



PROSTATE CANCER RESEARCH PROGRAM

Prostate cancer is the most commonly diagnosed cancer in men, accounting for 30% of all cancers in men. In 2005, approximately 232,090 men in the United States will be diagnosed with prostate cancer and an estimated 30,350 will die from the disease. Prostate cancer is second only to lung cancer as a leading cause of cancer deaths in men. Prostate cancer incidence rates remain significantly higher in African American men compared to Caucasian men, and the death rate for African American men remains more than twice that of Caucasian men.¹ Currently, there is no cure for locally advanced or metastatic prostate cancer.

PROGRAM BACKGROUND

The Department of Defense (DOD) Prostate Cancer Research Program (PCRP) was established in fiscal year 1997 (FY97) by Appropriations Conference Committee Report No. 104-863, which provided \$45 million (M) for research in prostate cancer. Today, the PCRP is the second leading source of extramural prostate cancer research funding in the United States managing \$650M in peer reviewed prostate cancer research from FY97 to FY05. A total of 1,245 awards have been made through FY04 aimed at preventing, detecting, treating, and improving the quality of life of those afflicted with the disease. The PCRP believes that building critical resources and collaborations, exploring groundbreaking concepts and ideas, training future leaders, and sponsoring clinical research will ultimately lead to the elimination of prostate cancer. An analysis of one award mechanism offered since the inception of the program has shown a great return on our investment (Read about the success of the New Investigator Award [NIA] mechanism in the box story on pages V-12 and V-13.) Appendix B, Table B-2, summarizes the congressional appropriations and the investment strategy executed by the PCRP for FY04 through FY05.

THE FISCAL YEAR 2004 PROGRAM

Congress appropriated \$85M in FY04 to continue the peer reviewed DOD PCRP. The emphasis for the FY04 program was placed on innovation, training, and the foundation for clinical trials. Table V-1 provides a summary of the FY04 PCRP award categories and mechanisms in terms of number of proposals received, number of awards made, and dollars invested. As illustrated in Figure V-1, the FY04 PCRP has developed a diverse research portfolio that encompasses basic, clinical, and population-based research.

Eleven award mechanisms were offered in FY04, nine of which were previously established by the PCRP. A total of 885 proposals were received, and 232 were funded. The Clinical Trial Development Award,

Vision: To conquer prostate cancer.

Mission: To promote innovative and multidisciplinary research directed toward eliminating prostate cancer.

Congressional Appropriations for Peer Reviewed Research:

- \$480M in FY97-03
- \$85M in FY04
- \$85M in FY05

Funding Summary:

- 1,013 awards from the FY97-03 appropriations
- 232 awards from the FY04 appropriation
- ~215 awards anticipated from the FY05 appropriation

¹ American Cancer Society, Cancer Facts and Figures, 2005.



Table V-1. Funding Summary for the FY04 PCRP

Categories and Award Mechanisms	Number of Proposals Received	Number of Awards	Investment
Research			
Clinical Trial Development	10	17 ^a	\$1.6M
Exploration—Hypothesis Development	162	33	\$3.7M
Exploration—Resource Development	30	9	\$1.0M
HBCU Collaborative Partnership	4	2	\$1.7M
Health Disparity Research—Prostate Scholar	10	5	\$2.3M
Idea Development	420	82 ^b	\$44.8M
New Investigator	114	27	\$9.1M
Training/Recruitment			
HBCU Undergraduate Collaborative Summer Training Program	4	3	\$0.6M
Health Disparity Training—Prostate Scholar	2	1	\$0.2M
Physician Research Training	18	9	\$5.9M
Postdoctoral Traineeship	111	44	\$5.5M
Total	885	232	\$76.4M

^a FY04 dollars were used to fund ten FY05 Clinical Trial Development Award proposals.

^b FY04 dollars were used to fund five FY05 Idea Development Award proposals.

Basic Research: 54%

- Cell Biology: 28%
- Genetics & Molecular Biology: 10.5%
- Pathobiology: 8%
- Endocrinology: 7.5%

Population-Based Research: 9%

- Epidemiology: 3.5%
- Research Resources: 3%
- Biobehavioral Sciences: 2.5%

Clinical Research: 37%

- Clinical & Experimental Therapeutics: 25%
- Detection & Diagnosis: 8%
- Complementary & Alternative Medicine: 2%
- Primary Prevention: 2%

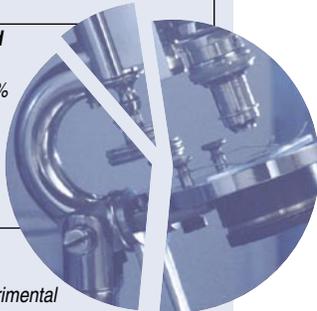
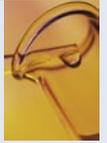


Figure V-1. FY04 PCRP Portfolio by Research Area

one of the new award mechanisms in FY04, resulted in the support of 17 awards to clinical investigators to develop collaborations and research resources that will serve as a foundation for clinical trials relevant to prostate cancer treatment, diagnosis, detection, or prevention. The other new award mechanism, the Historically Black Colleges and Universities (HBCU) Undergraduate Collaborative Summer Training Program, resulted in three awards to establish summer prostate cancer training programs at host institutions (which include for-profit, non-profit, public, and private organizations) to provide meaningful research experiences for undergraduate students enrolled at HBCU. The PCRP's investment in innovative, high-risk/high-gain research collectively resulted in 142 awards (Idea Development, New Investigator, and Exploration—Hypothesis Development Awards). To address the disparate incidence, morbidity, and mortality among African Americans and other ethnic groups, the PCRP collectively supported eight awards under the Health Disparity Prostate Scholar Awards and the HBCU Collaborative Partnership Awards. The funding of nine Exploration—Resource Development Awards is anticipated to develop critical resources needed to advance the field of prostate cancer research. Finally, the remaining training/recruitment awards, the Postdoctoral Traineeship and Physician Research Training Awards, supported 53 future leaders in prostate cancer research.



