

Section IV.

PROSTATE CANCER

RESEARCH

PROGRAM



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Prostate Cancer Research Program

Vision: To conquer prostate cancer

Mission: To support research that is innovative and multidisciplinary directed toward eliminating prostate cancer.

Congressional Appropriations for Peer-Reviewed Research
\$85M in FY97–98, \$50M in FY99, and \$75M in FY00

Award Summary

193 awards from the FY97–98 appropriations

104 awards from the FY99 appropriation

~140 awards anticipated from the FY00 appropriation

“In the war against prostate cancer, the DOD PCRP has served as the ‘Green Berets’—a high-impact, quick-strike capability that has rapidly put essential resources into the hands of expert investigators who have effectively pursued novel and intriguing hypotheses. Their successes are forging the way to major victories in understanding and eliminating this threat.”

*Andrew von Eschenbach, M.D.
Chair, Integration Panel*

The Disease

Prostate cancer is the most common male malignancy, aside from skin cancer, and the second most common cause of cancer death in men in the United States. In 2000, an estimated 180,400 men will be diagnosed with prostate cancer, and approximately 31,900 will die from the disease.¹ The impact is even higher among African American men, who have the greatest incidence rates in the world and whose mortality rates are more than twice those of Caucasians. In spite of the prevalence of prostate cancer, there is a relative paucity of information about the cause, prevention, and treatment of this disease.

History of the Prostate Cancer Research Program

—Program Background

The Department of Defense (DOD) Prostate Cancer Research Program (PCRPP) 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. At that time, the U.S. Army Medical Research and Materiel Command convened a meeting of expert scientists, clinicians, and consumer advocates drawn from academia, industry, military, urology and oncology organizations, consumer advocate organizations, and cancer research funding agencies. This group defined the goals and areas of emphasis of the program and identified underrepresented avenues of research and novel applications of existing technologies. The overall mission of the PCRPP remains essentially the same today as it was in FY97: to support innovative ideas and technology through both basic and clinical research aimed at preventing, detecting, treating, and improving the quality of life of those afflicted with prostate cancer.

¹ American Cancer Society – Cancer Facts & Figures 2000: Selected Cancers.

—Congressional Appropriation and Funding History

From FY97–00, Congress appropriated a total of \$210M to fund peer-reviewed prostate cancer research through the PCRP. In the first 3 fiscal years of the program, a total of 297 awards were made across the categories of research, training/recruitment, and infrastructure, as summarized in Appendix A. The investment strategy executed is consistent with congressional language and reflects the program’s vision to conquer prostate cancer. Appendix B, Table B–2, summarizes the directions from Congress for the PCRP appropriations, the program’s withholds and management costs, and the investment strategy executed by the PCRP for FY99–00. Additional details of the FY97 and FY98 programs may be found in the DOD Congressionally Directed Medical Research Programs (CDMRP) Annual Report, September 1999.

FY99 Program

Congress appropriated \$50M in FY99 to continue the DOD peer-reviewed PCRP. As in previous years, the central theme of the FY99 PCRP was to capture innovative ideas and to complement research initiatives of other funding agencies. The program emphasized scientific inquiry in three areas of research: (1) cancer biology, (2) prevention, and (3) therapy. All proposals solicited in FY99 addressed an issue relevant to one or more of these research areas.

The programmatic vision was implemented by requesting proposals in three award categories: (1) research, (2) training/recruitment, and (3) infrastructure. Research awards, which consisted of Idea Development and New Investigator Awards, aimed to stimulate and reward creative research ideas from established and new investigators, respectively. The training/recruitment category consisted of Postdoctoral Traineeships and Minority Population Focused Collaborative Training Awards (MPFCTA). The intent of the Postdoctoral Traineeships was to enable recent doctoral degree students to conduct research in prostate cancer; the MPFCTA placed emphasis on fostering collaborations between applicants and established prostate cancer researchers to study the disparity in prostate cancer incidence and mortality among different ethnic groups. To support infrastructure, Prostate Cancer Center Initiation Awards were offered to establish regional centers for the study and treatment of prostate cancer.

