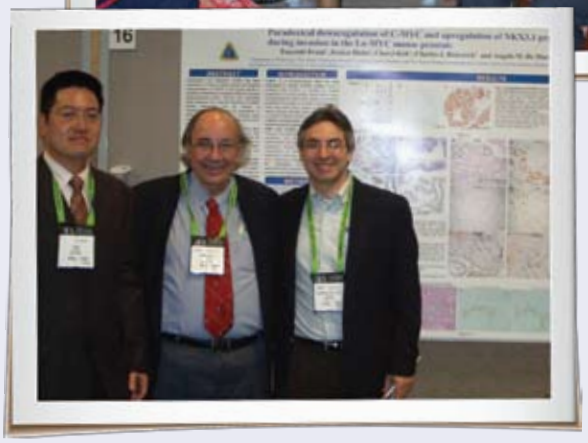
The PCRP is an outstanding example of how to organize and work toward the goal of conquering cancer in general and prostate cancer in particular. The unique manner in which the PCRP fosters collaboration among scientists, consumers, and administrators is an excellent and effective model for others to follow. I'm honored to have the opportunity to contribute."

Westley Sholes, M.P.A., California Prostate Cancer Coalition Integration Panel Member

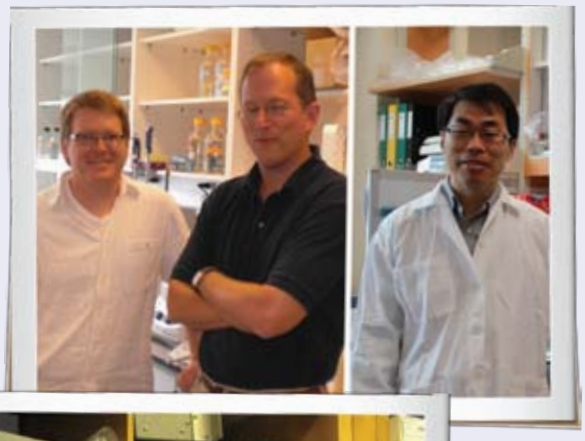
The Scientific Community

PCRP-funded investigators across the nation and around the world are working together to solve the most difficult problems in PCa today. From multidisciplinary, multi-institutional consortia collaborations to expedite clinical trials or uncover the causes of PCa health disparities to partnerships that synergize expertise and resources to solve complex problems, scientists are pushing the boundaries of innovation on the way to new breakthroughs in PCa. Take a look at some of the partnerships facilitated by PCRP funding:

Folakemi Odedina, Ph.D., University of Florida
An Integrative Personal Model of Prostate Cancer Disparity for African American Men (FY06 Health Disparity Research Award)



Angelo DeMarzo, M.D., Ph.D. and Tsuyosh Iwata M.D., Ph.D. (trainee), pictured with Donald S. Coffey, Ph.D., Johns Hopkins University
Interactions Between Dietary Factors and Inflammation in Prostate Carcinogenesis (FY05 Idea Development Award with Nested Resident and Medical Student Traineeship Award)



Darrel Irvine, Ph.D., Karl Wittrup, Ph.D., Jianzhu Chen, Ph.D., Massachusetts Institute of Technology
T-Pharmacytes for Prostate Cancer Immunotherapy (FY09 Synergistic Idea Development Award)

Lionel Banez, M.D. and Steven Freedland, M.D. (mentor), Duke University Medical Center
Racial Differences in the Association Between Statin Use and Prostate Cancer Progression Following Radical Prostatectomy (FY06 Health Disparity Training Award)

Innovative Minds in Prostate Cancer Today Meeting

March 9–12, 2011, Orlando, Florida

In March 2011 PCRP-funded investigators and consumer advocates from across the country will gather for 3 days of intensive learning, discussions, collaboration, and planning to forge new paths toward scientific discovery and translation in meeting the challenge of eliminating death and suffering from PCa.

Approximately 1,000 participants are expected for this innovative, progressive meeting. The schedule will include numerous scientific sessions ranging from large gatherings to smaller groups to foster partnerships, collaborations, and mentoring. Planned sessions include: 6 plenary, 12 symposia, 5 "meet the expert," and 2 poster sessions. In addition, town hall-type and trainee networking sessions will be conducted. As IMPaCT meeting co-Chair, Dr. Theresa Miller notes, "There is optimism and excitement in bringing the best minds in prostate cancer together to identify what is needed to achieve our goal of conquering prostate cancer." This interactive meeting of consumers, scientists, and clinicians will feature numerous speakers with varied expertise and approaches to finding a cure for cancer. The roster of speakers includes leaders in the field such as Donald Tindall, Arul Chinnaiyan, James Mohler, Kenneth Pienta, Peter Nelson, and Howard Scher, among others. Up-and-coming PCRP-funded leaders in the field such as Marianne Sadar, Arun Sreekumar, and Scott Dehm will also occupy the speaker podium while others will lead poster presentations and poster discussion sessions.

Critically important to these gatherings and the force behind all of the PCRP's efforts are the consumer advocates. Over 150 consumer advocates will participate in the meeting to listen, discuss, and collaborate with scientists and clinicians. Together, they will develop a clear understanding of where cancer care and treatment stand today, what is needed to alleviate death and suffering, and where we must focus our current efforts.

Challenges: The Major Issues for Prostate Cancer Research Today

On any given day, leaders in PCa care and research are thinking, strategizing, and working to overcome the greatest challenges facing clinicians today. Recently, the PCRP asked three of our nation's best scientists to reflect on what they perceive are the most significant challenges standing between PCa patients, complete cures, and optimal quality of life. Here is what they shared with us:

A. Oliver Sartor, M.D., C.E. and Bernadine Laborde Professor of Cancer Research, Departments of Medicine and Urology, Tulane University School of Medicine

We face many challenges in prostate cancer today. Some of the most important relate to better decision making at the time of diagnosis. Deciding who needs treatment and who does not is a huge issue, one of the most pressing issues in medicine today. In addition, we are in desperate need of better treatments for those with advanced disease. I only know one way to make progress and that is quality research; fortunately we have the CDMRP PCRP to help us achieve our goals.

Arul Chinnaiyan, M.D., Ph.D., Director, Michigan Center for Translational Pathology, American Cancer Society Research Professor, S.P. Hicks Endowed Professor of Pathology and Urology Investigator, Howard Hughes Medical Institute, University of Michigan Medical School

Tremendous progress has been made in targeting the androgen signaling axis in prostate cancer. This is exemplified most recently by the successful clinical trials of abiraterone, a drug that blocks the formation of testosterone, in men with castration-resistant disease. While these and other androgen-related therapies will potentially extend the survival of men with advanced prostate cancer, these approaches alone will likely not cure the disease. To achieve durable responses and to potentially achieve a cure, one will need to target the driving genetic mutations characteristic of prostate cancer, an example of which are recurrent ETS gene fusions found in 50%–60% of prostate tumors. Our studies suggest that prostate cancers can be divided into molecular subtypes, which include ETS gene fusions, RAF gene fusions, and SPINK1 overexpression. While drugs against the RAF pathway are available or in late-stage clinical development, there are currently no therapies targeting the ETS transcription factors or SPINK1, and this, consequently, will be a major challenge for the future. Furthermore, the advent of high-throughput, sequencing-based technologies will soon allow physicians to pinpoint the "actionable" genetic mutations of an individual prostate cancer patient and allow for tailored treatment.

The photo is courtesy of the Department of Pathology, University of Michigan

William G. Nelson, M.D., Ph.D., Marion Knott Professor and Director, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University

The prospects for men with prostate cancer today have never been better, but we still need to accelerate the pace of innovation to eliminate the disease as a threat of morbidity and mortality for men in the United States and the world. For localized prostate cancer, screening and early detection have maximized the survival benefits of surgery and radiation therapy but at a cost of overtreatment of many men with indolent disease. We need better tools for assessing the location, extent, and aggressiveness of prostate cancer at the time of diagnosis so that we can deliver intensive curative therapies to men who will benefit from them and more measured treatment strategies to men best managed conservatively. Hopefully, new imaging approaches and new molecular biomarker assays will be able to accomplish this treatment stratification. For advanced prostate cancer, I believe that the growing toolbox of available drugs targeting the androgen signaling pathway will ensure that men in the future will not die from prostate cancer driven by the androgen receptor. To build further on these successes and achieve cures of prostate cancer once disseminated, new drugs directed at new molecular targets will be needed.

Successes: Making Progress Toward a Cure

Despite the major challenges facing PCRP investigators in finding a cure for PCa, many are making significant progress toward better treatment options after PCa diagnoses, translating discoveries and delineating pathways underlying complex molecular paradigms. The PCRP's mission of supporting innovative ideas for high-risk, high-gain research has led to breakthroughs that will undoubtedly change clinical practice, influence the types of treatment delivered to patients and improve methods of prevention and detection. PCRP-funded investigators are pushing the boundaries of science and breaking into new areas of exploration. The following are areas of success stories in PCa research that will impact the lives of men with the disease:

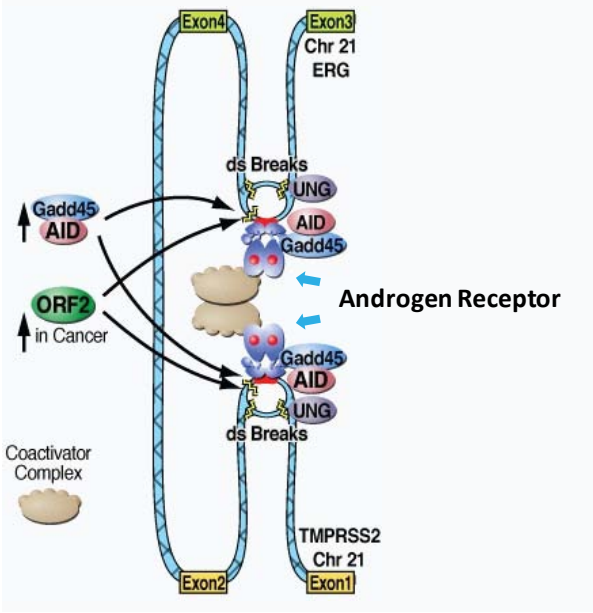
Metastasis and Biomarkers	Therapeutics	Novel Imaging Technologies	Tumor Immunology and **Inflammation**
Health Disparity	Training New Investigators	Quality of Life	Developing Needed Resources

Metastasis and Biomarkers

To distinguish indolent PCa from aggressive forms of the disease, PCRP-funded scientists are exploring biological pathways that lead to metastasis. The ultimate goal is to identify new biomarkers and targets for development of new therapies for metastatic disease. Identification of these biomarkers will help in determining which PCas are indolent and require no treatment versus those that are aggressive and require immediate treatment; this remains a critically unmet need. Meeting this need will require a concerted effort toward: (1) Identifying genes that may serve as suitable prognostic (measure of disease aggressiveness) biomarkers and (2) developing better detection and diagnostic tools that can be used in conjunction with these prognostic biomarkers for improved treatment.

Genetic changes have been known to play a key role in the development of cancer, which progresses to metastasis in many cases. Gene rearrangements have been shown to disrupt normal gene function, leading to uncontrolled cell growth and metastasis. These gene rearrangements occur from the frequent loss or gain of chromosomal regions that result in somatic gene fusions (translocations), which occur early in PCa cells. The most common gene rearrangement in PCa is one that brings the androgen-responsive TMPRSS2 gene in proximity to the ETS family genes, most commonly the ERG (ETS-related gene) or ETV1 (ETS variant gene 1). This interaction results in the expression of TMPRSS2-ETS gene fusions, which are controlled by androgens and androgen receptor (AR) activity. Consequently, tumors that harbor these TMPRSS2-ETS gene fusions (found in over 50% of patients with PCa) are also known to have increased expression of ETS genes. Studies are being conducted to determine the mechanism by which these structural changes occur resulting in these TMPRSS2-ETS gene fusions.