THE VISION FOR THE FISCAL YEAR 2005 PROGRAM

Congress again appropriated \$85M to continue the PCRCP in FY05. Twelve award mechanisms were offered to sustain the PCRCP's investment in innovation, training, and the foundation for clinical trials. Ten of these award mechanisms were previously established by the PCRCP and two were new to the program in FY05. The existing award mechanisms that were offered to boldly explore novel ideas include the Exploration—Hypothesis Development, Idea Development, and New Investigator Awards. A new feature of the Idea Development Award is the option for Nested Resident and Medical Student Traineeships. The PCRCP again invested funding in opportunities to address the health disparities in prostate cancer incidence, morbidity, and mortality rates among African Americans and other ethnic groups through the Health Disparity Research and Training—Prostate Scholar Awards. Existing training/recruitment awards that were again offered in FY05 to train future prostate cancer leaders include HBCU Undergraduate Collaborative Summer Training Program, Physician Research Training, and Postdoctoral Traineeship Awards. Additionally, the PCRCP remains committed to sponsoring clinical research that has the potential to impact the course of this disease. The three award mechanisms that were offered in clinical research include the Clinical Trial Development, Clinical Trial, and Clinical Consortium Awards, with the latter mechanism representing a new award opportunity in FY05. While the Predoctoral Traineeships have been successfully used in other Congressionally Directed Medical Research Programs (CDMRP), this award mechanism is new to the PCRCP in FY05 and is intended to train promising graduate students for careers that will impact the field of prostate cancer. A total of 1,056 proposals were received across the 12 award mechanisms, as shown in Table V-2, and approximately 215 awards are expected.



“I have been involved with prostate cancer research ever since my diagnosis in 1996. The work being done by the DOD in its cancer research programs is moving translational science faster and more efficiently than most people realize. History is being made every day with DOD cancer research and I am proud and privileged to be part of it.”

Ralph M. Burnett, FY05 PCRCP Consumer Programmatic Reviewer

SCIENTIFIC OUTCOMES AND ADVANCES

The PCRCP has supported 1,245 studies through FY04 that focus on prostate-specific research, and PCRCP grantees are continuing to advance discoveries in prostate cancer research. The following projects are a testimony to the dedicated investigators working to eliminate this life-threatening disease. Additional examples of scientific outcomes, products, and technologies resulting from PCRCP support can be found in this section as well as in Section III of this annual report.

Magnetic Resonance Imaging of Prostate Cancer

David L. Buckley, Ph.D., University of Manchester, Manchester, England

Advances in the development of effective local therapies for prostate cancer have been hindered by the lack of imaging techniques that can reliably identify the location of the cancer within the prostate.



Signs and Symptoms

Signs and symptoms do not typically accompany early cases of prostate cancer. However, some indicators of more advanced prostate cancer include:

- Frequent urination, especially at night
- Weak or interrupted urine flow
- Inability to urinate or difficulty starting or stopping the urine flow
- Painful or burning sensation when urinating
- Blood in the urine
- Continual pain in the lower back, pelvis, or upper thighs

However, most of these symptoms are nonspecific and are not always related to a serious condition.

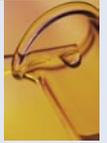
—American Cancer Society, *Cancer Facts and Figures*, 2005.



Table V-2. Award Mechanisms Offered and Proposals Received for the FY05 PCRP

Categories and Award Mechanisms	Number of Proposals Received
<i>Research</i>	
<i>Clinical Trial</i>	28
<i>Clinical Trial Development</i>	19
<i>Exploration—Hypothesis Development</i>	178
<i>Health Disparity Research—Prostate Scholar</i>	11
<i>Idea Development (with optional Nested Resident and Medical Student Traineeships)</i>	438
<i>New Investigator</i>	129
<i>Training Recruitment</i>	
<i>HBCU Undergraduate Collaborative Summer Training Program</i>	8
<i>Health Disparity Training—Prostate Scholar</i>	7
<i>Physician Research Training</i>	20
<i>Predoctoral Traineeship</i>	72
<i>Postdoctoral Traineeship</i>	132
<i>Research Resources</i>	
<i>Clinical Consortium</i>	14
Total	1,056