The Prostate Cancer Center Initiation Award was a highlight of the FY99 PCRP. This new mechanism was designed to expand the existing infrastructure to support prostate cancer research. The intent of this mechanism was to invigorate the research community, bring new investigators into the field of prostate cancer, and make strides toward eradicating prostate cancer by engaging experts from multiple disciplines to establish regional centers for basic and clinical research in prostate cancer. These awards were designed to provide institutions the opportunity to acquire the research experience, resources, data, and services needed to compete for future funding from other sources. Four Prostate Cancer Center Initiation Awards were funded; the recipients were Emory University, Vanderbilt University, the University of California at Los Angeles, and the University of Southern California. The funding summary for the FY99 PCRP is shown in the following table.

“The innovative and imaginative investment strategy developed and executed by the prostate cancer integration panel will be the catalyst that will accelerate and greatly enhance prostate cancer research in the United States as we enter the 21st century.”

*James Williams
Consumer Integration
Panel Member*

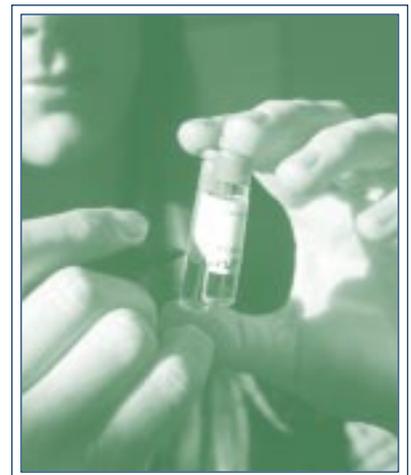


Table IV-1. Funding Summary for FY99 PCRP Awards

Award Mechanism	Number of Proposals Received	Number of Awards	Investment
Idea Development Awards	366	36	\$19.1M
New Investigator Awards	202	40	\$12.6M
Postdoctoral Traineeships	49	17	\$1.4M
MPFCT Awards	10	6	\$0.4M
Prostate Cancer Center Initiation Awards	20	4	\$8.5M

“The CDMRP’s unique funding mechanism has enabled me to conduct innovative studies that will complement ongoing human chemoprevention trials.”

David Waters, D.V.M., Ph.D.
PCR P Award Recipient

Figure IV-1 illustrates the diverse portfolio of research funded by the FY99 PCR P. The largest investment is in basic science in the discipline of cell biology (33%). Clinical Research (23%) is the second largest investment of the PCR P, with 17% of the portfolio in clinical and experimental therapeutics.

FY00 Program

The program’s continued success encouraged Congress to appropriate an additional \$75M in FY00 for the DOD PCR P. The programmatic vision for FY00 encompassed two award categories, research awards and training/recruitment awards. As in FY99, the PCR P research awards consisted of Idea Development and New Investigator Awards while training/recruitment awards consisted of Postdoctoral Traineeships and MPFCT Awards. A Program Announcement was released on February 23, 2000. A total of 580 proposals was submitted to the program. Peer review was conducted in July 2000, and programmatic review will be completed in October 2000. In addition, Phase II of the Dual Phase Research Awards is being executed using the FY00 appropriation.

A distinctive feature of the FY00 program is the implementation of Phase II of the Dual Phase Research Awards. These awards were established in the first year of the PCR P (FY97) to serve as a catalyst to invigorate prostate cancer research. The intent of these awards was to attract outstanding new investigators and established scientists working in prostate cancer or a related field to develop new directions, ideas, approaches, and technologies leading to a better understanding of prostate cancer. In Phase I of the Dual Phase Research Awards, investigators were challenged to explore innovative ideas, approaches, and technologies relevant to prostate cancer. In Phase II, they were further challenged to develop their Phase I work into scientifically promising projects with the potential for making significant advances in prostate cancer diagnosis and treatment. All investigators funded in Phase I were invited in FY00 to compete for 2 additional years of funding at double the initial award amount. Phase II awards will be made to those investigators who demonstrate the most productivity and innovation in