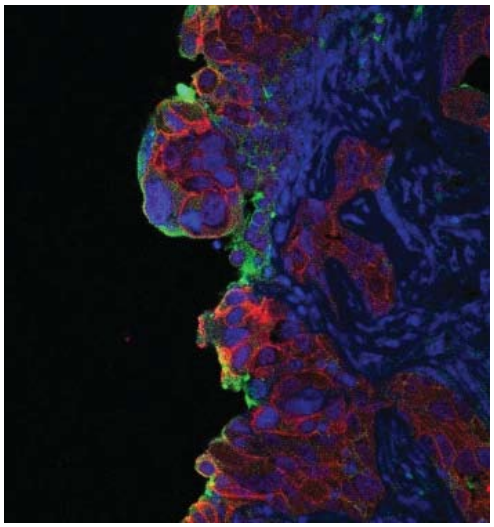
Dr. Michael Rosenfeld, FY07 PCRP Idea Development awardee from the University of California, San Diego, recently described a model in which AR is recruited to sites near common chromosomal breakpoints, inducing structural changes that bring the TMPRSS2 gene in proximity to ETS family genes and enable their fusion. Dr. Rosenfeld found that gene fusions between TMPRSS2 and either ERG or ETV in PCa are not random events, as previously thought, but rather are orchestrated by AR, thus establishing a key mechanism for how these genetic alterations arise in PCa. In fact, the ETS genes in the TMPRSS2-ETS gene fusions are under the control of androgen-inducible TMPRSS2 gene promoter elements; therefore, Dr. Rosenfeld examined the effects of androgens and radiation in the development of the TMPRSS2-ETS rearrangement in a cellular model of androgen-responsive PCa in which TMPRSS2-ETS translocations are not present. He observed that adding androgens or exposing normal prostate cells to radiation (to induce DNA breaks) resulted in the formation of TMPRSS2-



A schematic illustration of AR-mediated chromosomal translocations leading to formation of TMPRSS2-ETS gene fusions. The AR with bound androgen brings the TMPRSS2 and ERG genes (normally located at a distance from each other on chromosome 21 [light blue string]) close together near the sites of double-strand breaks (ds Breaks) resulting in fusion of the TMPRSS2 and ERG genes. High levels of activation-induced deaminase (AID) and Line-1 retroelement ORF2 endonuclease (ORF2) expressed in PCa cells (but not normal prostate cells) are brought to DNA breakage sites by AR along with Gadd45 (a transcriptional activator), uracil-DNA glycosylase, and coactivator proteins (Coactivator Complex) to facilitate formation of the gene fusion. Lin CL, Yang B, Tanasa K, Hutt BG, Ohgi JK, Zhang J, Rose DW, Fu XD, Glass CK, and Rosenfeld MG. 2009. Nuclear receptor-induced chromosomal proximity and DNA breaks underlie specific translocations in cancer. *Cell* 139(6):1069–1083.

ETS gene fusions. Fusion events with each treatment occurred at a low frequency (3% to 5% of the samples); however, application of androgens and radiation in combination induced higher levels of fusion transcripts (30% to 35% of the samples). Analysis of DNA and fusion transcripts from treated cells confirmed the presence of chromosomal breakpoints and fusion junctions similar to those found in tumors from PCa patients. Interestingly, in the presence of androgen, AR was recruited to binding sites near the breakpoints and induced conformational changes in the chromosomes that brought the TMPRSS2 gene close to ERG or ETV1 genes, suggesting a mechanistic "smoking gun" for fusion events. These gene fusions were not found in experiments performed in normal epithelial cells, suggesting that in cancer cells AR cooperates with other factors (such as aberrant gene expression) present in PCa cells to induce gene fusions. In other experiments, Dr. Rosenfeld identified two genes that may be responsible for this key difference: AID and Line-1 retroelement ORF2 endonuclease (ORF2). Although not normally present in the prostate gland, these genes were found to be expressed in PCa and recruited by AR to breakpoint regions. Both genes have previously been associated with the introduction of DNA breaks, suggesting that they may be critical to the formation of the gene fusions found in PCa. These new findings may explain why TMPRSS2-ETS gene fusions orchestrated by AR arise so frequently in PCa.

Understanding the molecular mechanisms underlying the formation of TMPRSS2-ETS gene fusions may help explain why they occur in so many prostate tumors and also tell us a great deal about PCa progression. Interestingly, TMPRSS2:ERG fusions are associated with increased expression of EZH2 protein in metastatic PCa cells. These fusions provide a link between disruption of AR signaling and potentiation of epigenetic alterations by EZH2 activation, which results in disruption of prostate epithelial cell differentiation and resulting in cancer progression. EZH2 turns off (silences) expression of genes that are involved in inhibiting growth and metastasis of PCa cells. **Dr. Karen Cichowski, FY07 PCRP Idea Development Award** recipient, at Brigham and Women's Hospital, identified a target gene of EZH2 (i.e., disabled homolog 2 interacting protein [DAB2IP]) gene, that is turned off (suppressed/silenced) in PCa. The concerted interplay between TMPRSS2:ERG fusions, increased EZH2 expression, and DAB2IP epigenetic silencing in PCa metastasis is not clearly understood. However, an understanding of how these processes may relate to each other in PCa metastasis may begin to unfold in work performed by Dr. Cichowski – she dissected the roles of Ras and nuclear factor–kB (NFkB) signaling pathways, which, when activated, accelerate uncontrolled cell proliferation and metastasis. Studies on PCa tissue showed that normal prostate cells express high levels of DAB2IP, whereas PCa cells showed weak or no DAB2IP expression. Decreased DAB2IP levels were associated with a higher Gleason score, indicating that progressive loss of DAB2IP correlates with more aggressive forms of the disease. Consistent with the data from prostate tissues, DAB2IP was also found to be expressed in normal prostate cells but is turned off in PCa cells. Using an orthotopic tumor mouse model, Dr. Cichowski demonstrated that loss of DAB2IP or epigenetic suppression by EZH2-induced invasive metastatic tumors by cooperatively activating the Ras oncogene and NFkB signaling pathways to promote uncontrolled cell growth and invasion, respectively. The observation that DAB2IP is turned off by EZH2, which has been shown to be upregulated in PCa cells during PCa progression, provides further understanding of how metastases arise and suggests that EZH2 and DAB2IP may serve as potential biomarkers for progression to metastasis or, possibly, new therapeutic targets. Further studies will delineate whether upregulation of EZH2 and loss of DAB2IP is selectively associated with TMPRSS2:ERG fusions.

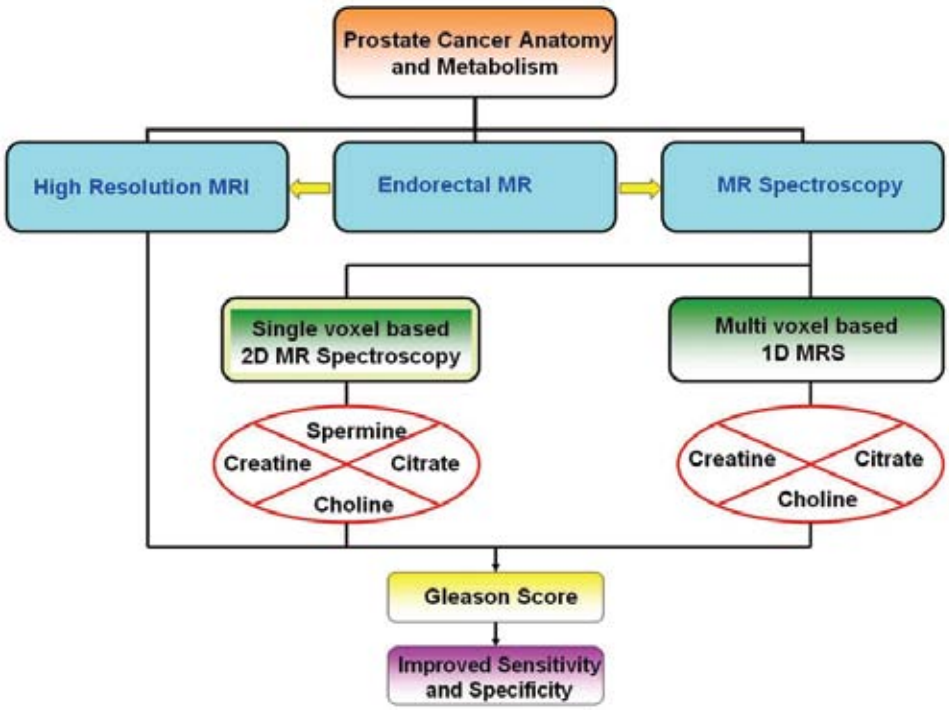


DAB2IP loss induces PCa metastasis by causing dramatic molecular changes at the invasive front of the tumor. This image shows a DAB2IP-deficient metastatic tumor in mice undergoing an epithelial to mesenchymal-like transition at the leading edge of the tumor. Green: the mesenchymal marker vimentin. Red: the epithelial marker e-cadherin. Blue: DAPI staining of cell nuclei. Min J, Zaslavsky A, Fedele G, McLaughlin SK, Reczek EE, De Raedt T, Guney I, Strochlic DE, Macconaill LE, Beroukhim R, Bronson RT, Ryeom S, Hahn WC, Loda M, Cichowski K. 2010. An oncogene-tumor suppressor cascade drives metastatic PCa by coordinately activating Ras and nuclear factor-B. *Nature Medicine* 16 (3):286–294.

In addition to identifying genes that may serve as suitable prognostic biomarkers, efforts are needed to develop better detection and diagnostic tools that can be used in conjunction with these prognostic biomarkers for improved treatment. The limitation of serum prostate-specific antigen in providing optimal specificity and sensitivity as a diagnostic marker for PCa to accurately and confidently guide therapeutic approaches continues to be a challenge. Other methods that are used to diagnose and differentiate between benign and malignant tumors, such as transrectal ultrasound-guided biopsy and magnetic resonance imaging (MRI), use invasive rectal coils and currently do not provide adequate sensitivity and specificity for clinical detection or diagnosis, nor do these advise treatment options. In the hope of developing a less invasive and more accurate metabolite imaging procedure for PCa, FY06 Idea Development Award recipient Dr. Michael Albert Thomas and co-workers used two-dimensional magnetic resonance spectroscopy (2D-MRS) to biochemically measure PCa metabolite levels of citrate, spermine, choline, and creatine in patients with prostate tumors, benign prostatic hyperplasia (BPH), and normal healthy subjects.

By using this novel technique and comparing it with biopsy results, Dr. Thomas was able to distinguish between patients with high-intermediate risk PCa (Gleason score 4+3) and those with low-intermediate risk PCa (Gleason scores 3+4) as well as distinguish PCa from BPH and healthy tissue. These preliminary findings suggest that detection of metabolites with 2D-MRS is a promising avenue of research and development for detection and diagnosis of PCa. Moreover, comparison with biopsy data suggests that 2D-MRS may be a powerful new tool for prognosis.

These innovative scientists supported by PCRP funding are identifying the underlying genetic, epigenetic, and biochemical changes responsible for development and progression of PCa to metastasis. Their studies identify new biomarkers for disease progression to help distinguish between indolent and the more aggressive/lethal forms of PCa disease, and they point the way to improved therapeutic strategies.

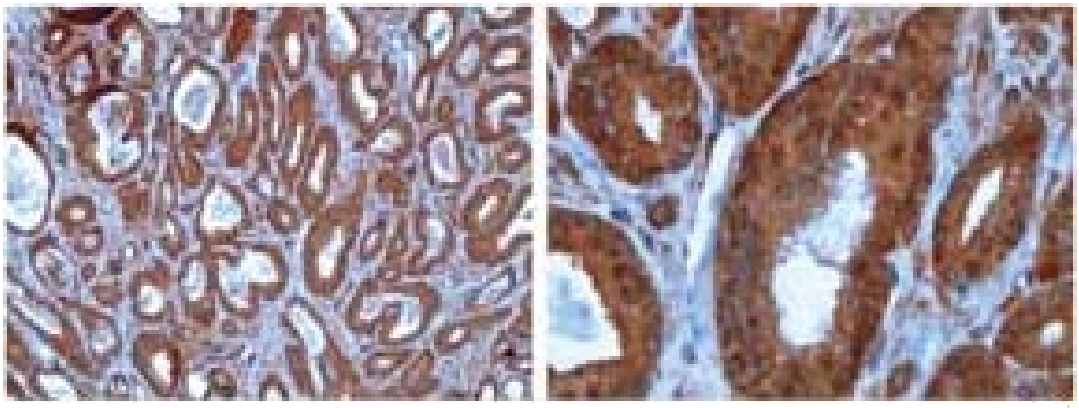


Improving the sensitivity and specificity of PCa detection and diagnosis through high resolution MRI and spectroscopy of metabolites.

Therapeutics

A major factor contributing to PCa death and suffering is the spread (metastatis) of PCa cells to other parts of the body where they may grow and establish new tumors. In PCa, metastases may either require androgens (testosterone and dihydroxytestosterone) for growth (non-castrate prostate cancer) or they may appear to be androgen-independent, also called castration-resistant prostate cancer (CRPC). The failure of most treatment strategies to improve long-term survival of PCa patients indicates clearly that new therapeutic approaches are needed if we are to reduce or eliminate PCa deaths. PCRP-funded investigators are making major breakthroughs to identify new approaches to target metastatic and CRPC, searching for more effective treatments and validating them in clinical trials to advance cancer treatment for PCa patients.

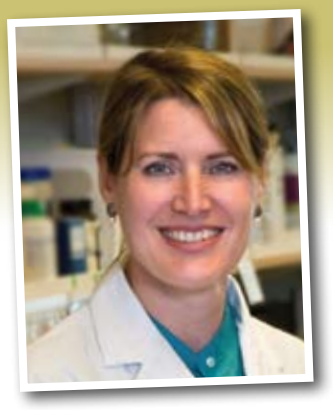
Another valid alternative for advanced PCa treatment is immunotherapy. The U.S. Food and Drug Administration recently approved the first therapeutic cancer vaccine (Sipuleucel-T, Provenge™) for some men with metastatic CRPC, which in clinical trials improved patient survival by 4.1 months compared to placebo (Kantoff et al. *NEJM* 2010). The success of immunotherapy depends on the ability of white blood cells (cytotoxic T lymphocytes, or CTLs) to reach the tumor and kill transformed cells. Dr. Antonella Viola, recipient of an FY06 PCRP Idea Development Award, demonstrated that generation of reactive nitrogen species (RNS) in prostate tumors is a dominant mechanism for suppressing the immune system. In human PCa, RNS are generated by the combined activity of the L-arginine metabolizing enzymes arginase (ARG) and nitric oxide synthase (NOS), which are overexpressed in PCas as compared to hyperplasic prostate; moreover, human PCa specimens exhibit an intense staining for nitrotyrosines, which are the product of tyrosine nitration mediated by RNS within the tumor microenvironment. Dr. Viola has investigated the role of RNS in tumor-induced immunosuppression, unveiling a previously unexplored mechanism of tumor escape based on post-translational modification of intratumoral chemokines. Typically, CTLs are unable to reach the core of the tumor mass and concentrate at the border of the lesion. Homing of T cells to tumors depends on the action of specific chemokines, which regulate the movement of T cells inside tissues toward specific areas. CCL2, an inflammatory chemokine involved in recruitment of CTLs to tumors is nitrated/nitrosylated in PCa specimens. Interestingly, RNS-induced modifications change the functional properties of the chemokine that, because of its reduced affinity for the receptor CCR2, can no longer attract tumor-specific CTLs. Other chemokines and cytokines may be modified by intratumoral RNS and, indeed, targeting RNS production in tumor may represent a novel strategy to improve cancer immunotherapy. An integral part of this research, a novel drug, AT38 ([3-aminocarbonyl]furoxan-4-yl)methyl salicylate) was designed to control RNS production by modulating ARG and NOS activity within tumor microenvironment. AT38 blocked the post-translational modification of chemokines, facilitated infiltration of immune cells within the tumor, and improved the efficacy of adoptive cell therapy with tumor-specific CTLs. AT38 might be useful to aid immunotherapeutic approaches for the treatment of PCa by creating a favorable tumor environment for the immune cells. AT38 might also be used in conjunction with cancer vaccination to aid in antitumor immunity.



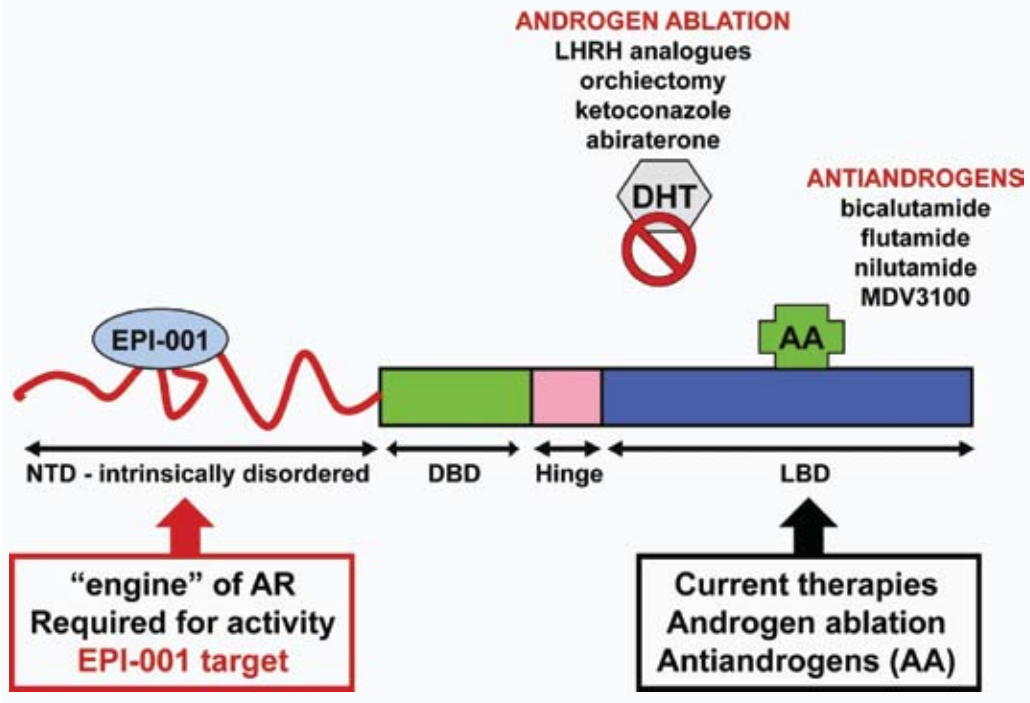
10X *40X*

Human PCa express nitrated proteins.

A major driving force underlying the growth of metastatic PCa and CRPC is the androgen receptor (AR), which turns on the expression of genes that cause PCa cells to grow and turns off genes that cause them to die. **Dr. Marianne Sadar, recipient of FY04 and FY06 PCRP Idea Development Awards**, used high-throughput screening techniques to search a library of over 1,700 marine sponge extracts for compounds that would inhibit AR activity in both androgen-dependent and -independent PCa cells. One promising extract, EPI-001, was selected, and Dr. Sadar showed that EPI-001 binds to the AR, blocks AR-induced gene expression regardless of whether androgens were present and inhibits the proliferation of PCa cells expressing the AR (LNCaP, MDA PCa2B, and 22RV1). She used a mouse model of androgen-independent PCa (LNCaP) prostate tumors to determine if EPI-001 would be effective in inhibiting the growth of CRPC. Prostate tumors were allowed to grow in mice that were deprived of androgen by castration. Then mice were treated by intravenous injection of EPI-001. After 2 weeks of treatment, the tumors in EPI-001-treated mice had decreased in size to less than half that of untreated mice. Similar experiments directly injecting the drug into the tumor showed a 12-fold decrease in tumor size by 25 days after beginning EPI-001 treatment. The results show that EPI-001 targeting the AR holds great promise for the development of an effective therapeutic for both metastatic and CRPC.



Together, these PCRP-funded investigators are pursuing a variety of different strategies for the treatment and prevention of aggressive forms of PCa including the immune system, and the AR. These strategies take advantage of new discoveries in the biology and chemistry of PCa to identify new therapeutic targets, pathways, and therapeutic modalities and molecules for the treatment and prevention of metastatic and CRPC.

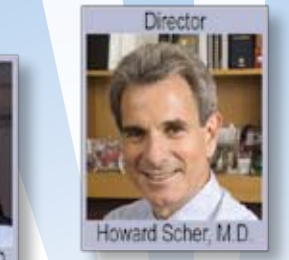


The N-terminal domain (NTD) of the AR is a therapeutic target. EPI-001 inhibits the NTD of the AR, which is required for its activity. Currently, all other therapies such as androgen ablation and antiandrogens target the ligand-binding domain. [DNA binding domain; dihydrotestosterone].

Accelerating the Pace in Clinical Prostate Cancer Research

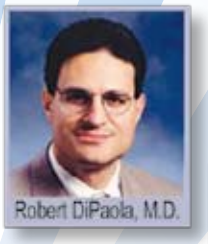
The PCRP has committed to a $41.3M investment over 8 years to bring together clinical experts from the nation's leading cancer treatment centers to accelerate progress toward a cure for PCa. In 2005, the PCRP supported the development of the Prostate Cancer Clinical Trials Consortium (PCCTC) with the goal of facilitating the rapid movement of collaborative Phase I/II and Phase II clinical trials of promising new therapeutic agents and treatment approaches into clinical practice to decrease the overall impact of this disease. Under the leadership of Dr. Howard Scher at Memorial Sloan-Kettering Cancer Institute (Coordinating Center), Principal Investigators (PIs) located at 13 leading cancer centers across the country have worked together to accelerate the pace of clinical research by centralizing management, streamlining processes, establishing scientific priorities, focusing on proof-of-concept, and validating biomarkers. The PCCTC harnesses the diverse expertise of individual PIs and their research teams (biomarkers, imaging, immunotherapy, data management, etc.) at each Consortium site to design clinical trials with definitive end points and to accelerate therapeutic advances through multicenter collaboration. A special emphasis has been placed on studies to better identify those patients most likely to benefit from a specific treatment by following a clinical states model of PCa that recognizes five clinically identifiable stages of the disease. To help individualize treatment, these include clinically localized disease, rising prostate-specific antigen (PSA), rising PSA-castrate, clinical metastases non-castrate, and clinical metastases-castrate. Since its inception, the PCCTC has conducted over 83 clinical trials (48 completed), enrolling more than 2,400 patients, including 10% representing minority patients. Since biomarkers are increasingly being recognized as essential in the evaluation of treatment response, as well as for risk assessment, early detection, prediction of aggressiveness, and/or progression of PCa, biomarker studies are being strongly pursued and validated across institutions. These efforts have helped bring five potential new therapeutics into Phase III clinical trials, including abiraterone acetate, which blocks formation of testosterone by inhibiting CYP17A1; dasatinib, a tyrosine kinase inhibitor; ipilimunab, a human monoclonal antibody that binds to CTLA4, a molecule on T cells that plays a role in regulating the immune response; MDV3100, which binds to the ligand binding domain of the AR, prevents nuclear translocation, and blocks AR interaction with coactivator proteins preventing transcription of AR-regulated genes and; IMC-A12 (cixutumumab), a human monoclonal antibody against the IGF-1 receptor; Sunitinib, a tyrosine kinase inhibitor; TAK-700, an androgen synthesis inhibitor; and Tasquinimod, an inhibitor of angiogenesis. By creating a mechanism for the rapid design, development, and implementation of early phase clinical trials on new agents and novel approaches, consortium researchers ensure that promising scientific initiatives are evaluated rapidly in the clinic with results being disseminated broadly, that the drug development process is accelerated, and, ultimately, that patients with PCa receive the highest level of care.

The Consortium's success at accelerating the clinical trial process, bringing new and more effective drugs to patients twice as fast as ever before, is a tribute to the collaborative effort of its members. Consortium members have pooled their scientific and clinical expertise to ensure selection of promising drug candidates, design meaningful clinical end points, execute clinical trials in a timely fashion, and determine which drugs should advance to larger Phase III clinical trials. The PCCTC is making a significant impact on the lives of PCa patients by keeping the pipeline primed with promising novel agents.

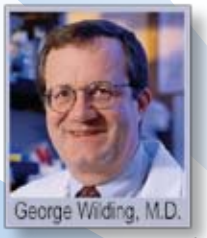


Memorial Sloan-Kettering Cancer Center

Wayne State University Karmanos Cancer Institute



Cancer Institute of New Jersey



University of Wisconsin Carbone Cancer Center

Dana-Farber/ Harvard Cancer Center

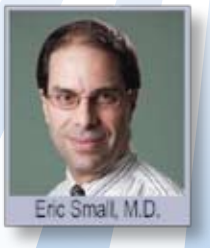
University of Washington/Fred Hutchinson Cancer Research Center

Duke University Cancer Center

University of Texas MD Anderson Cancer Center

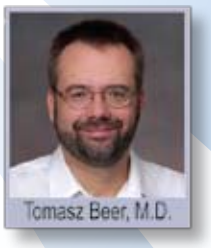
Johns Hopkins Sidney Kimmel Cancer Center

University of Michigan Cancer Center



UCSF Helen Diller Family Cancer Center

University of Chicago Cancer Research Center

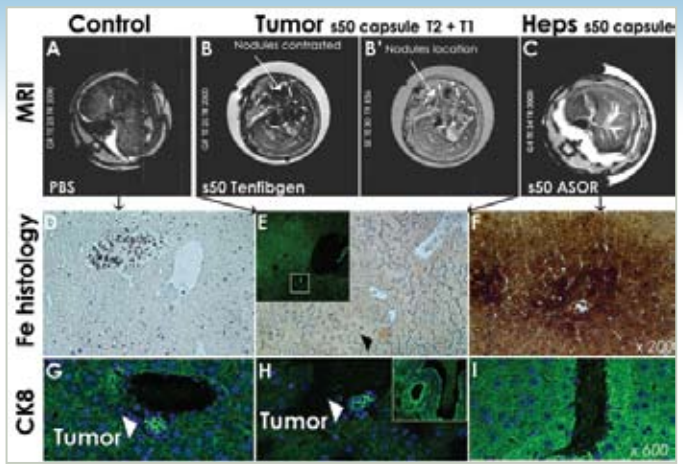


OHSU Knight Cancer Center

Novel Imaging Technologies

Existing approaches for diagnosing PCa such as prostate-specific antigen, digital rectal exam screening, and biopsy are sometimes imprecise; therefore, more effective detection strategies and techniques are much needed. Although the heterogeneity of PCa presents a challenge, advancements in imaging technologies may provide improved methods that more accurately target the tumor and provide precise and sensitive mapping of disease presence, grade, stage, and extent of spread. This may aid early detection and improve the initial evaluation of PCa, leading to improved patient management and outcomes. Breakthroughs in this field have come from PCRP-funded investigators, who have combined previous diagnostic tools with cutting-edge advances in imaging technology.

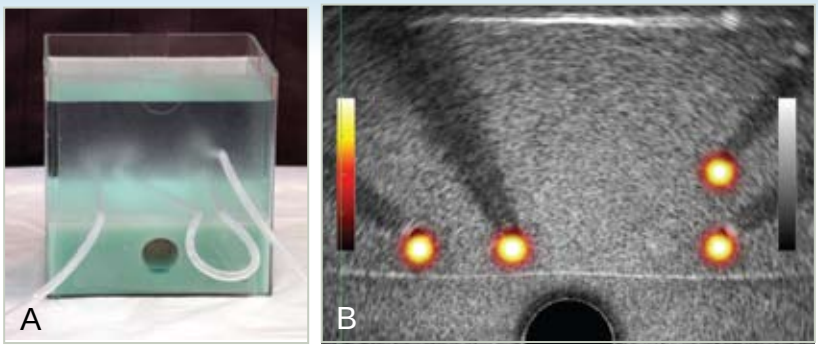
While directly imaging local and metastatic PCa remains a challenge, magnetic resonance (MR) spectroscopy can identify chemical signatures of tumor constituents. Although systemic contrast agents for MR spectroscopy can enhance imaging of tumor anatomy, these are nonspecific and cannot distinguish between neoplastic and normal tissue. FY06 PCRP Idea Development Award recipient Dr. Joel Slaton, in collaboration with GeneSegues, Inc., is developing novel technology that utilizes nanoparticle (sub-50 nanometer) capsules coated with molecules targeting specific proteins located on the surface of PCa cells to deliver cargos of MR contrast agents into tumor cells. Dr. Slaton found that MR contrast agents are suitable for encapsulating into nanoparticles and using the fibrinogen binding domain of tenascin (tenfibgen) to target tumor cells, he prepared tenfibgen nanoparticles. Analyses using PCa cells (PC-3) showed that the nanoparticles are taken up rapidly even at low concentrations without affecting cell viability. Using an animal model of PCa that metastasizes to the lymph node when injected into mice, Dr. Slaton demonstrated that the nanoparticles are taken up in tumors at concentrations 100-fold less than standard contrast agents, without any apparent toxicity. MR spectroscopy of treated live mice revealed a strong signal from the primary tumor, lymph node metastases, and even liver micrometatases. Incorporation of these contrast agents in nanoparticles and delivery to prostate tumors may improve MR spectroscopy sensitivity and specificity, and the accuracy of primary and metastatic PCa diagnoses.



s50 TBG capsules deliver FeO dextran MR spectroscopy contrast to prostatic micrometastases in liver. Mice with slowly developing flank tumors from a metastatic prostate tumor line (~30 d growth) were injected i.v. with (A) PBS, (B,B') 30 ug Fe/kg (500 nmol Fe/kg) of s50 TBG FeO Dextran, or (C) 30 ug/kg s50 ASOR capsules and sacrificed 8 (A,B) or 36 hr (C) later and fixed in formalin for imaging. Under T2 conditions (long repetition time, A,B,C not B'), iron signal from s50 capsules bearing contrast appears BLACK post-capsule disassembly. Slices show portal vein as landmark. Imaging is representative of 14,8 mice (TBG, ASOR). Fixed mice were sectioned for iron histology by Perl's Prussian Blue staining, (D) PBS, (E) s50 TBG, or (F) s50 ASOR. Brown signal denotes presence of iron. Panels G-I represent similar or exact regions shown in iron histology. Inset in Panel E (x200) illustrates orientation of magnified Panel H (x600). Broad arrows identify prostate tumor nests. Paraffin-embedded sections were also detected for G-I cytokeratin 8 (green) to detect PCa cells (bright green) and hepatocytes (green perimeter). H inset shows bright green CK8 signal in mouse prostate.

Another approach to directly image PCa takes advantage of the fact that radioactive choline (an amino acid) is taken up more efficiently by prostate tumors than normal tissue; since it can be detected by positron emission tomography (PET), it can be used to detect PCa and to determine tumor aggressiveness. However, the high relative uptake of radioactive choline in tumors blocks the visibility of other anatomical landmarks in PET images. PET imaging could be enhanced if its functional information could be fused with anatomical information such as transrectal ultrasound (TRUS) imaging, which uses sound waves to create an image of the prostate region. A small probe is inserted into the rectum that releases sound waves that create echoes that bounce back to a computer that translates the pattern of echoes into a

picture of the prostate region. Although the probe is uncomfortable, TRUS is essentially painless and well tolerated by most men and is used to guide the needle to the prostate during biopsy. Dr. Jennifer Huber, recipient of an FY06 PCRP Idea Development Award, proposed to combine these two imaging technologies to form a Dual PET–TRUS imaging system that will accurately localize PCa and monitor response to treatment. Over the course of the study, Dr. Huber designed and built a patient table equipped with a TRUS probe that fits into the PET scanner to optimize viewing the patient's prostate gland in the center of the scanner. She also developed PET-TRUS imaging software designed to reconstruct the PET and TRUS images to visualize both images in a single fused three-dimensional PET/TRUS image. To test the accuracy of the PET-TRUS imaging system, phantoms were developed to simulate a patient's prostate gland, and PET-TRUS imaging data were collected. The data showed that the image co-registration error was very small (within 1 mm axially and 2–6 mm in the transaxial plane), validating the accuracy of visualization of the prostate. Dr. Huber has received Institutional Review Board approval to begin human trials in the coming year. This novel dual-modality prostate imaging strategy should help to increase the accuracy of guiding needle biopsy procedures to cancer lesions, confirm initial diagnosis, determine where higher dose is needed for external beam radiation and brachytherapy, and detect early failure to response to radiotherapy, prostatectomy, and androgen ablation.

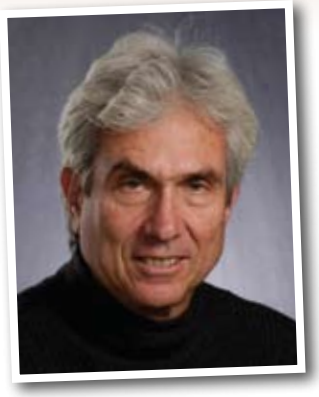


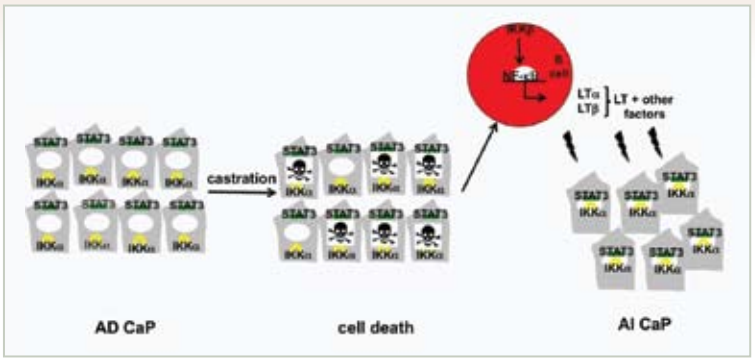
Dual PET-TRUS Imaging. (A) Photograph of the custom multi-line source phantom, showing four fillable line sources imbedded in tissue-like gel with a hole for the TRUS probe. (B) A fused PET-TRUS image of this multi-line source phantom. All four line sources are clearly visible for both PET (colored) and TRUS (grayscale), and only a small PET-TRUS co-registration error is seen.

Tumor Immunology and Inflammation

Although the precise cause of PCa is unknown, genetic and environmental factors are thought to play a significant role and may be intertwined with inflammation. Inflammation is a complex biological response to the presence of harmful stimuli, such as bacteria or cancer cells, and involves an increased movement of white blood cells from the blood into injured tissues. PCRP-funded investigators are beginning to understand the heterogeneity in the tumor microenvironment and the role of inflammation in PCa and are identifying new targets to prevent inflammation.

Metastatic prostate cancer is usually treated using androgen deprivation (or ablation) therapy (ADT) that causes hormone-dependent tumors to shrink, but over time, tumors emerge in an androgen-independent form capable of growing in a low-androgen environment. These androgen-independent/castration-resistant tumors are usually more aggressive than the original tumor, and the reasons underlying the eventual failure of ADT are poorly understood. Dr. Michael Karin, recipient of an FY03 PCRP Idea Development Award, has identified an inflammatory response triggered by dying PCa cells inside tumors. The dying tumor cells recruit B cells (white blood cells), which infiltrate the tumor and produce the protein lymphotoxin, an inflammatory cytokine. Lymphotoxin induces the proliferation of residual PCa cells, resulting in tumor growth in the absence of androgens.



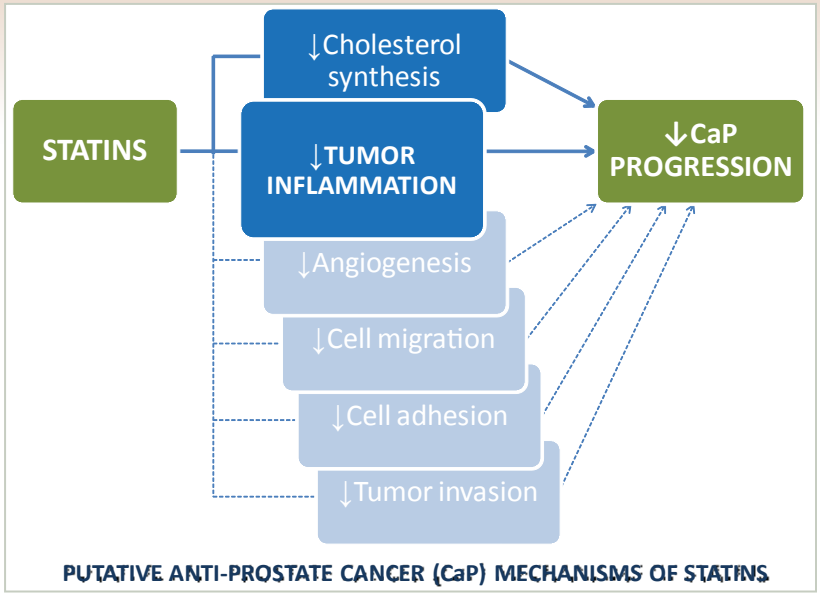


A model explaining how therapy-induced inflammation promotes emergence of androgen-independent PCa. Androgen withdrawal causes death of primary androgen-dependent PCa cells, which release mediators that lead to recruitment of inflammatory/immune cells, including B cells, into the tumor remnant. Activation of IKB kinase(IKK) b in B cells results in NF-KB-dependent production of lymphotoxinand other factors that activate IKKa and STAT3 in residual PCa cells. This results in enhanced cell survival, proliferation and growth of androgen-independent PCa. Ammirante M, Luo JL, Grivennikov S, Nedospasov S, Karin M. 2010. B-cell-derived lymphotoxin promotes castration-resistant prostate cancer. *Nature* 11;464(7286):302-5.

Using a mouse model of PCa, Dr. Karin allowed tumors to grow to a large size, after which the mice were androgen deprived by castration. He observed that PCa cells began to die, dramatically reducing tumor size 20-fold, suggesting that androgen deprivation can effectively kill tumor cells in mice. However, after 2 weeks, tumors began to re-emerge and increased to their original size within 4 weeks after androgen-deprivation therapy. Dr. Karin found that B cells, derived from the bone marrow and not present in the initial androgen-dependent tumors, had infiltrated the castration-resistant tumors, suggesting that the development of androgen-independent PCa was dependent on an inflammatory/immune response mediated by B cells. He showed that, as androgen-starved tumors began to die, they secreted a protein called CXCL13, whose function is to attract B cells to the sites of tissue injury, in this case, the dying prostate tumors. As the B cells infiltrate these tumors, they secrete lymphotoxin.

Lymphotoxin interacts with a receptor on the surface of PCa cells and activates cell signaling to NF-κB, a protein that turns on genes that stimulate tumor cell proliferation. Taken together, these results suggest that the inflammatory response to dying tumor cells contributes to the eventual failure of ADT. Further investigation by Dr. Karin showed that antibodies that block CXCL13 and inhibitors of NF-κB signaling can delay the emergence of androgen-independent PCa by 3–4 weeks after castration (androgen depletion). These results suggest that therapeutic interventions that prevent lymphotoxin production and/or signaling during ADT could delay the emergence of androgen-independent PCa in humans by up to 2–3 years.

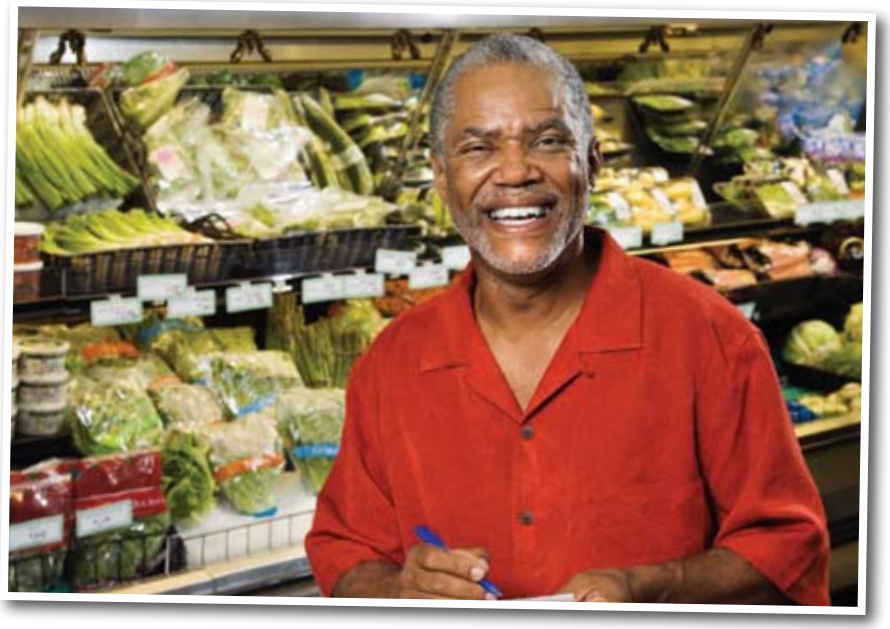
The use of statins is a treatment commonly used in heart disease. Statins are effective agents for lowering cholesterol levels in the blood, and recent studies suggest that statins may also reduce inflammation. Dr. Lionel Bañez, recipient of an FY06 Health Disparity Training-Prostate Scholar Award and an FY08 Health Disparity Research Award (Transitioning Investigator Category), considered the link between statins and reduced inflammation, and he hypothesized that statin use might slow or prevent the progression of PCa to advanced disease by decreasing inflammation within prostate tumors.



PUTATIVE ANTI-PROSTATE CANCER (CaP) MECHANISMS OF STATINS

To test this hypothesis, Dr. Bañez examined PCa tissues from 236 radical prostatectomy patients, 37 (16%) of whom had used statins for a period of 1 year before surgery. The degree of inflammation in PCa tissues was determined based on the number of inflammatory cells present in the tumors. He found that, in general, inflammatory cells were present in 82% of the prostate tumors and, among these, 36% of the tumors had high numbers of inflammatory cells. Comparison of prostate tumors from statin users and nonusers showed that the tumors from patients who had used statins had lower numbers of inflammatory cells. Dr. Bañez concluded that statin use was significantly associated with lower risk for prostate tumor inflammation, and the lower risk was even more pronounced in those patients who had used high doses of statins. This is the first study to show an association between preoperative statin use and a reduction of intratumoral inflammation in PCa patients. Although these findings require confirmation in larger clinical studies, the work suggests that statins reduce the risk of developing advanced PCa by preventing inflammation in the tumor.

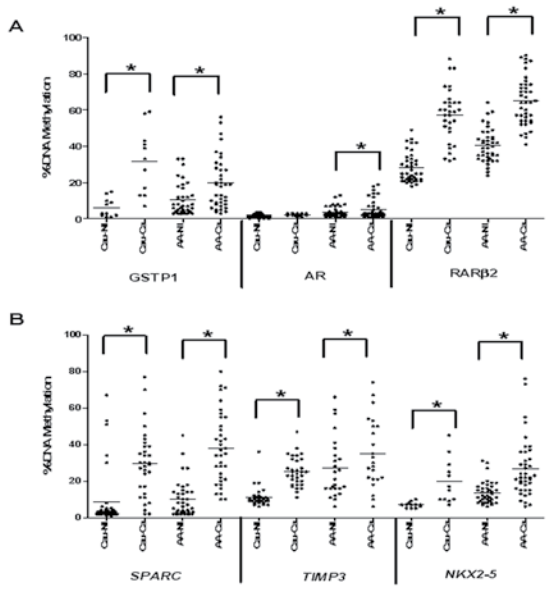
These PCRP-funded studies show that inflammation may be a key factor in the development of advanced PCa. The studies identify new potential therapeutic targets in the tumor microenvironment and also show that treatments that reduce inflammation in the tumor may have a preventive and/or therapeutic benefit.



Health Disparity

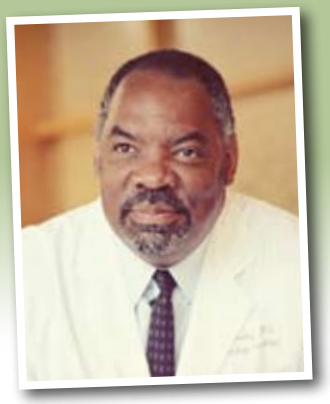
Great strides have been made in the detection, diagnosis, and treatment of PCa; however, the fact that there are still significant disparities in incidence and mortality rates among African American (AA) and Caucasian American (CA) men remains a cause of serious concern. Throughout its history, the PCRP has aggressively sought to invest in health disparity research studies that examine the genetic, biological, environmental, and socioeconomical factors that affect PCa risk. The multiple "fronts" in the battle against PCa health disparities have been addressed through both team science, such as that provided by the landmark Prostate Cancer Project Consortium (see page 35), and efforts by individual outstanding researchers. Two of these researchers, described below, have focused on studies to determine if disparities are observed in detection methods and in the use of therapies.

Dr. Bernard Kwabi-Addo of Howard University has used his **FY07 PCRP Idea Development Award** to conduct epigenetic studies to investigate age-related DNA methylation patterns in AA and CA men. These patterns can identify genes that could be useful as ethnically sensitive biomarkers for PCa detection. Epigenetic gene silencing plays an important role in PCa by switching off genes that suppress cell proliferation, apoptosis, and metastasis. In PCa, more than 40 genes have been identified as targets of epigenetic gene silencing by methylation, but only a few have shown promise as PCa biomarkers similar to prostate-specific antigen. Dr. Kwabi-Addo analyzed DNA samples from normal and cancerous prostate tissue from 57 AA and 80 CA patients for methylation status of six genes (GSTP1, AR, RARbeta2, SPARC, TIMP3, and NKX2-5). The results showed that five of the six genes were methylated in cancerous but not benign prostate tissue ($p<0.001$), with exception of AR. Methylation levels of five of the six genes were significantly higher in AA compared to CA men ($p<0.05$), with exception of GSTP1. Further analysis to measure the sensitivity and specificity of the gene's methylation status for distinguishing normal versus tumor tissue showed that DNA methylation of GSTP1, RARbeta2, and NKX2-5 offer potential as predictive genes for PCa detection in both AA and CA patients. Dr. Kwabi-Addo has shown that the SPARC gene showed higher sensitivity and specificity in AA samples, suggesting an "ethnic sensitive" biomarker, which will require confirmation in larger population studies. Dr. Kwabi-Addo's research has led to a publication in *Clinical Cancer Research*.



Quantitative DNA methylation analysis in human prostate tissues. The % DNA methylation level of promoter CpG islands were analyzed in bisulfite modified genomic DNA extracted from matched pairs of normal (Nl) and PCa (Ca) tissue samples obtained from AA and Caucasian (Cau) cancer patients who had undergone radical prostatectomy. Y-axis represents the percentage of methylated cytosines in the samples as obtained from pyrosequencing. X-axis represents Nl and Ca tissues obtained from AA and Cau. * shows statistically significant data as determined by Mann Whitney t-test, with significance set at the level of $p< 0.05$. A. Quantitative methylation analysis for GSTP1, AR, and RARβ2. B. Quantitative methylation analysis for SPARC, TIMP3 and NKX2-5. *Clin Cancer Res*. 16(14): 3539-47, 2010

In addition to biomarker discovery for better detection and assessment of risk, there exists a great need to determine how well the state-of-the-art treatment modalities are being utilized once they do become available to AA and CA men.

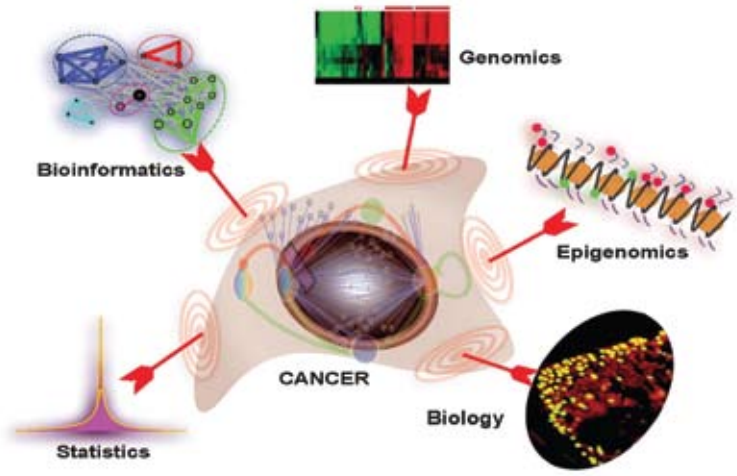


Dr. Paul A. Godley of the University of North Carolina at Chapel Hill used his FY06 PCRP **Health Disparity Research Award** to compare trends and differences in the use of adrogen deprivation therapy (ADT) including orchiectomy and luteinizing hormone releasing hormone (LHRH) agonists in patients diagnosed with advanced metastatic PCa. Using the Surveillance, Epidemiology, and End Results cancer database and the linked Medicare claims database, he obtained data from 5,273 patients who were 65 years of age or older and were diagnosed with advanced Stage IV PCa during 1991–1999. In this study, 28.3% of the patients did not receive any ADT, 29% received an orchiectomy, and 42.7% received an LHRH agonist. The mean time to ADT treatment was no different between AA and CA patients; however, a higher proportion of AA patients did not receive ADT (38.8%) compared to CA patients (25.5%, $p<0.001$). Men 80 years of age or older were less likely to receive an LHRH agonist (35.3%) compared to younger age groups (48%). Dr. Godley found that from 1991–1999, overall use of orchiectomy decreased (from approximately 50% to 10%) as the use of LHRH agonists increased (from approximately 28% to 60%) while the proportion of patients who did not receive any ADT stayed relatively stable. However, in the months following the diagnosis of advanced PCa, AA patients were less likely than CA patients to receive some form of ADT ($P<0.001$). The proportion of patients using LHRH increased in AA and CA patients and was not significantly different by race, but AA patients have lagged behind CA patients in the adoption of LHRH therapy. Dr. Godley concludes that these findings suggest that racial differences persist in the treatment of advanced stage PCa, and further research is needed to identify and address factors that contribute to racial disparity in ADT use and time to receipt of therapy for metastatic PCa.

Training New Investigators

To find and fund the best research that will one day lead to the eradication of PCa, the PCRP has invested in the development of outstanding researchers at an early stage in their career paths toward independence. These bright scientists have demonstrated great potential in conducting research that will directly impact the PCa field, performing studies that have the potential to shed light on key genes involved in the progression of PCa, promote a greater understanding of hormonal action, and identify prognostic markers and therapeutic targets.

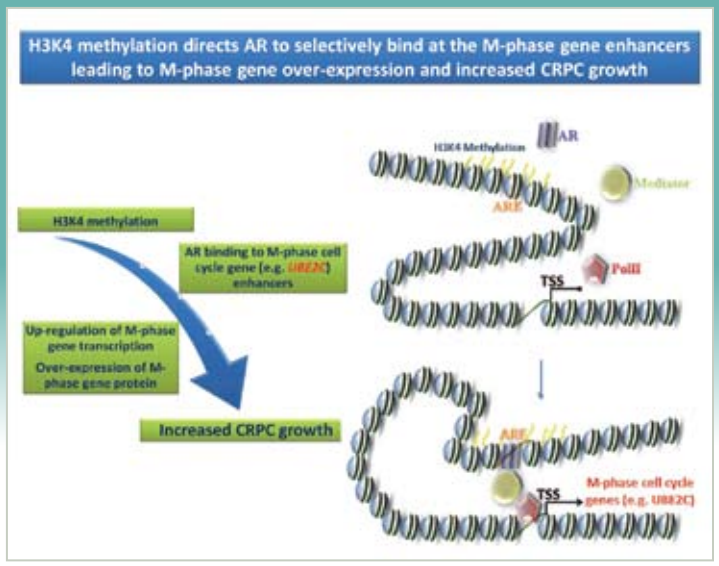
The PCRP's quest to effectively eliminate death and suffering from PCa requires intense concerted efforts to better understand the mechanisms of action of key genes involved in the progression of this disease. Enhancer of zeste homolog 2 (EZH2) is one of the key genes known to be upregulated in PCa progression; this gene has also been known to turn off genes through the process of gene silencing. While at the University of Michigan, Dr. Jindan Yu used her FY06 PCRP Postdoctoral Training Award to conduct genomic analyses to identify mechanisms underlying the role of the transcriptional repressor EZH2 in PCa progression. Under the mentorship of Dr. Arul Chinnaiyan, Dr. Yu used high-throughput genomic analyses to identify adrenergic receptor beta-2 (ADRB2) as a major target gene of EZH2 repression. Expression analysis of ADRB2 in human PCa tissues showed that it was low in localized PCa and either absent or low in a majority of metastatic PCas, suggesting an association between loss of ADRB2 expression and poor prognosis. Functional analyses demonstrated that inhibition of ADRB2 induces oncogenic transformation/invasion in normal prostate epithelial cells, whereas re-activation of ADRB2 inhibits tumor growth in a mouse prostate tumor model. These important findings have led to six publications (including a recent paper in *Cancer Cell*) and a patent application on the use of ADRB2 as a cancer prognostic marker. Dr. Yu has joined the faculty of Northwestern University where she is using her FY08 PCRP New Investigator Award to conduct further research to delineate the regulatory network of master transcription factors in PCa.



Deciphering the mechanisms underlying PCa initiation and progression for improved disease treatment by combining high-throughput genomics and epigenomics techniques with cutting-edge bioinformatics and biostatics approaches to shed light on the gene regulatory networks within cancer cells and open new paradigms for biomarker discovery and therapeutic designs.

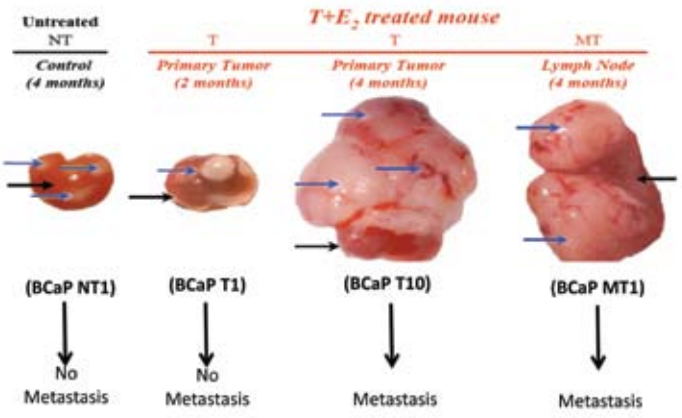
Another key research area that requires more effort involves understanding the role of the androgen receptor (AR) in PCa so that better targeted treatment regimens can ultimately be developed. With funding from an FY04 PCRP Postdoctoral Training Award, Dr. Qianben Wang conducted dual studies at the Dana-Farber Cancer Institute to identify transcription factors and coregulators recruited to regulatory regions of androgen-responsive genes (which are potential molecular markers for disrupted AR function) and to identify new therapeutic targets for PCa. Dr. Wang, in collaboration with his mentor Dr. Myles Brown, identified over 8,000 AR binding sites in the human genome and determined the differential expression profile of androgen-responsive genes in LNCaP cells in the presence or absence of dihydroxytestosterone. Dr. Wang's research has led to five publications,

including a recent work published in *Cell* comparing AR binding and AR-dependent gene expression in both androgen-dependent and -independent PCa cells. The article elucidates a distinct AR-dependent program in androgen-independent PCa cells that upregulates M-phase cell cycle genes, leading to increased cell proliferation. Dr. Wang is currently a tenure-track Assistant Professor at the Ohio State University Comprehensive Cancer Center where he continues to conduct research in PCa.



A histone modification governs androgen receptor to bind to regulatory regions of a class of cell cycle genes in castration-resistant PCa but not in androgen-dependent PCa. This leads to over-expression of cell cycle genes and accelerated growth of castration-resistant PCa.

Studies aimed at understanding AR signaling are also greatly needed to ultimately aid in improved targeting for the treatment of PCa. It has been widely established that PCa progression is mediated by androgens on AR in prostate epithelial cells. Nikesha Haynes, a participant of the FY06 PCRP Collaborative Undergraduate HBCU Student Summer Training Program Award to Dr. David Lubaroff, seeks to challenge this paradigm by focusing her attention on elucidating the mechanisms that underlie stromal AR involvement in early carcinogenesis of prostate epithelial cells and on identifying androgen-regulated stromal-derived factors that are involved in promoting PCa progression. This study will help determine whether blocking stromal AR signaling is a possible target for PCa chemoprevention efforts. Ms. Haynes completed her summer training in Dr. Michael Henry's laboratory at the University of Iowa and currently is completing her doctoral studies in Dr. William Ricke's laboratory at the University of Rochester, using funds from an FY09 Prostate Cancer Research Training Award. She will conduct experiments using a tissue recombination model in which human prostatic epithelial cells (huPrE) are mixed with stromal cells isolated from mouse urogenital tissues. The stromal cells provide factors capable of initiating growth and differentiation of huPrE when transplanted into mouse kidney. In this model, the prostate epithelial cells mimic the journey of normal cells developing into metastatic cancer cells. This PCa progression model will be used to determine if anti-androgens can be used as a preventative or early intervention treatment for PCa and whether AR signaling in stromal cells is required for PCa progression.



In vivo growth of tissue recombinants consisting of Rat embryonic stroma (UGM) combined with the non-tumorigenic human prostatic epithelial cell line – BPH-1. These grafts were grown under the kidney capsule in either the presence or absence of testosterone and estradiol3β for a period of 2 to 4 months. The epithelial cells were isolated and re-grafted to determine their tumor-forming capacity and ability to metastasize. BCaP NT-1s showed no growth and were non–tumorigenic and no metastasis was found. BCaP T1s were tumorigenic with small masses with no visible metastasis. BCaP T10s were tumorigenic and had large masses with lymph node metastases. BCaP MT1s that were derived from a lymph node metastasis formed large tumors and also metastasized.

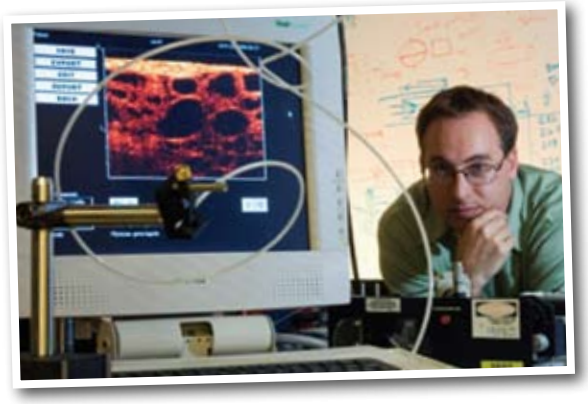
Quality of Life

Studies on the impact of treatment on the well-being of PCa patients and their families are also being carried out by PCRP-funded investigators. A majority of the PCa cases diagnosed are characterized as localized PCa, and several treatment options available for these patients include active surveillance, radical prostatectomy, external beam radiotherapy, and brachytherapy. Radical prostatectomy, the most common treatment, involves the surgical removal of the cancerous prostate by either "open" surgery (radical retropubic prostatectomy [RRP]) or minimally invasive radical prostatectomy (MIRP). As with any surgical procedure, there are potentially serious quality of life (QOL) issues associated with treatment, and these include long-term adverse events affecting urinary, sexual, and/or bowel function.

Although the number of patients electing to have MIRP with or without robotic assistance has surged in the last 10 years, there is a dearth of comparative data on these treatment options in regard to their utilization, outcomes, and cost, as well as the QOL issues associated with these treatments. As a recipient of an FY07 PCRP Physician Research Training Award, Dr. Jim Hu sought to determine the comparative effectiveness of RRP versus MIRP. Using the SEER Medicare-linked database, Dr. Hu identified almost 9,000 diagnosed PCa patients who had undergone PCa surgery between the years 2003 to 2007. He found that most men chose RRP (n=6,899) over MIRP (n=1,938), but the percentage of patients selecting MIRP increased from 9% to 43% between 2003 and 2007. He uncovered notable differences in surgical approaches to radical prostatectomy following racial, sociodemographic, and geographic patterns, including that African American and Hispanic men were more likely to choose RRP than Asian men, who were more likely to undergo MIRP; men with higher levels of education and income were more likely to undergo MIRP as well.

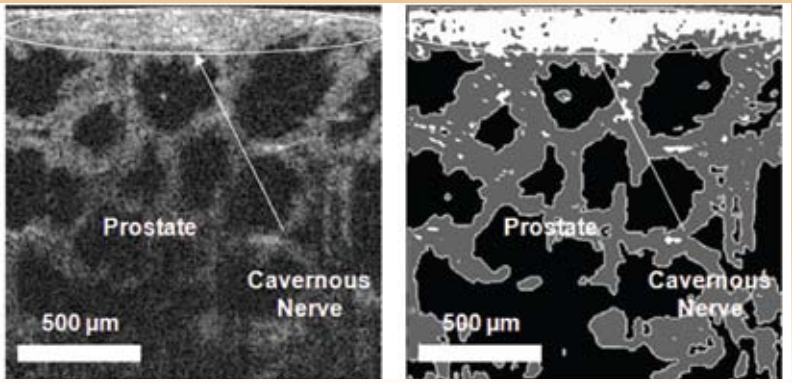
Looking at the QOL issues associated with MIRP and RRP, Dr. Hu found a number of benefits for men undergoing MIRP, including a shorter length of time spent in the hospital (2 versus 3 days) and fewer blood transfusions (2.7% versus 20.8%). However, he identified several disadvantages. Among these, he found that MIRP was associated with more genitourinary complications (4.7% versus 2.1%) including incontinence and erectile dysfunction. Dr. Hu concluded that the mixed outcomes associated with MIRP over the gold standard of RRP may be a reflection of a society and health care system that is enamored with new technology not disseminated optimally.

Given that most men diagnosed with PCa choose radical prostatectomy, one of the major QOL issues is preservation of sexual function. This is challenging because there is significant variability in the size and location of the cavernous nerves among patients, making preservation of the nerves during surgery difficult; this results in a wide range of reported sexual potency rates after surgery (ranging from 9%–86%). Responsible for normal erectile function, the cavernous nerves are two distinct microscopic nerve fibers that follow a course along the surface of the bladder, prostate gland, and urethra. Because of their close proximity to the prostate gland, these crucial nerves are at risk of damage during surgical removal of the prostate. Thus, to improve the QOL for PCa patients, a better means of identifying and preserving these nerves is needed. FY07 Idea Development Award recipient Dr. Nathanial Fried, in collaboration with Dr. Arthur Burnett at Johns Hopkins Medical School, has conducted studies that utilize three new optical technologies to aid in the identification, imaging, and visualization of the cavernous nerves for better preservation of sexual function following PCa surgery.



Dr. Fried designed and built a compact laparoscopic laser nerve stimulation probe as a more spatially selective method for stimulation of the cavernous nerves. Using animal models, he optimized the laser parameters to produce the most rapid and strongest

erectile response so that the probe may be used as a potential intra-operative diagnostic tool. The optical nerve stimulation was shown to be safe and reproducible. Using optical coherence tomography (OCT), a relatively new high-resolution, noninvasive imaging technology based on near-infrared light to obtain real-time, cross-sectional images in vivo of the tissue of interest, Dr Fried demonstrated that the cavernous nerves could be differentiated from surrounding tissues including the prostate gland. Additionally, he determined the laser wavelength for optimal optical penetration depth in the prostate gland. Future studies will entail applying a third optical technology to rapidly and precisely dissect and remove the prostate from the cavernous nerves in an in vivo animal model and to assess and optimize the laser parameters for PCa surgery. The new laparoscopic laser nerve stimulation probe and improved image quality of OCT could aid the clinician in differentiating the cavernous nerves from the prostate gland during PCa surgery to preserve sexual function, thus leading to direct patient benefit in terms of QOL.

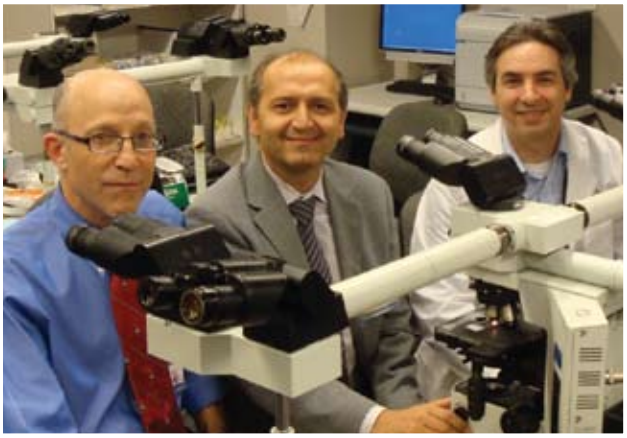


OCT of the cavernous nerves on the surface of the rat prostate. (a) Original image (b) Image after application of denoising, segmentation, and edge detection algorithms. The cavernous nerve can be clearly differentiated from the prostate gland.

Developing Needed Resources

PROSTATE CANCER BIOREPOSITORY NETWORK

The Prostate Cancer Biorepository Network (PCBN) is a collaboration between the Johns Hopkins School of Medicine, the New York University Medical Center, and the DOD. The goal of the PCBN is to develop a biorepository with high-quality, well-annotated specimens obtained in a systematic, reproducible fashion using optimized and standardized protocols and an infrastructure to facilitate the growth of the resource and its wide usage by the PCa research community. The specimens in the PCBN will include tissues from biopsies, prostatectomies, warm autopsies, serum, plasma, buffy coat, prostatic fluid, and derived specimens such as DNA and RNA, linked to clinical and outcome data, and supported by an informatics infrastructure centered around caBIG (Cancer Bioinformatics Grid) tools. The PCBN will also conduct and support biospecimen science that characterizes critical parameters in the biospecimen "life cycle" that influence the molecular integrity of research tissues. The PCBN capitalizes on the extensive specimen availability and experience in PCa pathology and biomarker research of scientists at Johns Hopkins and New York University, as well as the availability of a strong bioinformatics infrastructure to facilitate access to the biorepository. We believe that the combination of expertise, experience in leadership of collaborative biomarker studies, and substantial availability of biospecimens will contribute to the success of the PCRP in its mission to advance understanding of tumor biology and speed the clinical translation of biomarker research.



Johns Hopkins School of Medicine
Bruce Trock, Ph.D.
George Netto, M.D.
Angelo DeMarzo, M.D., Ph.D.

New York University Medical Center
Jonathan Melamed, M.D.
Peng Lee, M.D., Ph.D.

The Prostate Cancer Project (PCaP) Consortium was established in FY02 with a Consortium Award funded by the PCRP to evaluate multiple factors contributing to PCa health disparity. Roswell Park Cancer Institute, University of North Carolina at Chapel Hill, and Louisiana State University Health Science Center collaborated to conduct in-home interviews, retrieve medical records, and collect biological specimens. This enormous volume of epidemiological data and vast collection of biological specimens are unparalleled in health disparity research. This resource includes a characterized cohort of 1,130 African American (AA) and 1,128 Caucasian American (CA) men newly diagnosed with PCa. Over 98% of patients have consented to continued follow-up, which will greatly increase the value of the annotated repository specimens. Future studies using these data and specimens have the potential to provide definitive answers to the factors associated with PCa risk, especially those that are responsible for the disproportionate incidence and death rate of PCa in AA men. With the PCaP data sets finalized and quality assured, the data and repository specimens have been made available (http://www.ncla-pcap.org/) for additional studies by the PCa research community. Approval for use of the resources is dependent upon availability of desired samples or data, as well as scientific merit. Available resources include:

- A comprehensive centralized database of clinical, epidemiological, and interview data from each participant.
- A biorepository of high-quality specimens collected from PCaP participants and linked to the PCaP Central Database, including:
  - 6,284 diagnostic and 8,328 radical prostatectomy tissue blocks
  - 10 tissue microarrays, permitting the simultaneous analysis of hundreds of genes
  - Blood samples: Serum, plasma, red blood cells, and immortalized lymphocytes
  - Other bodily samples: Mouthwash, urine, abdominal adipose (fat) tissue, and toenail clippings
  - DNA processed from either blood or mouthwash samples for over 98% of participants

PCaP Discoveries

- AA men tended to be younger than CA men upon PCa diagnosis and demonstrated a greater likelihood for more aggressive cancer.
- AA men also tended to have lower income and education levels and were less likely to report general good health, visit the same doctor more than once, or to have had prior PCa screening.
- The family history of PCa was similar in both races and states.
- Radical prostatectomy was the preferred primary treatment for both AA and CA men although this procedure was more common in North Carolina than in Louisiana.
- Personal interactions and levels of trust in the care received were found to be important criteria in overall satisfaction with the health care system. CA men placed greater trust in their physicians than AA men, likely because they were also more likely to visit the same physician on multiple visits.
- Genetic studies comparing the expression of genes and single nucleotide polymorphisms (SNPs) in AA and CA men with PCa have found few SNPs that appear significant in both AA and CA men.

For additional information on PCaP and its resources, please visit the PCaP website at: http://www.ncla-pcap.org/.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Co-director


Elizabeth Fontham, Dr.PH.


Joseph Su, Ph.D.


Merle Mishel, Ph.D.


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Gary Smith, Ph.D.


Jeannette Bensen, Ph.D.
Co-director

Horizons: The Next Frontier in Prostate Cancer Research and Clinical Care

While there has been some decline in the death rate from PCa, perhaps due to lifestyle changes, screening, early detection, and improvements in treatment, a significant amount of work remains to be accomplished to end the suffering and death caused by PCa. Over the past few years, the landscape of PCa research and patient care has been changed significantly by major advancements. Additional progress is on the near horizon and the PCa research landscape will undoubtedly change again as a result; how and when it will change, however, is unknown. For example, many dedicated investigators are trying to develop the ability to clearly distinguish lethal from nonlethal disease and enable better solutions for clinical management of PCa. But when they will succeed and through what advances are unknown. The following three outstanding leaders in PCa research and clinical care share their innovative vision to conquer PCa.

Advances in molecular technology over the past decade have given basic scientists the license to explore beyond the boundaries of the current understanding of cancer growth. Elucidation of prostate-specific pathways and transcriptional events has opened the way for the application of "smart" molecular therapeutics and for the identification of specific prostate cancer biomarkers linked to prostate cancer incidence and aggressiveness. Discovery efforts delivered powerful technology, including genomic, proteomic, and imaging approaches, that promise accurate detection and effective intervention. Resources thus generated will enable clinicians to use metabolonomics to predict prognosis and therapeutic responses and provide the community with an understanding of emerging opportunities to cure prostate cancer and improve quality of life. Long-standing partnerships between basic and clinical research programs in diverse communities continue the cross-fertilization of brilliant ideas. The next frontier of prostate cancer research is defined by novel bioinformatics, comprehensive and multifunctional databases, new imaging tools allowing high-resolution detection of cellular events, widespread use of models for functional assessment of signaling pathways, nanoparticle-based targeted therapeutics, and mass spectrometry for precise analysis of proteins.

For over a decade, the PCRP has supported the development of young scientists. As these scientists emerge as independent prostate cancer investigators, the time is fast approaching where additional focus may be required to facilitate their successful transition into leaders of the field. As such, program decisions may begin to reflect the necessary investment in human talent required for saving and improving the lives of men with prostate cancer. The PCRP-supported Prostate Cancer Clinical Trials Consortium led the way to new therapies targeting castration-resistant prostate cancer, and the Prostate Cancer Project Consortium provided tremendous epidemiological resources on patient-health care system interaction to understand racial differences in cancer incidence, mortality, and treatment response. Enriched by the diversity of expertise and nurtured with intensity throughout the program's existence, the continued partnership of prostate cancer survivors, scientists, and clinicians will have a remarkable impact in the fight against prostate cancer. The new horizons as projected by the 2011 IMPaCT scientific meeting exploit an alchemy of nanotechnology, functional genomics, and health care outcomes. The vision for the 2011 IMPaCT meeting has set the bar to conquer prostate cancer. We can, we must, and we will—as the PCRP leads the way.

Natasha Kyprianou, Ph.D., James F. Hardymon Chair in Urology Research,
Professor of Urology, Molecular Biochemistry, Pathology and Toxicology,
University of Kentucky Medical Center, FY11 Integration Panel Chair

Recent progress in prostate cancer research has directed the field on a course that should lead to several major discoveries and accomplishments over the coming years. A key step will be the ability to distinquish lethal from indolent prostate cancer. Using pathological, genetic, and epigenetic signatures, the lethal phenotype will be defined and will lead to more intensive treatments of those patients while allowing more conservative treatments for the remaining hundreds of thousands of localized Gleason 6 and 7 cancer patients diagnosed each year. Within tumors bearing this lethal phenotype, the signaling pathways responsible for metastases to bone, stroma, nodes, and visceral organs (predominantly lung and liver) will be identified. Although there may be multiple and redundant pathways (e.g., cMET and hedgehog), blocking them will noticeably and measurably alter the natural progression of metastatic disease. Inhibitors of these signaling pathways will be developed, some of which may block more than one pathway. These inhibitors will be tested in clinical trials, alone or in combination with other approved therapeutics, and approved by the U.S. Food and Drug Administration (FDA) for prostate cancer clinical use.

Several other advances in prostate cancer therapeutics will soon emerge as well. Androgen receptor (AR) is one target that will be exploited for therapeutic benefit. Inhibitors of AR, enzymes involved in androgen synthesis, and other AR signaling molecules will be FDA-approved and used widely at all stages of prostate cancer. Another attractive therapeutic target will be fully characterized, namely, prostate cancer stem cells. Agents that irreversibly damage the DNA and other key features of these cells will continue to be discovered, tested, and FDA approved. In fact, five new agents targeting prostate cancer stem cells will be on the market within the next 10 years.

Nicholas Vogelzang, M.D.
Chair and Medical Director, Developmental Therapeutics, and Co-Chair, GU Committee—
US Oncology Research and Comprehensive Cancer Centers of Nevada
PCRP Integration Panel (IP) Member FY97–05, IP Chair FY04

In the last year, whole genome sequencing of high-grade prostate cancers has demonstrated that this is a disease of chromosomal fusions. Furthermore, analysis of copy number variants (CNVs) suggests that a high frequency of CNVs is associated with aggressive prostate cancer, and analysis of the transcriptome resulted in the identification of 23 different prostate cancer gene fusions. In the coming years, the research community must focus on translational studies that further define the functional significance and clinical implications of these genomic alterations to determine the critical signal transduction pathways and "oncogene addiction" pathways that must be blocked in each subtype of prostate cancer to create remissions. These studies will enable the development of new clinical trials that will select patients for a particular medicine based on their molecular profile. Leaders in clinical research are already beginning to develop novel combination therapies that inhibit parallel signaling pathways to ablate mechanisms of resistance to late-stage therapies such as Abiraterone and MDV3100. Studies aimed at improving clinical outcomes of immunotherapies, such as Provenge, through blockade of checkpoint inhibitors (monoclonal antibodies such as Ipilimumab and anti-PD-1) are under way. New progression biomarkers, such as circulating tumor cells, are under rigorous clinical qualification and promise to dramatically accelerate the drug development pipeline. Finally, advances in medicinal chemistry have opened the door to drugging the "currently undruggable" transcription factors, an area of research that may promote the development of novel small molecule inhibitors.

Johnathon W. Simons, M.D.
President and Chief Executive Officer, Prostate Cancer Foundation

PCRP FY10 Investment

In FY10, the PCRP developed an investment strategy to address two overarching challenges: (1) The development of effective treatments for advanced disease and (2) the ability to distinguish aggressive from indolent disease. Ten award mechanisms were offered by the program, which focused efforts on impact, innovation, translation, and training, and the major problem of overtreatment of primary PCa. The award mechanisms provided various levels of support to both established and new investigators in PCa. The PCRP received 1,179 applications in FY10 following preproposal screening, and 161 awards were recommended for funding.

Focus	*Award Mechanism*	*Applications Received*	*Awards*
Impact Research	*Population-Based Research Award:* Supports high-impact approaches to PCa research from the perspective of population-based studies that will generate unique information and/or tools that can be achieved only from the perspective of statistical analysis.	20	2
	Impact Award: Supports high-impact studies toward reducing or eliminating the problem of overtreatment of primary PCa.	22	3
Innovative Research	*Idea Development Award:* Supports new ideas that represent innovative, high-risk, high-gain approaches in PCa research.	458	52
	Exploration–Hypothesis Development Award: Supports highly innovative, untested, potentially groundbreaking concepts in PCa research.	385	27
	Synergistic Idea Development Award: Supports new and existing partnerships between two or three independent investigators to address a central question in PCa that may include high-risk, provided there is potential for significant impact.	61	13
	Health Disparity Research Award: Supports new ideas that represent innovative, high-risk/high-gain approaches to PCa health disparity research.	41	5
Translational Research	*Laboratory-Clinical Transition Award:* Supports goal- and product-driven preclinical studies of novel lead agents or targets that may revolutionize PCa clinical care.	13	3
Training/ Recruitment	*Physician Research Training Award:* Supports training of physicians with clinical duties for careers in PCa research.	7	6
	Prostate Cancer Training: Supports PCa research training for individuals in the early stages of their careers.	164	44
	Health Disparity Training Award: Supports predoctoral and postdoctoral trainees for a career in PCa health disparity research.	8	6
	Totals	*1,179*	*161*

Vision for FY11

In FY11, the PCRP developed an investment strategy that focuses on continued support for PCa research with high innovation and impact and that addresses critical issues in PCa today. With two overarching challenges to the research community, (1) the ability to distinguish aggressive from indolent disease and (2) the development of effective treatments for advanced disease, 12 award mechanisms were proposed for FY11. The award mechanisms include the Clinical Trial, Collaborative Undergraduate HBCU* Student Summer Training Program, Exploration-Hypothesis Development, Health Disparity Research, Health Disparity Training, Idea Development, Impact, Laboratory-Clinical Transition, Physician Research Training, Population-Based Research, Postdoctoral Fellowship, and Synergistic Idea Development Awards. The PCRP for the second consecutive year will offer the Impact Award to address the overtreatment of primary PCa.

The PCRP will rely on its foundation of partnership between scientists, clinicians, and consumers to realize its vision of conquering PCa. The promise of a cure for PCa lies in the expert knowledge of scientists who are willing to challenge the status quo in science and find ways to revolutionize clinical care practice. From basic discoveries, translation of new findings, clinical trials and investigations into factors associated with PCa health disparity, PCRP-funded investigators are poised for breakthroughs that will improve lives and advance research into the next frontier by sharing resources and engaging in multidisciplinary and multi-institutional collaborations. The program is proud of the scientific accomplishments of the scientists it has supported and looks with anticipation to even more impactful breakthroughs in the coming years.

When I started out in Vancouver in 1998, I had the same dilemma as a young scientist that many other young scientists encounter: I could not be appointed an academic position without having independent funding, but I could not obtain independent funding without an academic position. This career logjam was broken by the first grant of my career, the New Investigator Award from the PCRP. This resulted in an academic appointment, and from there other funding opportunities were opened up to me, and I was able to progress in my work. The PCRP award kick-started my career as an independent academic scientist in prostate cancer research. Twelve years later, I am still completely immersed in the field of prostate cancer research and have been awarded over $12M in funding. I am grateful for the opportunity the PCRP gave me to contribute to scientific knowledge and ultimately, I hope, to benefit prostate cancer patients.

Marianne Sadar, Ph.D., British Columbia Cancer Agency

Founded 20 years ago in the Chicago area by men with prostate cancer, and their families, Us TOO has grown to encompass a peer-support network of 325 local community groups. The volunteers active in this organization know the battle to beat prostate cancer is not over and it requires action as America and the world ages. The PCRP is important to Us TOO and provides hope that by working together we can conquer prostate cancer. We are pleased to be able to recommend so many people to serve as consumer reviewers and hear their positive comments about the experience. I believe the next frontier in our battle will require a clearer understanding of the disease itself and a continued effort to find better tools to detect and accurately diagnose prostate cancer. This will help us move past the controversy and confusion so many men and their loved ones face. We also see the need to push forward and find more options for men living with advanced disease. Recent FDA approvals show we are making progress for those most in need, but the battle is far from over.

Thomas N. Kirk, President and Chief Executive Officer
Us TOO International Prostate Cancer Education and Support Network

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