Magnetic resonance imaging (MRI) is a promising candidate for imaging the prostate because it can provide sharp images in soft tissue, multidimensional images, and unique biological information not available with other imaging modalities. However, MRI is rarely used as a first-tier imaging modality for prostate cancer because current systems are limited in their sensitivity and specificity. Prostate cancer growth is accompanied by the development of a large network of immature, leaky blood vessels that may cause an increase in blood flow, blood volume, and permeability in the area of their development. FY99 NIA recipient Dr. David Buckley has developed techniques to measure this vascular signature of prostate cancer. He used MRI coupled with computer technology to measure blood flow, blood volume, and vasculature permeability by tracking a contrast agent, a type of MRI “dye,” over time. In a study of 22 men with adenocarcinoma of the prostate, the addition of the MRI contrast agent showed that blood flow to the prostate cancer tissue exceeded that to the non-cancerous prostate tissue. Dr. Buckley was able to produce three-dimensional images of the prostates that could distinguish tumor tissue from the surrounding normal tissue with this MRI technique. The areas of the images visualized as tumors were confirmed by pathology reports. He also found that there was little difference in blood volume or vasculature permeability between normal and tumor tissue. This is consistent with pathologists’ observations of the differences between



tumor vasculature and normal vasculature. This MRI technique represents considerable promise in improving prostate cancer diagnosis and prognosis.

For additional reading about this research, please refer to the following publications:

Buckley DL, Roberts C, Parker GJM, et al. 2004. Prostate cancer: Evaluation of vascular characteristics with dynamic contrast-enhanced T1-weighted MR imaging initial experience. *Radiology* 233:709–715.

Buckley DL. 2002. Uncertainty in the analysis of tracer kinetics using dynamic contrast-enhanced T1-weighted MRI. *Magn Reson Med* 47:601–606.

Prostate Cancer Recurrence Following Prostatectomy

Stephen J. Freedland, M.D., Duke University School of Medicine, Durham, North Carolina

Approximately 35% of prostate cancer patients who have undergone radical prostatectomy (removal of the prostate) will develop recurrent cancer within 10 years following surgery, as determined by prostate-specific antigen (PSA) levels. PCRP-supported investigator Dr. Stephen J. Freedland has identified several factors that are associated with prostate cancer recurrence following radical prostatectomy. Dr. Freedland and his colleagues make up one of two groups to first demonstrate that obesity is a strong risk factor for aggressive prostate cancer regardless of race. In this study, Dr. Freedland showed that tissues from obese men previously treated with radical prostatectomy scored consistently higher on a scale of aggressive growth for prostate cancer. Patients with a body mass index greater than 35 kg/m² had more than a fourfold greater chance of developing symptoms associated with prostate cancer recurrence. Additionally, Dr. Freedland's group at the Brady Urological Institute Johns Hopkins School of Medicine evaluated clinical factors to estimate survival rates in men with prostate cancer recurrence in an effort to help risk-stratify patients faced with recurrence after radical prostatectomy. Dr. Freedland studied a cohort of 379 patients treated with radical prostatectomy who had signs of recurring prostate cancer. The risk factors included the rate at which PSA in serum doubles after surgery and the time, in years, from surgery to recurrence. These results were correlated with Gleason scores, which are a measurement of prostate cancer aggressiveness. Relatively short time intervals for PSA doubling and prostate cancer recurrence, along with high Gleason scores, correlated with aggressive, lethal tumors. Survival rates for patients with low Gleason scores were greater than 15 years. These preliminary findings may serve as useful guidelines to identify high-risk patients so as to enroll them in

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

**John L. Willey, FY05 PCRP
Consumer Programmatic
Reviewer**



“As a prostate cancer survivor and member of the Integration Panel of the PCRCP, I have seen that this program is essential to achieving success in eradicating prostate cancer. Under the Department of Defense, the CDMRP provides the means by which our country’s top researchers conduct breakthrough projects to develop next-generation diagnostics and therapies for this proliferating disease. Further, the program provides the essential mechanisms and funding to attract the brightest young minds in science and medicine to this battle, presenting them with the opportunity to choose to dedicate their careers to attaining the victories we so critically need. We are at a pivotal point in prostate cancer research, and the continued funding of the CDMRP gives us the best hope of success against this disease.”

Wendall Van Auken, FY03–05
Consumer Integration Panel
Member

early aggressive treatment trials. Using the data from both of these studies, prostate cancer patients at an increased risk of recurrence may be identified. As an expert on prostate cancer, Dr. Freedland was interviewed by a number of different media outlets including *Health Day News*, *Men’s Health*, *Medical News Today*, and *USA TODAY*. Dr. Freedland has generated more than 20 publications and a review article on prostate cancer risk factors and prostatectomy in 2 years since receiving his first PCRCP award under the Health Disparity Research-Prostate Scholar Award mechanism. He has recently transferred to a position at Duke University School of Medicine.

For additional information about this research, please refer to the following publications:

Freedland SJ, Humphreys EB, Mangold LA, et al. 2005. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA* 294(4):433–439.

Freedland SJ, Grubb KA, Yiu SK, et al. 2005. Obesity and risk of biochemical progression following radical prostatectomy at a tertiary care referral center. *J Urol* 174(3):919–922.

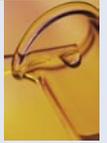
Freedland SJ, Terris MK, Platz EA, et al. 2005. Body mass index as a predictor of prostate cancer: Development versus detection on biopsy. *Urology* 66(1):108–113.

Freedland SJ, Isaacs WB, Mangold LA, et al. 2005. Stronger association between obesity and biochemical progression after radical prostatectomy among men treated in the last 10 years. *Clin Cancer Res* 11(8):2883–2888.

Getting to the Bones of Prostate Cancer

Zelig Eshhar, Ph.D., *The Weizmann Institute of Science, Rehovot, Israel*

Bones are a common site of spread for many cancers including prostate cancer. Prostate cancer bone metastases cause bone pain and fractures, severely reducing the quality of life for the patient. Treatment for prostate cancer bone metastases has been aimed primarily at reducing the pain and delaying the time to bone fractures through the use of hormone therapy and/or chemotherapy, radiation therapy, or bisphosphonates. Professor Zelig Eshhar and his colleagues at the Weizmann Institute of Science (Rehovot, Israel) and the Sheba Medical Center (Tel Hashomer, Israel) have shown that a common treatment for prostate cancer may help redirect immune cells to prostate cancer in the bones. The treatment uses immune cells from the patient’s body that are engineered to detect specific cancer cells and have the capacity to fight and kill the invading cancer cells. Dr. Eshhar called these custom-modified cells T bodies. After developing a strategy to create these cells, he and his colleagues needed the T bodies to reach the



bone metastases. Initial experiments using mice with prostate cancer growing in their leg bones and bone marrow showed that the T bodies did not appear to be able to reach these metastases. However, a significant drop in the tumor marker PSA, a reduction in the tumor load, and increased survival time were observed when prostate cancer-bearing mice were “preconditioned” using some common forms of cancer therapy such as low doses of radiation or chemotherapy drugs before T body injection. Dr. Eshhar believes that the preconditioning cancer therapy produces bone marrow disruption, causing the bone marrow to release chemical distress signals to the immune system. These signals not only warn immune cells of potential danger in the bone marrow but also help attacking immune cells pinpoint the problem area and traverse barriers that otherwise might prevent them from getting to the treatment site. This method, developed in an experimental mouse model, holds promise for treating bone metastases in prostate cancer and other types of disseminated cancers resistant to conventional therapy. This research was made possible with funding from an FY97 PCRP Idea Development Award.

Additional details about this research have been published in the following journal article:

Pinthus JH, Waks T, Malina V, et al. 2004. Adoptive immunotherapy of prostate cancer bone lesions using redirected effector lymphocytes. *J Clin Invest* 114:1774–1781.

Prostate Cancer Vaccine Development

Douglas McNeel, M.D., Ph.D., University of Wisconsin, Madison, Wisconsin
David Peace, M.D., University of Chicago, Chicago, Illinois

Both Dr. Douglas McNeel of the University of Wisconsin and Dr. David Peace of the University of Chicago are developing vaccines for the treatment of prostate cancer. These PCRP-supported investigators believe the immune system holds the key to curing prostate cancer. Both investigators plan to exploit a cellular mechanism that invites an immune system attack on prostate cancer cells. For example, when healthy prostate cells become malignant, proteins not ordinarily expressed by the prostate are produced. Presentation of fragments of these abnormal proteins on the cells’ surfaces can signal the body’s T lymphocytes (“killer T cells”) to destroy the malignant cells. Both research programs have focused on identifying protein fragments that readily convert a patient’s T lymphocytes into effector killer cells for prostate cancer and vaccination strategies capable of eliciting these cells. The cells would selectively target prostate cancer cells expressing the abnormal protein fragments.

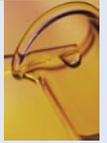




Early in his career, Dr. McNeel showed that a T cell response against prostate cancer could be elicited in patients. He has also considered the receptor tyrosine kinase ligand, FLT3, as a possible adjuvant for vaccine-based therapies. He discovered that treatment with FLT3 may aid in the production of an antigen-specific immunogenic response, by stimulating dendritic cells, which can in turn stimulate the production of killer T cells. Dr. McNeel has closely examined the mechanism leading to an immunogenic response against prostate cancer and is now focusing his research on identifying novel prostate cancer-specific antigens. To date, Dr. McNeel has identified several proteins that may generate novel prostate cancer antigens (MAD-CaP-5, MAD-PRO-34, and NY-CO-7). When used as antigens for vaccines, these could represent a potential vaccine for prostate cancer. Dr. McNeel's distinguished career has been funded extensively by the PCRP. His career in prostate cancer was fostered with a PCRP Postdoctoral Traineeship. Funds from subsequent PCRP awards in FY02 (New Investigator) and FY04 (Clinical Trial Development) were used to support his vaccine development research. The success and critical findings of his vaccine-based research have generated additional PCRP funding for FY05. These awards focus on androgen deprivation therapy and new antigenic proteins for vaccine development and translation of previous PCRP-funded research into a human clinical trial, respectively. Dr. McNeel has more than 10 publications relevant to prostate cancer vaccine development and has written two reviews on the subject. Additional funding from the University of Wisconsin Robert Draper Technology Innovation Fund (TIF) Grant was also awarded to Dr. McNeel.

Dr. Peace has concentrated on identifying immunogenic peptides from two well-characterized proteins expressed by most prostate cancers. PSA and prostate-specific membrane antigen (PSMA) are reciprocally expressed in many prostate tumors. An immunogenic response to both proteins may have additive or synergistic therapeutic effects. To date, Dr. Peace has identified a peptide fragment of PSA that elicits a cytotoxic T lymphocyte response in patients with hormone refractory prostate cancer. The potential treatment would currently be limited to patients of the common HLA-A2 immunological phenotype. With this proof-of-concept in hand, Dr. Peace initiated a study with genetically modified dendritic cells that expressed either PSA or PSMA. A protective immune response was noted in volunteers against specific tumor challenge. Dr. Peace is planning to optimize this treatment by evaluating the cytokine response of patients with differing concentrations of serum PSA. Generation of a cytokine profile will identify patient groups who may benefit greatly from this type of treatment. This will also lead to modifications of the gene therapy approach so that a wider patient base can be included. Dr. Peace has received two





awards totaling a million dollars from the PCR (both Idea Development Awards), which have resulted in three publications. The clinical aspect of his research was funded by the National Cancer Institute and resulted in the establishment of a multi-prostatic peptide vaccine protocol for use in the Phase 1/2 clinical trials. The Illinois Department of Health has also funded his vaccine work. His research was profiled in the press by *Chicago Magazine*, Reuters News, NBC-Chicago and Chicago CAN TV. His excellent work has resulted in his promotion to Associate Professor of Medicine with tenure. Dr. Peace's laboratory is well established and has a variety of unique research tools available including cell lines and a repository of blood and serum samples.

Additional details about Dr. McNeel's research can be found in the following publications:

Dunphy EJ and McNeel DG. 2005. Antigen-specific IgG elicited in subjects with prostate cancer treated with flt3 ligand. *J Immunother* 28(3):268–275.

Johnson LE, Frye TP, Arnot AR, et al. 2005. Safety and immunological efficacy of a prostate cancer plasmid DNA vaccine encoding prostatic acid phosphatase (PAP0). *Vaccine* [in press].

McNeel DG and Malkovsky M. 2005. Immune-based therapies for prostate cancer. *Immunol Lett* 96(1):3–9.

Dunphy EJ, Eickhoff JC, Muller CH, et al. 2004. Identification of antigen-specific IgG in sera from patients with chronic prostatitis. *J Clin Immunol* 24(5):492–502.

McNeel DG, Knutson KL, Schiffman K, et al. 2003. Pilot study of an HLA-A2 peptide vaccine using flt3 ligand as a systemic vaccine adjuvant. *J Clin Immunol* 23(1):62–72.

The following publications contain additional information pertaining to Dr. Peace's research:

Medin JA, Liang S-B, Hou J W-S, et al. 2005. Efficient transfer of PSA and PSMA cDNAs into DCs generates antibody and T cell antitumor responses in vivo. *Cancer Gene Ther* 12(6):540–551.

Perambakam S, Hallmeyer S, Reddy S, et al. 2005. Induction of specific T-cell immunity in patients with prostate cancer by vaccination with PSA146-154 peptide. *Cancer Immunol Immunother* [in press].

Perambakam SM, Srivastava R, and Peace DJ. 2005. Distinct cytokine patterns exist in peripheral blood mononuclear cell cultures of patients with prostate cancer. *Clin Immunol* [in press].

Perambakam SM, Xue BH, Sosman JA, et al. 2002. Induction of Tc2 cells with specificity for prostate-specific antigen from patients with hormone-refractory prostate cancer. *Cancer Immunol Immunother* 51(5):263–270.

(Continued on page V-14)

“The ‘War on Cancer’ must be fought on the simultaneous fronts of Education, Prevention and Research if we are to ultimately meet the goal of eliminating the suffering and death from cancer. The Prostate Cancer Research Program of the CDMRP effectively provides support to each of these elements through a broad portfolio of targeted research initiatives.”

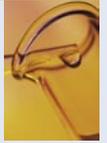
**Virgil Simons, FY03–05
Consumer Integration
Panel Member**



ADVANCING RADIATION-BASED TREATMENTS FOR PROSTATE CANCER

In the past, radiation therapies suffered from inaccurate targeting that allowed tumor cells to escape treatment while normal tissue was damaged. Recent advances hold the key to sophisticated treatment planning that will establish a higher standard of care for prostate cancer patients. PCRP-funded researchers have increased the accuracy and precision of externally administered radiation therapies by using novel imaging techniques to guide application. For example, intensity-modulated radiation therapy (IMRT) is rapidly growing in popularity, with preliminary clinical data demonstrating reduced incidence of such side effects as incontinence and erectile dysfunction. IMRT uses a conformal blocking pattern (CBP), allowing the oncologist to contour the radiation dosages to the precise spatial dimensions of the malignancy. The development of CBPs currently requires complicated data analysis of computed tomography (CT) images. The current standard is time consuming and does not take full advantage of the precision and accuracy that IMRT offers. Several PCRP researchers are working to improve the quality of the images used in CBPs.

- Dr. Lei Xing, of the Stanford University School of Medicine, is optimizing CT-based IMRT by developing software that compiles images from high-field magnetic resonance spectroscopic imaging (MRSI) and CT. Dr. Xing has developed an imaging package capable of producing clinically sensible maps for the guidance of IMRT.
- Dr. Lili Chen of the Fox Chase Cancer Center hopes to reduce the number of CT imaging sessions needed during IMRT. Dr. Chen conceives of MRSI as a stand-alone technique to guide IMRT with high precision and accuracy. Preliminary studies show that this could minimize the number of CT imaging sessions that are needed to find the locations of bony landmarks. MRSI in conjunction with ultrasound techniques will strongly complement CT imaging in directing IMRT.
- Dr. Geordi Pang, of the University of Toronto, has a different perspective on improving CT scans; he plans to make the detection technology more efficient (current detectors are only about 4% efficient). Boosting the efficiency will minimize the amount of time needed to acquire high-quality data for IMRT planning. This will subsequently reduce the cost and patient



discomfort associated with this technique. These innovative and diverse approaches promise to greatly improve IMRT and have a positive impact on patient prognosis and comfort.

Physicians and researchers are developing another radiation-based technique that provides a useful alternative to IMRT. Brachytherapy involves the implantation of a radioactive source directly into the prostate, thus bombarding lesions with lethal radiation. This therapy is sometimes used in conjunction with lower doses of externally delivered radiation, and the treatment regimen has similar complications to IMRT. However, patients can more readily continue their daily routines, and using a local radiation source minimizes residual damage to normal, healthy tissue. Therefore, the key to effective brachytherapy treatment is the accurate placement of the radioactive source.

- Dr. Jean Pouliot, of the University of California at San Francisco, has studied high dose-rate (HDR) brachytherapy and has assessed five critical parameters associated with the MRSI-based HDR treatments of prostate cancer for fast and accurate targeting. The study resulted in a “class solution” model that was highly effective and efficient for targeting lesions using MRSI-assisted brachytherapy.
- Dr. Paul Cho, of the University of Washington, has taken an innovative approach to verifying seed placement during treatment, coupling the results from two imaging devices into a diagnostic tool. Using ultrasound to locate the prostate gland and X-ray fluoroscopy to determine individual seed locations, Dr. Cho may be able to perform real-time intraoperative updates on seed placement with millimeter-scale resolution.

The PCRFP is funding advanced research into these two radiation-based treatment plans for prostate cancer. All of the techniques described depend on imaging to boost the efficacy and minimize patient discomfort. The PCRFP has, therefore, defined a comprehensive portfolio of researchers who will ensure that advances in imaging technology benefit prostate cancer patients. The PCRFP hopes that these innovative researchers will develop a versatile imaging suite that can both detect and treat prostate cancer.

Fiscal Year 2005 Integration Panel Members

Robert Dreicer, M.D. (Chair)
The Cleveland Clinic Foundation

**Nicholas Vogelzang, M.D.
(Chair Emeritus)**
Nevada Cancer Institute

**Jean deKernion, M.D.
(Chair-Elect)**
University of California, Los Angeles
School of Medicine

**Timothy Ratliff, Ph.D.
(Member-at-Large)**
University of Iowa

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

Thomas Carey, Ph.D.
University of Michigan Comprehensive
Cancer Center

Monica Liebert, Ph.D.
American Urological Association

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

Gail Prins, Ph.D.
University of Illinois at Chicago

Mack Roach III, M.D.
University of California, San Francisco

Joseph Smith Jr., M.D.
Vanderbilt University School of
Medicine

Howard Soule, Ph.D.
Prostate Cancer Foundation

Wendell Van Auken, M.B.A.
University of California, San Francisco
Comprehensive Cancer Center

Frederic Waldman, M.D., Ph.D.
University of California, San Francisco



THE NEW INVESTIGATOR AWARD MECHANISM: A RETURN ON INVESTMENT

Adapted from an abstract presented by Giambarresi LI, Carey TE, Vogelzang NJ, et al. at the American Association for Cancer Research 96th Annual Meeting entitled "A five-year analysis of the New Investigator Award mechanism of the Department of Defense (DOD) Congressionally Directed Medical Research Programs (CDMRP) Prostate Cancer Research Program (PCRP)."

Since its inception, the PCRP has offered New Investigator Awards (NIAs) to draw early-career investigators into the field of prostate cancer research. To determine the success of this award mechanism at selecting and retaining talented early-career investigators, the productivity of NIA recipients from a single year (FY99) was scrutinized for publications and subsequent funding for the years 2001 to 2004. Data were obtained from publicly accessible databases (PubMed, NIH CRISP, etc.) and from internal CDMRP databases.

In FY99, 45 NIAs (funded investigators) were chosen from 225 candidates not only because of the scientific merit of their proposals but also to ensure portfolio balance and programmatic relevance. Data for the 45 top non-funded investigators (based on scientific peer review scores) were collected and analyzed as a basis for comparison with the NIA-funded investigators (Figures V-2–V-5). Analyses of post-award funding activity and publication records of the 45 new investigators supported by the FY99 PCRP NIA show that:

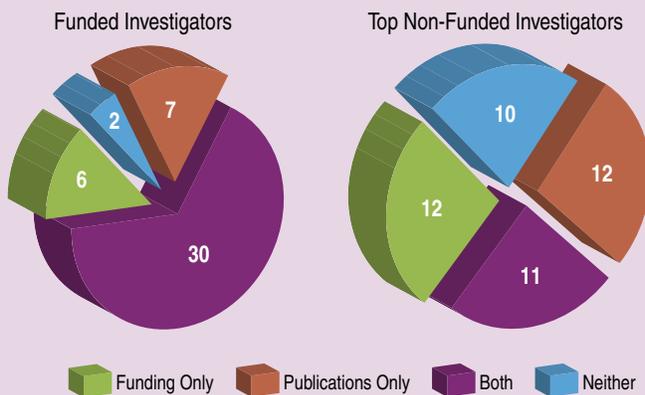


Figure V-2. Assessment of Continuing Contribution of Top 90 FY99 NIA Candidates

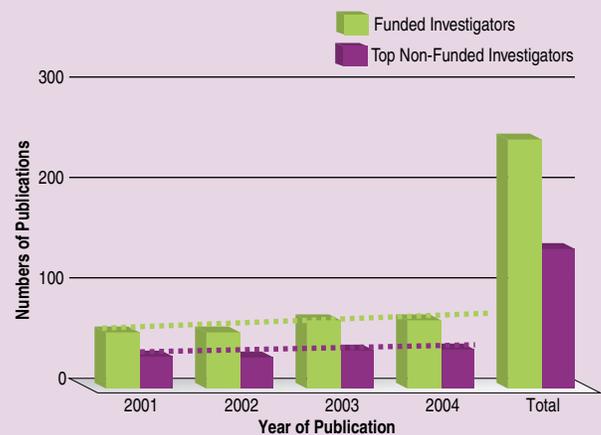


Figure V-3. Prostate-Specific Publications by FY99 NIA Candidates



- 96% have contributed to prostate cancer research and
- the original \$14.3M investment has resulted in the acquisition of \$88M in prostate cancer-specific funding and about \$156M in funding for all areas of research.

These results suggest that the NIA mechanism has successfully attracted and identified talented early-career researchers, and encouraged them to focus on prostate cancer research. In just 4 years, every dollar invested by the CDMRP in the NIAs has contributed to \$11 in additional research funds. The escalating annual publication record of these investigators suggests that they will remain active in the field.

Internal reviews by the CDMRP showed that the FY99 NIA recipients have made substantial contributions to prostate cancer research. Their work has already contributed to clinical trials, potential gene therapies, identification of novel risk factors, and characterization of novel molecular markers for accurately identifying and classifying, in addition to increasing our basic understanding of, prostate cancer.

The PCRP is significantly contributing to attracting early-career investigators to the nation's prostate cancer research effort.

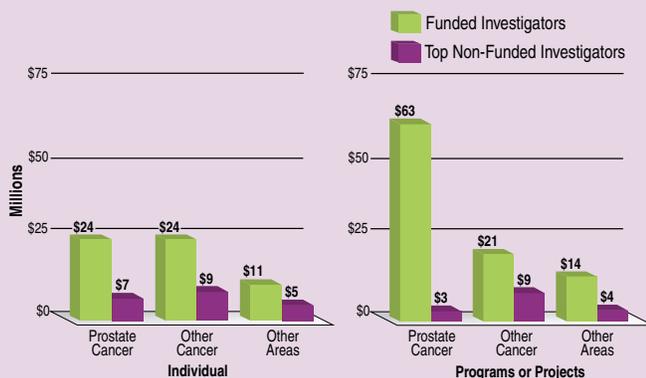


Figure V-4. Distribution of Subsequent Funding for the FY99 NIA Candidates



Figure V-5. Total Subsequent Funding Awarded to FY99 NIA Recipients



“The DOD PCRP has become an important force for promoting multidisciplinary prostate cancer research in this country. Many of our highly productive researchers were supported during the critical early years of their career, an investment that will return important research for decades to come.”

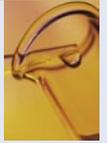
**John Petros, M.D., FY99
Prostate Cancer Center
Initiation Award Recipient**

A New Genetic Link to Increased Prostate Cancer Risk

John Martignetti, M.D., Ph.D., and Scott Friedman, M.D., Mount Sinai School of Medicine, New York, New York

Identifying the genes that contribute to an increased risk of prostate cancer is critical in developing diagnostic tools and novel therapeutic strategies. Familial prostate cancer is associated with a few “high-penetrance” genetic mutations, which often lead to prostate cancer. Non-familial, or sporadic, prostate cancer may be associated with “low-penetrance” mutations that rarely cause prostate cancer, but are associated with an increased risk of developing the disease. These low-penetrance mutations are predicted to have high prevalence in the population. Drs. John Martignetti and Scott Friedman of the Mount Sinai School of Medicine have proposed that one such candidate is the Krüppel-like factor 6 gene (KLF6), a tumor suppressor that inhibits cell growth through p53-independent activation of p21 (WAF1/CIP1). Previous studies showed that DNA containing the KLF6 gene is deleted and/or mutated in a majority of spontaneous prostate cancers. These studies were expanded to determine whether subtle genetic variations of KLF6, called single nucleotide polymorphisms (SNP), which are present at birth and detectable in blood might represent low-penetrance mutations that contribute to the development of all forms of prostate cancer.

Supported in part by funding from the FY02 PCRP, the Mount Sinai team collaborated with other researchers to catalog the genetic variants of KLF6. These investigators screened the KLF6 gene for SNPs in blood samples from a cohort of 3,411 men that included patients with sporadic or familial prostate cancer, and a control group of healthy men. These studies confirmed that the presence of a particular variant of this gene increases prostate cancer risk about 50% regardless of family history of the disease. These findings are significant because this KLF6 SNP is the first reported high-prevalence, low-penetrance prostate cancer susceptibility allele. The intronic KLF6 SNP, in contrast to many other SNPs, has functional significance. It results in the generation of a novel, truncated form of KLF6, which no longer suppressed cell growth, but instead, promoted growth. The team then performed targeted inhibition studies of the two KLF6 forms to better understand their biologic effects. As anticipated, inhibition of the truncated cytoplasmic KLF6 isoform caused marked decreases in key hallmarks of cancer growth and spread: cell proliferation, anchorage-independent growth, invasion, tumorigenicity, and angiogenesis. This research strongly supports the hypothesis that a specific variant of the KLF6 tumor suppressor gene is responsible in part for increased prostate



cancer risk. These studies also demonstrated that the novel dual growth-promoting/growth-suppressing effects of the KLF6 gene and its variants could provide a target for preventive/diagnostic strategies, ultimately lowering prostate cancer risk for men.

Additional details about this exciting work can be referenced in the following publications:

Li D, Yea S, Dolios G, et al. 2005. Regulation of kruppel-like factor 6 tumor suppressor activity by acetylation. *Cancer Research* 65(20): 9216–9225.

Narla G, DiFeo A, Yao S, et al. 2005. Targeted inhibition of the KLF6 splice variant, KLF6 SV1, suppresses prostate cancer cell growth and spread. *Cancer Research* 65(13):5761–5768.

Narla G, DiFeo A, Reeves HL, et al. 2005. A germ line DNA polymorphism enhances alternative splicing of the KLF6 tumor suppressor gene and is associated with increased prostate cancer risk. *Cancer Research* 65(4):1213–1222.

Kaiser J. 2004. New prostate cancer genetic link. *Science* 306:1285.

PCRP RESEARCH IN THE NEWS

April 15, 2005 - Boston, Massachusetts

Massachusetts General Hospital News and Information

MR spectroscopy may be superior for determining prostate cancer prognosis

Detailed analysis of tissue chemistry could identify most appropriate treatment; more study needed.

A new way of evaluating prostate tumors may help physicians and patients choose the best treatment strategy. Using magnetic resonance (MR) spectroscopy, which provides detailed information on the chemical composition of tissue samples, researchers from Massachusetts General Hospital (MGH) have shown that chemical profiles of prostate tissue can determine a tumor's prognosis better than standard pathological studies do. The report appears in the April 15 issue of *Cancer Research*.

“Our study indicates that analyzing prostate tissue’s metabolic profile may give clinicians additional information about the biologic status of the disease that could allow them, in consultation with their patients, to make better-informed decisions on the next steps to take,” says Leo L. Cheng, Ph.D., of the MGH Radiology and Pathology Departments, the report’s lead author.

Since the prostate-specific antigen (PSA) test became widely used to screen for prostate cancer, tumor detection rates have increased dramatically, particularly among those at early stages of the disease.





But increased detection has led to a clinical dilemma, since standard histologic evaluation, based on a biopsy sample's appearance under a microscope, often cannot distinguish which tumors are going to spread and which are not. Many men live for years with slow-growing prostate tumors before they die of unrelated causes, and treating such patients could cause more harm than benefit, Cheng notes. So finding a better way to determine which patients need aggressive treatment and which can try watchful waiting has been a major challenge.

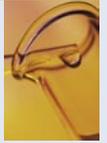
Another problem is that a biopsy sample from one area of the prostate may miss malignant cells elsewhere in the gland. Removal of the entire prostate can give a more definitive diagnosis, but if the tumor is a slow-growing one, the patient would have undergone unnecessary surgery. Surgery also is not appropriate when cancer has already spread beyond the prostate, since that situation requires other therapeutic approaches such as chemotherapy or drugs that block testosterone's action.

Although MR spectroscopy has been used for many years to measure the chemical composition of materials, including biological samples, it has not been useful for analyzing tumor specimens. In recent years, Cheng and his colleagues have been developing a spectroscopic technique called high-resolution magic angle spinning that provides detailed analysis of a sample's components without destroying its cellular structure. The current study was designed to evaluate the technique's potential for providing information useful for clinical decision-making in prostate cancer.

The researchers used MR spectroscopy to analyze tissue samples from 82 patients in whom prostate cancer had been confirmed by prostatectomy. Almost 200 separate samples were studied, including many that appeared benign to standard histological examination. They then compared the spectroscopy results—detailed profiles of each sample's chemical components—with the information gathered from pathological analyses of the removed glands and the patients' clinical outcomes.

Several chemical components of the tissue samples were found to correlate with the tumors' invasiveness and aggressiveness, supporting the potential of these metabolic profiles to provide valuable clinical information. Perhaps most significantly, even samples of apparently benign tissue had components that could successfully identify more and less aggressive tumors elsewhere in the prostate.

“Not only are the spectroscopy studies as good as histopathology in differentiating cancer cells from benign cells, they may be even better if they can find these metabolic differences in tissues that look benign,” says Cheng. “We need to do a larger scale, more systematic study of this technique before it can be applied to clinical practice. And we hope



to collaborate with other institutions to identify different metabolic profiles that could provide additional information.” Cheng is an assistant professor of Radiology and Pathology at Harvard Medical School.

The study’s co-authors are Melissa Burns, Jennifer Taylor, Chin-Lee Wu, M.D., Ph.D., and Wenlei He, M.D., Ph.D., of MGH Pathology; Elkan Halpern, Ph.D., MGH Radiology; and Scott McDougal, M.D., Chief of MGH Urology. The study was supported by grants from the National Institutes of Health and the U.S. Department of Defense.

BOTTOM LINE

Since 1997, the DOD PCRP has been responsible for managing \$650M in congressional appropriations, resulting in 1,245 awards from FY97 to FY04. Together, PCRP-supported investigators are changing the landscape of prostate cancer research. Research highlights, award data, and abstracts of funded PCRP proposals can be viewed on the CDMRP website (<http://cdmrp.army.mil>).