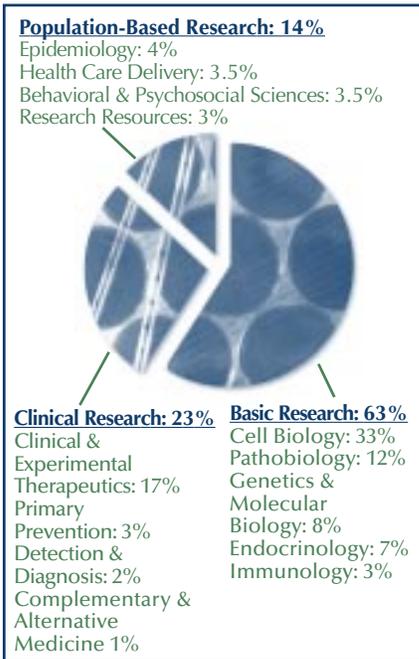


Figure IV-1. FY99 PCR P Portfolio by Research Area

Phase I and who show the greatest potential for making significant contributions to diagnosing and treating prostate cancer in Phase II. Of the original 168 Phase I awardees, 100 applied for Phase II funding; it is expected that 33 of these applicants will receive Phase II support.

Scientific Achievements

While the PCRP is a relatively young program, it is anticipated that funded research will provide the framework and foundation for contemporary and future scientific discoveries. For example, investigators funded in Phase I of the Dual Phase Research Awards have already had an impact in the fight against prostate cancer. After only 18 months of research, these investigators have disseminated their research results and presented their latest research advances in more than 155 publications in prestigious science journals (including *Nature Genetics*, *Nature Medicine*, *Cancer Research*, and *Journal of Clinical Investigations*). Additionally, more than 175 abstracts were presented at national and international forums (including Gordon Research Conferences, the Symposium on Cancer Research, and annual meetings of the American Association for Cancer Research and the American Urological Association). The development of more than 30 cell lines/animal models by Dual Phase investigators will provide resources that will sustain future biomedical research on prostate cancer. Additionally, support for clinical trials will offer the potential to revolutionize prostate cancer patient care.

Table IV-2. 18-Month Outcomes of Phase I Awards

Number of Awards	100
Publications (includes manuscripts in press)	> 155
Abstracts/Presentations	> 175
Patents/Licensures (including applications)	> 20
Clinical Trials (includes submitted protocols)	> 15
Cell Lines/Animal Models Developed	> 30

“Although my father and younger brother were less fortunate than I and died victims of prostate cancer, I have survived, 5 years and counting. I hope and pray with optimism for the continued success of the Prostate Cancer Research Program, thus giving my 20-year-old son a fair shot at a decent quality of life.”

Winston Dyer

Consumer Integration Panel Member



Addressing Disparities in Prostate Cancer

The PCRP has made a concerted effort to address the disparity in prostate cancer incidence and mortality among ethnic groups and to attract grants from investigators at Historically Black Colleges and Universities/Minority Institutions (HBCU/MI). An innovative award mechanism has been designed—the MPFCTA.¹ This mechanism was intended to enable investigators to develop a prostate cancer research concept that focuses specifically on the ethnic disparities in prostate cancer incidence and mortality.

An additional goal of these awards is to establish collaborations between applicants and established investigators. In an ongoing effort to attract proposals from investigators at HBCU/MI, two new award mechanisms were designed in FY00. Nested HBCU/MI Traineeships were offered as an optional component to Idea Development Awards to assist in the research training of HBCU/MI predoctoral and postdoctoral scientists in prostate cancer research. The HBCU/MI Academic Development Award was offered to provide education, training, and scientific development for predoctoral and postdoctoral trainees at HBCU/MI. ♦

¹ This award mechanism was originally conceived in FY98 as the Minority Population Focused Training Award (MPFTA). To emphasize its collaborative focus, the name was changed in FY99 to the Minority Population Focused Collaborative Training Award (MPFCTA).



The projects described below represent a sampling of some of the exciting advances in prostate cancer research that are supported by the Dual Phase Research Awards mechanism. This broad portfolio of research is laying the foundation for drug discovery and development, clinical trials, vaccine development, diagnostic and prognostic tests, and disease prevention.

Vaccine Studies Demonstrate the Promise of Immunotherapy: The notion of developing vaccines to treat and prevent cancer has tantalized scientists for many years. Studies supported by the DOD PCRP exemplify promising approaches to the development of cancer vaccines. For instance, investigators at the University of Illinois are developing methods to stimulate the immune system of prostate cancer patients to selectively destroy prostate cancer cells.

Research performed during the first phase of this study was based on the observation that two proteins, prostate specific antigen (PSA) and prostate specific membrane antigen (PSMA), are found on most prostate tumor cells. Investigators found that portions of these proteins (called peptides) can be used to target the immune system to destroy cancer cells. This important research provides the possibility of being able to directly vaccinate prostate cancer patients with prostate-specific peptides to treat their tumors. In the second phase of this project, a clinical trial to test the safety and effectiveness of a PSA peptide as a vaccine for treating prostate cancer is expected to be under way soon. Investigators also anticipate identifying additional PSA and PSMA peptides that will lead to the design of even better, more effective vaccines for the treatment of prostate cancer.

Antiestrogens and Tetracycline Show Potential for the Treatment of Advanced Prostate Cancer: Estrogens have historically been used to treat prostate cancer. Tamoxifen, an antiestrogen that prevents the full effect of estrogens, has also been used for the treatment of prostate cancer. However, these

hormonal therapies result in a number of adverse side effects, and their effectiveness decreases over time. The anticancer action of estrogens and antiestrogens is not well understood. A better understanding of how these hormones work is critical to the development of safer and more effective forms of hormonal therapies. Investigators at the University of Massachusetts Medical Center (UMMC) are addressing this critical issue.

It is known that estrogens and antiestrogens attach to a protein in the cell called estrogen receptor alpha (ER-alpha). Recently, a new type of estrogen receptor has been discovered called estrogen receptor beta (ER-beta). This receptor appears to be involved in different activities from those regulated by ER-alpha. PCR/P Dual Phase researchers at UMMC are studying the roles of ER-alpha and ER-beta in the development of prostate cancer. During the first phase of the study, investigators found that ER-beta, but not ER-alpha, is found in prostate cancer cells that have spread to bone (bone metastases). They also demonstrated that certain antiestrogens can stop prostate cancer cell growth after attaching to ER-beta, thus providing a much-needed avenue for treating bone metastases. In fact, these findings have led the investigators to initiate a clinical trial using antiestrogens to treat advanced prostate cancer. The trial is expected to enter the second phase shortly at the UMMC.

Under the PCR/P Dual Phase, investigators at the University of Miami School of Medicine have also been identifying novel therapies for the prevention and treatment of advanced prostate cancer. Tetracycline compounds, traditionally used as antibiotics, have been shown to inhibit many tumor cell functions such as growth and invasion. Additionally, tetracycline compounds are known to accumulate in the bone, a tissue also adversely affected by metastatic prostate cancer. Miami researchers have found CMT-3, a synthetic tetracycline, to be toxic to prostate cancer cells, to inhibit their growth, and to block enzymes that are needed to clear a path for cell invasion. In the first phase of this work, researchers showed that CMT-3 reduced tumor growth and increased the life span of rats with prostate cancer bone metastases. During the next phase of this research, combinations of CMT-3 will be tested with other drugs and with radiation therapy in a rat model of advanced prostate cancer and in mice with transplanted human prostate tumors. This study is expected to lead to the design of more effective treatments for advanced prostate cancer.

New Prostate Cancer Genes: PCR/P Dual Phase investigators at Case Western Reserve University and The Cleveland Clinic Foundation are studying genetic factors involved in the development of prostate cancer. Several lines of evidence point to a genetic basis for prostate cancer. These investigators localized a gene that may play a role in prostate cancer. This gene, called a “tumor suppressor,” is important because a tumor may develop if the gene is not working properly. Researchers also studied another gene that may be involved in prostate cancer, called CYP3A4. They demonstrated that African American men with one form of CYP3A4 are more likely to be diagnosed with advanced disease than are men with another form of the gene. Other researchers have showed that this is also true for Caucasian men. Taken together, these results have laid the foundation for the





second phase of the study. Investigators plan to study the potential prostate cancer tumor suppressor gene, as well as better understand the role of the CYP3A4 gene in prostate cancer. In addition to improving our knowledge of prostate cancer, these studies are preparing the groundwork for improved diagnostic and prognostic tests.

Another group of PCR-P Dual Phase investigators is also identifying genetic changes in prostate cancer. Researchers at the University of Virginia analyzed more than 200 prostate cancer tumor samples to identify abnormal genes that may be responsible for the development and severity of prostate cancer. Efforts were focused on studying a part of chromosome 13 that is frequently missing in aggressive prostate cancers. These researchers have identified two new tumor suppressor genes on chromosome 13. These newly identified genetic changes will be used to develop critically important tests for the detection of aggressive prostate cancer. Based on data obtained during the first phase of this study, the investigators were able to continue their research with a grant from the National Institutes of Health.

Radioimmunotherapy as a Treatment for Prostate Cancer: Radioimmunotherapy is a form of cancer treatment that involves delivering radioactive agents directly to tumor cells by augmenting the immune system. The radioactive agents are attached to antibodies that then travel through the blood stream and bind specifically to proteins on the tumor cell surface. In this way, many antibody molecules can bind to the tumor and deliver a lethal radiation dose to the tumor.

PCR-P Dual Phase researchers at the Cornell University Medical Center are making significant progress in developing radioimmunotherapy as a potential treatment method for prostate cancer. During the first phase of this study, researchers developed a radioactive antibody that attaches to the PSMA molecule on prostate cancer cells. Currently, investigators will conduct a Phase 1 clinical trial to determine the radioactive dose of the antibody that is safe and effective in humans. This study is one of the first major clinical trials to use radioimmunotherapy as a treatment for prostate cancer.

Dietary Preventions and Supplements for Prostate Cancer: It is believed that diet plays a significant role in the development of cancer. For instance, overconsuming some foods, such as fat, or underconsuming others, such as green vegetables, may contribute to the development of prostate cancer. Selenium is an essential nutrient that has been shown to inhibit cancer development in animals and reduce the risk of several cancers in humans, including prostate cancer. These data have raised hopes that selenium can be used to prevent cancer. Currently, the National Cancer Institute (NCI) is supporting a large-scale clinical trial to help decide whether selenium can prevent prostate cancer. Nevertheless, the anticancer action of selenium is not well understood.

PCR-P Dual Phase researchers at the Purdue Research Foundation are studying the anticancer action(s) of selenium in dogs, the only nonhuman species that naturally develops prostate cancer. This study complements ongoing human clinical trials and should give us a better understanding of exactly how selenium

acts against prostate cancer. The results from this study will guide the design of future human clinical trials in this area.

Prostate cancer researchers at Stanford University are also investigating a number of compounds that may prevent prostate cancer. These include compounds from cruciferous vegetables (e.g., cauliflower and broccoli), soybeans, tomatoes, and green tea. To determine why these compounds may be protective, these researchers are using a new technology called cDNA microarrays to determine which genes are turned on or off after adding these compounds to prostate cells. This information will be used to develop a “blueprint” to describe which cellular pathways may prevent normal prostate cells from transforming into cancerous cells. In the first phase of the study, investigators identified a potential cancer preventive agent called sulforaphane, a compound in broccoli and related cruciferous vegetables. The second phase will focus on using cDNA microarrays to identify how this compound may work to prevent prostate cancer as well as identify other cancer preventive dietary agents.

Molecular Basis for the Development of Hormone-Resistant Prostate Cancer: Most prostate cells will die if a receptor called the androgen receptor (AR) is no longer stimulated by androgen hormone. This is the basis for androgen ablation therapy in prostate cancer. However, the cancer-controlling effects of this critical and effective therapy become lost as the cancer cells progressively lose their dependence on AR stimulation (hormone-resistant disease). This is a critical turning point in prostate cancer treatment because so few therapeutic options remain. Therefore, a better understanding of how these cells begin to grow independent of AR stimulation is crucial.

Scientists at the Burnham Institute in La Jolla, California, discovered BAG-1L, a molecule that binds to the AR and amplifies this receptor’s functions. Research conducted in the first phase revealed higher levels of BAG-1L on the surfaces of most prostate tumor cells, as well as higher levels in more aggressive tumors. In the second phase of this study, these investigators will unravel the role of BAG-1L in the progression of prostate cancer and identify potential new therapeutic avenues for treating the disease.

PCRP Dual Phase scientists at Columbia University are focusing on a molecule called protocadherin PC (“PC” for prostate cancer) to understand and ultimately treat hormone-resistant prostate cancer. Protocadherin PC is a molecule that is highly expressed in hormone-resistant prostate cancer cells. Most prostate cells respond to androgen hormone deprivation by undergoing cell death. The Columbia University researchers are studying the possibility that protocadherin PC prevents cell death and causes hormone independence. In the first phase, these scientists discovered that there are two forms of protocadherin PC, a normal (membrane) form and a short (cytoplasmic) form that is overexpressed in hormone-resistant prostate cancer cells. Future efforts will be directed at establishing the relationship between protocadherin PC expression and the development of hormone-resistant prostate cancer with the expectation of developing new treatment modalities for hormone-resistant disease.



Identifying Aggressive Prostate Cancer Tumor: PSA is a protein produced by the prostate gland that becomes elevated in prostate cancers. While most prostate cancer cases can be detected by a blood test for PSA, this test does not distinguish cancers that progress rapidly (aggressive tumors) from those that progress slowly. Thus, it is very important to develop a test that can distinguish between these two types of tumors.

PCRP Dual Phase researchers at the University of Massachusetts Medical Center are studying the role of centrosomes (complex structures that play a critical role in cell division and organization) in aggressive prostate cancer. These investigators were among the first to discover that the number of centrosomes and their structures are abnormal in all cancers, including prostate cancer. During the second phase of this study, the investigators will determine whether these centrosome abnormalities can be used to predict whether or not a tumor is aggressive. This study is expected to lead to the development of a simple blood test that can predict how a tumor may behave over time. This will improve the ability to identify patients with aggressive disease and help design new therapies.

“The Army has provided us with a unique funding mechanism for cancer research that bridges studies on basic biological mechanisms of tumorigenesis with clinical aspects of cancer, such as diagnostic and prognostic indicators and identification of drug targets.”

*Steven Doxsey, Ph.D.
PCRP Award Recipient*

Summary

The DOD PCRP is supporting innovative, multidisciplinary research directed toward eliminating prostate cancer. While the program is relatively young, the diverse portfolio of funded research is already making important contributions to understanding, preventing, detecting, diagnosing, and treating prostate cancer. Projects funded by the PCRP are yielding results that are ready for clinical testing and application, thus aiding in the national effort to improve the well-being of all people. Congress has directed the DOD to continue supporting prostate cancer peer-reviewed research and has appropriated \$100M for the FY01 program.

FY00 Integration Panel Members

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Chair-Elect, Carl Olsson, M.D.: Professor and Chairman, Department of Urology, College of Physicians and Surgeons, Columbia University. Director of Urological Service, The Presbyterian Hospital and the Squier Urological Clinic.

Lucile Adams-Campbell, Ph.D.: Director, Howard University Cancer Center. Professor of Medicine, Howard University College of Medicine. Associate Director, Division of Epidemiology and Biostatistics, Howard University Cancer Center.

For more information about the PCRP and other programs managed by the CDMRP, visit <http://cdmrp.army.mil>

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