

Section IV.

PROSTATE CANCER

RESEARCH

PROGRAM



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Prostate Cancer Research Program

Vision: To conquer prostate cancer.

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

Congressional Appropriations for Peer Reviewed Research
\$135M in FY97–99, \$75M in FY00, and \$100M in FY01

Award Summary

297 awards from the FY97–99 appropriations

142 awards from the FY00 appropriation

~200 awards anticipated from the FY01 appropriation

“The DOD’s Prostate Cancer Research Program is playing an important role in the ‘war’ against prostate cancer. The peer review process, involving some 18 panels followed by a final review by the Integration Panel, has proved to be an effective way to select for funding the proposals which best meet program objectives. As a prostate cancer survivor, I have been particularly pleased with the emphasis on translational research in this program.”

—Richard Howe, Ph.D.
National Prostate Cancer Coalition
FY00 Integration Panel Member

The Disease

Current estimates are that one in every six American men will be diagnosed with prostate cancer in his lifetime. Prostate cancer is the second most common cause of cancer death in men in the United States and approximately 31,500 will die from this disease in 2001. An estimated 198,100 men in the United States will be diagnosed with prostate cancer in 2001. African Americans have the highest incidence of prostate cancer in the world and are 50% more likely to develop this disease and over twice as likely to die from prostate cancer than Caucasian Americans.¹ In spite of the prevalence of prostate cancer, we are only now beginning to understand this disease and how to develop more effective prevention and treatment measures.

History of the Prostate Cancer Research Program

—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. 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, urology and oncology organizations, consumer advocate organizations, industry, military, 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

¹ American Cancer Society – *Cancer Facts and Figures 2001*.



technologies. The mission of the PCRP is to promote innovative, multi-institutional, multidisciplinary, and regionally focused research directed toward eliminating prostate cancer.

—Congressional Appropriation and Funding History

From FY97–01, Congress appropriated a total of \$310M to fund peer reviewed prostate cancer research through the PCRP. A total of 439 awards have been made across the categories of research, training/recruitment, and infrastructure. The PCRP has developed a multidisciplinary research portfolio that encompasses both basic and clinical research aimed at preventing, detecting, treating, and improving the quality of life of those afflicted with prostate cancer. Each fiscal year’s investment strategy focused on the program’s vision to conquer prostate cancer. Appendix B, Table B–2, summarizes the congressional appropriations and the investment strategy executed by the PCRP for FY00–01. Additional details of the FY97–99 programs may be found in the *DOD Congressionally Directed Medical Research Programs Annual Reports* of September 1999 and of September 2000.

“The DOD Prostate Cancer Program precipitated my move to cancer research midcareer, and it is helping me to build a cadre of promising young investigators with fresh new ideas. Thanks!”

*—James C. Coyne, Ph.D.
Professor and Co-Director of
Health Services and Behavior
Sciences, University of
Pennsylvania
PCRPAward Recipient*

FY00 Program

Congress appropriated \$75M in FY00 to continue the peer reviewed DOD PCRP. The FY00 PCRP challenged the scientific community to design innovative prostate cancer research that would foster new directions, address neglected issues, and bring new investigators into the field. Awards were made in areas that represent underinvestigated avenues of research or novel applications of existing technologies. The programmatic vision was implemented by requesting proposals in two award categories: research and training/recruitment. Table IV–1 provides a summary of the FY00 PCRP award mechanisms in terms of dollars and number of awards. As illustrated in Figure IV–1, the portfolio of research supported by the FY00 PCRP is diverse.

The PCRP continued its emphasis on innovation by awarding 93 Idea Development and New Investigator grants. Both awards aim to stimulate and reward creative research ideas that represent the start of something new, or create or introduce a unique or unusual approach to the study of prostate cancer. In addition, 33 Phase II Idea Development and Phase II New Investigator Awards were made in FY00. These Phase II Awards completed the execution of the PCRP’s FY97/98 Dual Phase awards (see related box story on page IV–6).

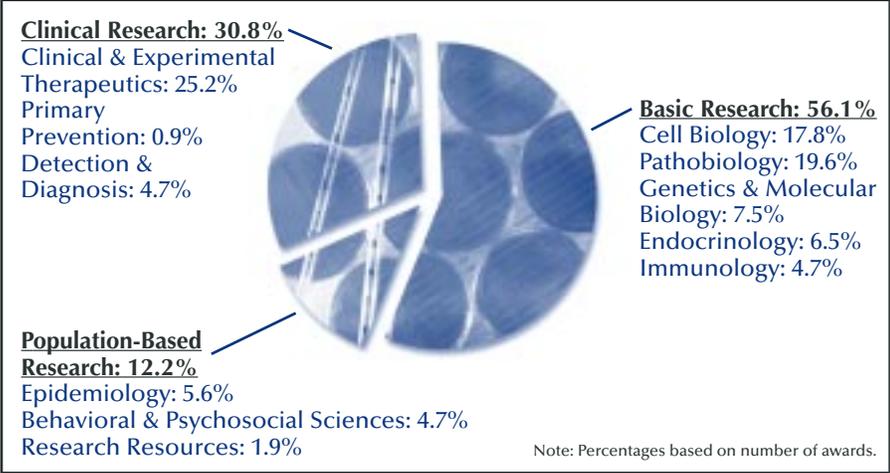


Figure IV–1. FY00 PCRPAward Portfolio by Research Area

“I retired after 20 years of active service in the Navy specifically to assume the position of Program Manager for the PCRCP—a decision I have not regretted. As a basic scientist trained in cancer research, I find it personally and professionally gratifying to be in a position where I can facilitate progress in such a critical area as prostate cancer. The program is without equal. It is a rare opportunity to be able to work with such dedicated, passionate, and tireless individuals as the researchers who participate in the program, the prostate cancer consumer advocates, and the scientists, staff, and contractors who make up the CDMRP.”

—Leo Giambarresi, Ph.D.
PCRCP Program Manager



Table IV–1. Funding Summary for FY00 PCRCP

Category Mechanism	Number of Proposals Received	Number of Awards	Investment
Research			
Idea Development	297	52 ¹	\$28.9M
New Investigator	215	41	\$13.6M
Phase II Idea Development	81	23	\$14.9M
Phase II New Investigator	19	10	\$4.3M
Training/Recruitment			
Postdoctoral	64	15	\$1.4M
MPFCT	4	1	\$0.1M
HBCU/MI Academic	0	0	0
Total	680	142	\$63.2M

¹ Two awards included nested Historically Black Colleges and Universities/Minority Institutions (HBCU/MI) Traineeships.

The Training/Recruitment Awards encouraged investigators to pursue careers in prostate cancer research. Including the awards made in FY00, the PCRCP has made a total of 38 Postdoctoral Traineeship Awards. The Minority Population Focused Collaborative Training Awards (MPFCTA) were offered by the PCRCP for a third time in FY00 and resulted in 24 total awards that are fostering collaborations between applicants and established prostate cancer researchers to study the disparity in prostate cancer incidence and mortality among different ethnic groups.

FY01 Program

Congress continued the program in FY01 with a \$100M appropriation. In addition to continuing to offer Idea Development, New Investigator, and Postdoctoral Traineeship Awards, five new mechanisms were launched in FY01.

- ◆ Prostate Cancer Clinical Trial Awards are intended to fund new prospective Phase 1 or Phase 2 clinical trials in the areas of prostate cancer therapy, diagnosis, detection, and prevention.



- ◆ The Prostate Cancer Consortium Award is being launched through the Consortium Development Award in FY01. Recipients of the 1-year Consortium Development Award will compete for Consortium Awards in FY02, pending an FY02 appropriation. Consortium Awards are intended to involve leading prostate cancer researchers through multidisciplinary/multi-institutional collaborations and will support goal/product-driven research efforts focused on a critical area of prostate cancer research.
- ◆ Health Disparity Training – Prostate Scholar Awards are intended to provide training opportunities at the predoctoral, postdoctoral, and postresidency level that focus on the disparate burden of prostate cancer in African Americans.
- ◆ Health Disparity Research – Prostate Scholar Awards are intended to encourage investigators in the early stages of their careers to focus research on the disparate burden of prostate cancer in African Americans.
- ◆ HBCU Collaborative Partnership Awards will provide support at the institutional level to establish stable, long-term partnerships between an applicant HBCU and collaborating institution.



In response to two FY01 PCRP Program Announcements, 782 proposals were received. Scientific peer review and programmatic review will be completed by August and October 2001, respectively. More than 200 awards are anticipated.

Scientific Achievements

PCRP award outcomes are exciting and present promise for the future. The outcomes of PCRP-funded research can be gauged, in part, by the number of resultant publications, abstracts/presentations, and patents/licensures reported by awardees. This information is summarized in Table IV-2. The projects highlighted below represent a sampling of some of the exciting advances in prostate cancer research. This broad portfolio of research is laying the foundation for increasing basic knowledge about prostate cancer, treating prostate cancer, improving the lives of individuals affected by this disease, and preventing prostate cancer.

Table IV-2. FY97-98 PCRP Award Outcomes

Number of Awards	193
Publications in Scientific Journals	>130
Abstracts/Presentations at Professional Meetings	>175
Patents/Licensures (including applications)	>25

Invigorating Prostate Cancer Research: Dual Phase Awards

During the first year of the PCRCP, the Integration Panel was faced with the challenge of invigorating and catalyzing the field of prostate cancer research. This challenge was met by developing the successful Dual Phase Awards. In FY97, investigators were encouraged to apply for Phase I Awards. Only initial awardees would be eligible to apply for Phase II support in FY00 for an award double that of the Phase I grant. While the competition for Phase II Awards was limited, investigators were judged on their Phase I productivity. Of the 168 Phase I Idea Development and New Investigator Award recipients, 100 competed for Phase II support and 33 Phase II Awards were made. The overall success of this initiative is evident. Phase II applicants reported 155 publications in print or submitted to scientific journals, applications for 20 patents/licensures, submission or initiation of over 15 clinical trial protocols, and development of over 30 animal/cell lines. ♦



Perceptions of Prostate Cancer in Married Couples. Ulrike Boehmer, Ph.D., Boston University: The diagnosis of advanced prostate cancer is a deeply disturbing event. While it has been assumed that in married couples, wives would share in the diagnosis and treatment decision making, there is little formal evidence to support that assumption. A PCRCP awardee at Boston University has examined this issue by comparing the perceptions of both husbands and wives regarding the diagnosis of metastatic prostate cancer and their respective roles in the treatment decision-making process. Married men previously diagnosed with metastatic prostate cancer and their wives were interviewed separately in focus groups. Both the husbands and their wives were asked the same questions, and their accounts were examined for similarities and differences. The study found that many men did not share their prostate-related health problems, including events surrounding their initial diagnosis, with their wives, and chose their treatment with little spousal consideration. Men usually formed a decision-making bond with their physicians, excluding their wives in the process. Their wives were, in turn, poorly informed about treatment discussions between their husbands and their physicians and were minimally involved in prostate cancer treatment decision making. These findings suggest that physicians have a crucial role in the decision-making process. In addition to providing clinical information to the patient, physicians are also uniquely situated to influence the decision-making style of couples. This may include helping both members of the couple to support and guide each other through the difficult mental and physical challenges that each of them faces.

Homing in on Metastatic Prostate Cancer Cells. Samuel R. Denmeade, M.D., The Johns Hopkins University: Few treatment choices exist for men with metastatic prostate cancer where androgen ablation therapy has failed. Furthermore, drugs that may be capable of killing metastatic cancer cells also kill normal noncancerous cells. Therefore, drugs and treatments that can specifically target and kill metastatic prostate tumor cells, wherever they are in the body, without causing damage to normal cells are urgently needed. PCRCP researchers at the Johns Hopkins University are addressing this critical issue. Their approach

is to chemically transform active, cell-killing drugs into inactive forms (prodrugs) that will become activated only in areas of the body that contain the cancer cells.

Specifically, these investigators are using a drug called thapsigargin that is a natural plant product that kills cells by inducing apoptosis. To target thapsigargin's ability to kill only prostate cancer cells, the researchers have produced several different thapsigargin prodrugs that are activated into their active cell-killing forms by prostate-specific membrane antigen (PSMA), a protein which is produced in high levels by prostate cancer cells. This work represents an exciting and promising approach to specifically target the potent cell-killing ability of a chemotherapeutic agent, thapsigargin, to prostate cancer cells while avoiding side effects to the rest of the body.

Green Tea Inhibits Prostate Cancer Cell Growth and Metastasis. Hasan Mukhtar, Ph.D., Case Western Reserve University: Treatment of prostate cancer is currently limited to surgery, radiation therapy, hormone therapy, or “watchful waiting,” depending upon the age and overall health of the man at the time of diagnosis. Preventive therapies, especially natural, nutritional therapies that could inhibit prostate cancer development, slow tumor growth, and limit the spread of more advanced prostate tumors, could have a major impact on the incidence of the disease in men. PCRFP-supported researchers at Case Western Reserve University have studied the effects of green tea, a popular drink throughout Asia that has an increasing popularity in Western countries, on prostate cancer prevention. Specific chemical components of green tea, called polyphenolics, were separated from green tea. Using a mouse model that closely mimics prostate cancer in humans (called TRAMP for transgenic adenocarcinoma of the mouse prostate), the polyphenolics were given to the mice at a dose equivalent to six cups of green tea a day. TRAMP mice that did not receive the green tea compounds developed prostate cancer by 20 weeks of age, and by 32 weeks, all of the untreated TRAMP mice had metastatic prostate tumors. However, treated TRAMP mice developed prostate tumors at a much lower rate, and when tumors did develop in the mice, none spread to other organs. The green tea polyphenols also increased the average survival time for the TRAMP mice from 42 weeks without treatment to 68 weeks with the green tea therapy. Future research with these compounds may provide a treatment that could slow or possibly even prevent the development of prostate cancer.

Understanding Prostate Gene Expression. Peter S. Nelson, M.D., Fred Hutchinson Cancer Center: The key to understanding human health and disease is found within each cell in the body and is represented by the complete set of genes that are expressed in that cell. Because each cell type in the body expresses a different set of genes, a catalogue of genes expressed in a particular normal cell type is necessary before those genes whose expression changes during disease can be identified. Two awards made to the Fred Hutchinson Cancer Center and the University of Washington are supporting the development and use of a comprehensive database

“The funding provided by the DOD has greatly assisted our research into understanding the basic mechanisms of prostate cancer through the identification of that portion of the human genome that is used or expressed by prostate cells. This molecular inventory is the first step in deciphering gene networks that operate to allow cells to proliferate, grow in an androgen-depleted environment, and metastasize. The DOD has allowed us to pursue high-risk projects that have the potential to greatly advance the field of prostate cancer research.”

—Peter S. Nelson, M.D.
Assistant Professor, Fred Hutchinson
Cancer Research Center
PCRFP Award Recipient





of gene expression called the Prostate Expression Database (PEDB). This genetic resource capitalizes on the results of the Human Genome Project and uses advanced molecular biology and bioinformatics techniques and approaches to catalogue the thousands of genes that are expressed in prostate cells. In essence, this integrated database provides a blueprint of gene expression in normal prostate cells and can track changes in that blueprint that are associated with the transformation of normal cells to prostate cancer cells.

In addition to developing this resource, these investigators are focused on using it to identify differences that may occur in the androgen receptor pathway in prostate cells as normal cells transform into prostate cancer cells. Using the PEDB and associated techniques, they identified a novel prostate-specific gene that is related to androgen metabolism and that is highly expressed in primary and metastatic prostate carcinoma. The PEDB developed by the Fred Hutchinson group is rapidly becoming an important international genetic resource. It is being used by prostate cancer researchers worldwide to identify, study, and obtain prostate-associated molecules for detailed molecular, epidemiological, diagnostic, and therapeutic uses.

Increasing the Effects of Radiation through Gene Therapy. Alan Pollack, M.D., Ph.D., University of Texas M.D. Anderson Cancer Center: In treating patients with locally advanced high-risk prostate cancer, the combination of androgen ablation and external beam radiation therapy is more effective than either treatment alone. In this treatment combination, androgen ablation acts as a radiosensitizer, i.e., it makes androgen-responsive cancer cells more susceptible to the killing effects of radiation. Investigators at the University of Texas M.D. Anderson Cancer Center are examining ways to achieve radiosensitization while minimizing long-term side effects. The basis for their work is the knowledge that androgen ablation exerts its effect by increasing the rate of a specific type of cell death called apoptosis. These researchers hypothesized that manipulating proteins that govern whether a cell undergoes apoptosis after radiation should result in significant radiosensitization but without serious side effects. One of the key factors that controls apoptosis is the p53 protein which is produced by the p53 gene. These researchers succeeded in infecting prostate cancer cells with a genetically engineered virus into which they inserted the p53 gene. The infected prostate cancer cells showed increased p53 expression accompanied by a greatly enhanced radiosensitization and increased apoptosis. Experiments were also done in mice bearing tumors formed from injected human prostate cancer cells. These experiments showed that tumors injected with the p53-containing virus and exposed to radiation were more sensitive to radiation. This work demonstrates that gene therapy combined with radiation therapy holds great promise as a treatment regimen for patients with high-risk prostate cancer, and has served as a basis for a clinical trial which is now being developed.

Summary

Since 1997, the DOD PCRP has been responsible for managing \$310M in congressional appropriations, resulting in 439 awards directed toward eliminating prostate cancer. The diverse portfolio of funded research is already making important contributions to understanding, preventing, detecting, diagnosing, and treating prostate cancer.

FY01 Integration Panel Members

Chair, 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.

Chair-Elect, Ralph DeVere White, M.D.: Medical Director of the Cancer Center, and Professor and Chair of Urology, University of California, Davis.

Chair Emeritus, Andrew von Eschenbach, M.D.: Executive Vice-President and Chief Academic Officer; Director, Program Center – Genitourinary Cancers, Special Assistant for External Affairs; Roy M. & Phyllis Gough Huffington Chair in Urologic Oncology; Professor, Department of Urology and Consulting Professor of Cell Biology at The University of Texas, M.D. Anderson Cancer Center. President-Elect (2002) of the American Cancer Society.

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.

Thomas E. Carey, M.D.: Director, Laboratory of Head and Neck Cancer Biology, Department of Otolaryngology Laboratory, University of Michigan.



Encouraging Research on Prostate Cancer Disparity

The PCRP continues to address the disparity in prostate cancer incidence and mortality among ethnic groups. In FY98 through FY00, the PCRP offered MPFCTAs that allowed investigators to develop prostate cancer research strategies that focus on the ethnic disparities of prostate cancer incidence and mortality. Many of the 24 researchers funded by these mechanisms have used the information gathered from their grants to strengthen collaborations and secure further research funding to broaden the scope of their initial studies.

Additional opportunities were provided in FY01 to focus training and research efforts on the disparate burden of prostate cancer in African Americans. The Health Disparity Training – Prostate Scholar Awards and the Health Disparity Research – Prostate Scholar Awards were offered to give investigators in the very beginning of their research careers and young, established investigators the opportunity to focus on research in prostate cancer in the African American community. The HBCU Collaborative Partnership Awards seek to increase the number of HBCU scientists who are trained as prostate cancer researchers and clinicians. As with the Prostate Scholar Awards, the focus of HBCU Collaborative Partnership Awards is on the ethnic disparity in prostate cancer. ♦

Donald Coffey, Ph.D.: Catherine Iola and J. Smith Michael Distinguished Professor of Urology, Professor of Oncology, Professor of Pharmacology and Molecular Sciences, and Professor of Pathology, The Johns Hopkins School of Medicine. Director of Research Laboratories, Department of Urology.

Robert Dreicer, M.D.: Director, Urologic Oncology, Department Hematology and Oncology, The Cleveland Clinic Foundation.

Winston Dyer: Consumer; Member of the Board of Directors, CapCURE.

Richard Howe, Ph.D.: Consumer; Member of the Prostate Health Council. Advisory Board of Baylor's Specialized Programs of Research Excellence. Co-Chair, National Prostate Cancer Coalition's Medical/Scientific Committee.

Phillip Kantoff, M.D.: Director, Prostate Cancer Program at the Dana-Farber Harvard Cancer Center and Director, Lank Center for Genitourinary Oncology, Harvard University.

Monica Liebert, Ph.D.: Director, Office of Research, American Urological Association.

Ronald Morton, Jr., M.D.: Chief of Urology, Houston Veterans Affairs (VA) Medical Center. Director of Laboratories, