CDMRP
Department of Defense
Prostate Cancer Research Program

PCRP erspectives

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In This Issue

Featured Opinion

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Fiscal Year 2010 Integration Panel Member

Multiple factors such as age, family history, environmental exposures, and race contribute to the high incidence and prevalence of prostate cancer (PCa). Prostate specific antigen (PSA) screening has resulted in a dramatic decrease in stage at diagnosis, with the majority of PCa being localized to the prostate. While the Gleason score at the time of diagnosis prevails as the key to predicting prognosis in the context of organ-confined disease, it is beginning to lose discriminatory power. Unfortunately, very few biomarkers that either help us detect PCa with increased accuracy or, more importantly, aid in the distinction between aggressive and indolent disease, have been introduced to date in clinical practice. As a result, we are overtreating most men and inadequately treating those men with the most aggressive form of the disease.

Approaches toward the development of better biomarkers, discussed in this issue of PCRP Perspectives and generously sponsored by the PCRP, address some of these questions. For example,

» continued, **SEE OPINION, PG. 5**

PCRP Launches Fiscal Year 2010 with New Integration Panel Leadership and Ambitious Research Challenges

The annual "Passing of the Gavel" ceremony, marking a new year for the Prostate Cancer Research Program (PCRP) Integration Panel (IP), took place during the yearly Vision Setting meeting in Vienna, Virginia, on Tuesday, 17 November 2009, with CDMRP Director Captain E. Melissa Kaime, IP members, and CDMRP-PCRP staff in attendance. The symbolic wooden gavel, representing transfer of the chairmanship, was passed from the fiscal year 2009 (FY09) Chair, Dr. Oliver Sartor, Piltz Professor of Urology and Medicine of Tulane University, to the FY10 Chair, Dr. Donald Tindall, Professor, Director and Vice Chair of Urologic Research at Mayo Clinic College of Medicine. The FY10 IP also welcomed Dr. Natasha Kyprianou, James F. Hardymon Chair of Urology Research at the University of Kentucky as FY10 Chair-Elect. Three new IP members, representing a wide spectrum of prostate cancer expertise and research experience, joined the panel, including Dr. Maha Hussain,

» continued, **SEE FY10 INTEGRATION PANEL, PG. 4**

Biomarkers: PCRP Investigators Find Clues to Answer Critical Questions

Estimates for 2009 predicted that 192,280 men would be diagnosed with prostate cancer and 27,360 would die from the disease (American Cancer Society, *Cancer Facts & Figures* 2009). However, determining which men diagnosed with prostate cancer will eventually die from the disease remains largely unpredictable. This subject reveals some of the most critical questions in prostate cancer research today. Which men must be treated quickly and aggressively to minimize the risk of loss of life? Which men will respond well to primary treatment but nevertheless progress to advanced and incurable disease? Which men have truly indolent disease that may never require treatment, which itself carries the risk of potentially debilitating consequences and major health care costs?

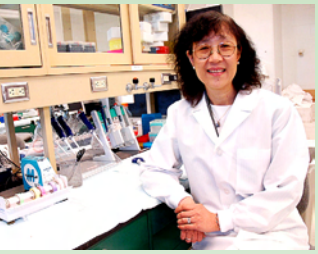
» continued, **SEE BIOMARKERS, PG. 2**

VISION: Conquer prostate cancer.
MISSION: Fund research that will end death and suffering from prostate cancer.

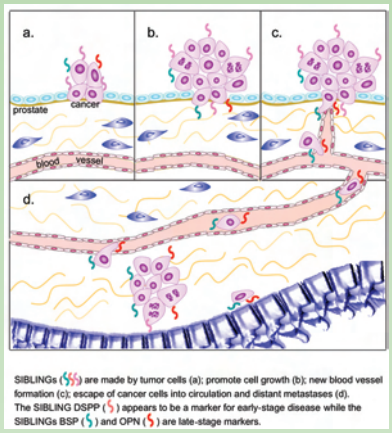
» BIOMARKERS FROM PG. 1

PCRP investigators are working diligently to characterize prostate cancer and identify biomarkers that may have the potential to answer these questions and ensure that therapeutic intervention is appropriately tailored to each patient's disease. PCRP-funded studies are making breakthroughs to identify potential new biomarkers and strategies for prostate cancer detection, diagnosis, prognosis, and/or therapeutic intervention.

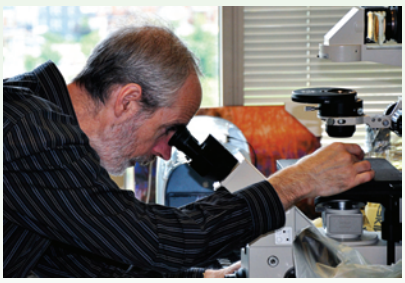
The usefulness of prostate specific antigen (PSA) screening, and whether and for whom it should be used, has been a subject of significant debate in the past year (*Nature Med* 15(12):1339-43). However, it is easy to find agreement that better biomarkers or other tools for the detection of prostate cancer are still needed. **Dr. Shuk-Mei Ho** of the University of Cincinnati recently used her FY05 PCRP Idea Development Award to develop a more reliable, cost-effective, and minimally invasive assay for the detection of prostate cancer (*J Urol* 181:2508-13, 2009). Dr. Ho and colleagues performed duplex quantitative RT-PCR assays for the prostate cancer biomarkers AMACR (alpha-methylacyl-CoA racemase), PCA3 (prostate cancer gene 3), and PSA using RNA isolated from urine sediments recovered after digital rectal exams in 43 patients with prostate cancer and 49 patients without prostate cancer. Normalization of AMACR and PCA3 transcripts to PSA transcript expression and receiver operating characteristics analyses showed that the combination of AMACR and PCA3 in dual marker tests increased the level of sensitivity to 81%, and improved the specificity to 84% for prostate cancer detection over the serum PSA test alone (sensitivity, 77%, and specificity, 45%). This urinary test, more effective than a serum PSA test for detecting prostate cancer, could be used in parallel with the serum PSA test to improve detection practices or to conduct surveillance in patients with repeated negative biopsies.



Another challenging facet of managing prostate cancer is the lack of information about how or when abnormal prostate cells may progress from benign to cancerous states and beyond, including cancer recurrence after primary treatment and metastasis. **Dr. Neal Fedarko** of Johns Hopkins University has been supported by an FY04 PCRP Idea Development Award to identify biomarkers of prostate cancer progression and has focused his efforts on the gene family of small integrin binding ligand N-linked glycoproteins (SIBLINGS), comprising bone sialoprotein (BSP), osteopontin (OPN), dentin matrix protein-1, and dentin sialophosphoprotein (DSPP), which are induced in some cancers and have been shown to bind and modulate the enzymes involved in tumor progression and angiogenesis. Dr. Fedarko compared the distribution and expression levels of SIBLINGS in the blood of individuals with or without benign prostatic disease or prostate cancer to determine whether SIBLINGS can be used as markers of prostate cancer progression, metastasis, and/or response to treatment (*Clin Cancer Res* 15:5199-5207, 2009). His analyses of patient blood samples showed that there was a significant increase in BSP and OPN levels as tumors progress to late-stage prostate cancer, whereas DSPP levels were significantly elevated in early stages. OPN levels, but not BSP or DSPP, correlated with serum PSA and immune activation. Protein analyses confirmed that elevated levels of DSPP were associated with prostate cancer in serum from prostate cancer patients compared to that from men without prostate cancer, suggesting that both BSP and DSPP show potential for use as markers of prostate cancer progression.



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



Once a diagnosis of prostate cancer has been made, patients and their physicians face the difficult decision of "what now." With several treatment options available, including postponing treatment in favor of "active surveillance," predictors of whether a prostate cancer is indolent or aggressive are critical, yet currently unavailable. **Dr. Lorelei Mucci** of the Brigham and Women's Hospital at Harvard Medical School is using support from an FY05 PCRP New Investigator Award to address this problem. Using two large, established cohorts–the Physicians' Health Study (PHS) and the Health Professionals' Follow-up Study (HPFS)–Dr. Mucci tested a set of molecular and clinical predictors at diagnosis to discriminate between lethal and indolent prostate cancer. A 12-gene model (previously reported, Stark et al., 2009) was used to predict prostate cancer outcome while a survival model will be developed by combining clinical and genetic markers to predict risk of developing aggressive or lethal disease. Immunohistochemical analyses were performed on tumor tissue microarrays, and the results, combined with clinical and pathologic data from medical records/reports, showed that the Gleason grade at the time of diagnosis is a significant predictor of lethal versus indolent prostate cancer. At diagnosis, high PSA levels and older age were also significantly associated with the development of lethal prostate cancer. Additionally, Dr. Mucci showed that several biomarkers (BRCA1, p63, cIAP1, MTA1) were associated

» continued, **SEE BIOMARKERS, PG. 4**

Prostate Cancer Research Program

For more information:
http://cdmrp.army.mil/pcrp/default.htm

General Questions:
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Proposal Requirements:
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E-mail: cdmrp.pa@amedd.army.mil

Consumer Involvement:
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E-mail: cdmrpconsumers@amedd.army.mil

In This Issue

In Memory

John Lee Willey
Leader, Veteran, Advocate, and PCRP Integration Panel Member

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

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

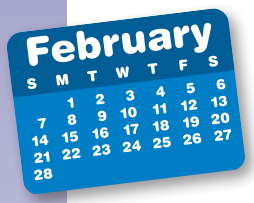
John advocated for more impactful research as a central part of the PCRP investment strategy. On behalf of the advocate community, he argued energetically for increased investment in early-stage research, effective prevention, minimally invasive screening, better treatment options for advanced prostate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

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

Program News

- For FY10, the PCRP will offer 10 different award mechanisms to support prostate cancer research and training. Details for each award mechanism are described in the Program Announcements, available at http://grants.gov, http://cdmrp.army.mil/funding/pcrp.htm, and https://cdmrp.org.
- The FY10 PCRP is focused on two overarching challenges in prostate cancer research and clinical care: (1) develop effective treatments for advanced prostate cancer and (2) distinguish indolent from lethal disease.
- The program has launched the new FY10 PCRP Impact Award mechanism to reduce or eliminate overtreatment of primary prostate cancer.
- In response to the prostate cancer community's need for increased access to disproportionately affected populations and collaborative partnerships, the PCRP Health Disparity Research Award mechanism has been revised for FY10 to include the opportunity for additional funding for the Qualified Collaborator Option.
- The PCRP is preparing to launch the new Prostate Cancer Pathology Resource Network Awards, which will establish a virtual biorepository of prostate cancer specimens with a Coordinating Center at Johns Hopkins University.
- The next PCRP Innovative Minds in Prostate Cancer Today (IMPaCT) Meeting will be held in March 2011 in Orlando, Florida. The Meeting will highlight progress in prostate cancer research supported by the PCRP and will serve as a forum to discuss critical issues and explore new avenues of research.

Calendar of Events



FEBRUARY

1–4: Cell Death Mechanisms and Cancer Therapy; San Diego, California. Sponsor: AACR

5–9: AACR-JCA 8th Joint Conference: Cancer Genomics, Epigenomics, and the Development of Novel Therapeutics; Waikoloa, Hawaii

Feb. 27–March 2: The Role of Telomeres and Telomerase in Cancer Research; Fort Worth, Texas. Sponsor: AACR

Feb. 28–March 2: EMT and Cancer Progression and Treatment; Arlington, Virginia. Sponsor: AACR

MARCH

5–7: Genitourinary Cancers Symposium: Progress in Multidisciplinary Management; San Francisco, California. Sponsor: American Society of Clinical Oncology

15–16: 6th Annual National Symposium on Prostate Cancer; Atlanta, Georgia. Sponsor: Clark Atlanta University

APRIL

17–21: AACR 101st Annual Meeting; Washington, DC

Did You Know...

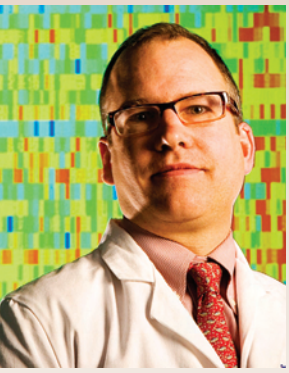
- ☞ One in six men in the United States will be diagnosed with prostate cancer.
- ☞ The frequency and mortality rate of prostate cancer is higher in African Americans than in any other race/ethnic group.
- ☞ The PCRP received more than $1.0 billion in congressional appropriations since 1997, including $80 million in FY10 to fund prostate cancer research.
- ☞ The PCRP has provided more than 2,000 awards for prostate cancer research and training.

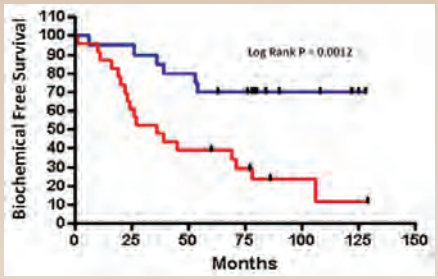
In This Issue

» BIOMARKERS, CONTINUED FROM PG. 2

with increased prostate cancer mortality 20 years after diagnosis. These results are leading the field closer to being able to predict which men with prostate cancer should be treated and which men can continue their lives without medical intervention.

Currently, the majority of men diagnosed with prostate cancer receive primary treatment for their disease. Being able to predict which of these men will later go on to develop recurrent disease would be a major advancement toward developing treatment and monitoring strategies. **Dr. Phil Febbo** of Duke University, recipient of an FY05 PCRP New Investigator Award, is making headway toward uncovering biomarkers that may be able to predict prostate cancer recurrence. Dr. Febbo has shown that transforming growth factor (TGF)-beta stimulates the activation of multiple pro-growth signaling pathways in genetically engineered prostate epithelial cell lines. These downstream pathways include those for insulin-like growth factor 1, interleukin 6, and platelet-derived growth factor pathways, and their activation results in an expression-based "signature" of TGF-beta activity. Correlation of the TGF-beta expression "signature" with microarray data from a set of 102 radical prostatectomy samples showed that the TGF-beta signature is associated with biochemical recurrence (i.e., increases in PSA levels) of prostate cancer after surgery. In addition, analysis of a larger dataset including 596 localized prostate tumors also found TGF-beta activity to be associated with recurrence and the development of metastatic disease. Together, these findings implicate TGF-beta as a potential biomarker for prostate cancer recurrence and, importantly, a potential therapeutic target for treating aggressive prostate cancer.





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

Through their innovative ideas and diligent investigation, these and other investigators funded by the PCRP for biomarker research are making scientific breakthroughs that may lead to major gains for prostate cancer patients through better options for treatment decision making and better therapeutics for reducing the impact of prostate cancer on their lives.

References:

Hughes V. 2009. Markers of dispute. *Nature Med* 15(12):1339-43.

Ouyang B, Bracken B, Burke B, Chung E, Liang J, and Ho SM. 2009. A duplex quantitative polymerase chain reaction assay based on quantification of alpha-methylacyl-CoA racemase transcripts and prostate cancer antigen 3 in urine sediments improved diagnostic accuracy for prostate cancer. *J Urol* 181(6): 2508-2513.

Stark JR, Perner S, Stampfer MJ, Sinnott JA, Finn S, Eisenstein AS, Ma J, Fiorentino M, Kurth T, Loda M, Giovannucci EL, Rubin MA, and Mucci LA. 2009. Gleason score and lethal prostate cancer: Does 3 + 4 = 4 + 3? *J Clin Oncol* 27(21):3459-3464. Epub 2009 May 11.

Jain A, McKnight DA, Fisher LW, Humphreys EB, Mangold LA, Partin AW, Fedarko NS. 2009. Small integrin-binding proteins as serum markers for prostate cancer detection. *Clin Cancer Res* 15:5199-5207.

» FY10 INTEGRATION PANEL, CONTINUED FROM PG. 1

University of Michigan, Dr. Massimo Loda, Dana Farber Cancer Institute, and Dr. Jianfeng Xu, Wake Forest University. Together, the 16-member panel will help shape the direction of the program to ensure that it continues to move prostate cancer research toward the program's vision of conquering prostate cancer.

During Dr. Sartor's successful tenure, the program launched two new award mechanisms: one to emphasize population-based research and the other to support the development of a biorepository network. Dr. Sartor also chaired the External Advisory Board, an oversight committee for the activities of the Prostate Cancer Clinical Trials Consortium. This PCRP-funded entity is the backbone for over 60 Phase II and Phase I/II clinical trials and has successfully moved five drugs into Phase III trials. The PCRP also launched "PCRP Perspectives" in September 2009, a newsletter to communicate program information and activities with the prostate cancer research and advocate communities.

Following his investiture as IP chair, Dr. Tindall acknowledged the efforts of the Department of Defense to provide new initiatives responsive to the needs of the prostate cancer research and consumer advocate community. The IP developed an ambitious investment strategy for the $80 million FY10 congressional appropriation, addressing major priorities in the field of prostate cancer. With two overarching challenges to the research community, (1) the development of effective treatments for advanced disease and (2) the ability to distinguish lethal from indolent disease, PCRP IP members voted to release 10 program announcements for FY10. The award mechanism categories include **innovation-based** (Exploration–Hypothesis Development, Health Disparity Research, Idea Development, and Synergistic Idea Development Awards), **population-based** (Population-Based Research Award), **training/recruitment-based** (Prostate Cancer Training—predoc and postdoc, Physician Research Training, and Health Disparity Training Awards), and **translational** (Laboratory Clinical Transition Award) award mechanisms, along with an award mechanism focused on soliciting a wide range of proposals prepared to make a major contribution to a single important problem in prostate cancer—overtreatment (the Impact Award). Investigators will again be required to focus their applications on one or more of the six PCRP focus areas—*biomarkers, genetics, imaging, therapy, tumor biology, and survivorship*—in addition to explaining how their proposed project meets either of the two FY10 overarching challenges.

In This Issue

Summary of FY09 PCRP Award Recommendations

Resource Award

Prostate Cancer Pathology Resource Network 2 Awards

Research Awards

Health Disparity Research 6 Awards

Idea Development 38 Awards

New Investigator 28 Awards

Synergistic Idea Development 14 Awards

Training/Recruitment Awards

Collaborative Undergraduate HBCU Student Summer Training 4 Awards

Health Disparity Training 1 Award

Physician Research Training 8 Awards

Prostate Cancer Training 62 Awards

TOTAL 163 Awards Recommended

» OPINION, CONTINUED FROM PG. 1

Dr. Ho has reported on a more sensitive approach to improving the accuracy of the PSA test. Improved technologies are also contributing to the betterment of other current biomarkers. The use of tissue microarrays allows the simultaneous analysis of hundreds of formalin-fixed, paraffin-embedded, archival tumor cases resulting in a more uniform staining procedure while reducing costs. The development of automated image analysis systems with high throughput and more precise quantification is now progressively replacing the subjective, semiquantitative, manual scoring previously performed by pathologists. These important technical advances have recently allowed Dr. Mucci to discover a "molecular signature" that identifies and distinguishes aggressive and indolent prostate cancer and to refine the distinction of Gleason scores previously thought to predict similar behavior.

Also highlighted in this newsletter, Dr. Fedarko has utilized multiple biomarkers in peripheral blood that predict progression, metastasis, and/or response to treatment. Finally, Dr. Febbo's group has shown that a transforming growth factor (TGF)-beta signature obtained by gene expression profiling predicts the development of metastases.

These selected discoveries underscore the complexity of prostate cancer and its multifaceted nature but hold promise that biomarkers, if utilized with a specific end point in mind, can greatly aid the clinician in the difficult choice between therapeutic strategies. Importantly, biomarkers can be used to predict biologic behavior in PCa. While much more work needs to be done in biomarker development, the tools at our disposal have become extremely sophisticated and the future appears promising: We are on the right track!

Grant Writing Tips

- Be sure your proposal is responsive to the intent of the award mechanism as described in the program announcement.
- If there is a strong emphasis on innovation in the award mechanism to which you are applying, be clear and specific in describing how your proposed research is innovative, i.e., represents a new paradigm, challenges existing paradigms, or looks at existing problems from new perspectives.
- Enlist strong collaborators and include letters that clearly describe how they will contribute to the proposed research.
- Submit your proposal early, at least 72 hours before the submission deadline.
  - A large volume of proposals usually arrives on the last day of submission, which results in a slower response by Grants.gov. Early submissions will allow time for Grants.gov to provide notification errors and allow for resubmission, if necessary, of the application package.

Watch for more tips in the next issue!

Visit the PCRP Webpage for Up-to-Date Program Information

The DOD Prostate Cancer Research Program (PCRP) supports innovative ideas and technologies to accelerate our vision to conquer prostate cancer through individual, multidisciplinary, and collaborative research. These efforts are focused toward basic research discoveries and translating discoveries into clinical practice to improve the quality of care and life of men with prostate cancer. For more information on PCRP initiatives, highlights of funded research, and consumer profiles, please visit the PCRP webpage at

http://cdmrp.army.mil/pcrp/default.htm

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In This Issue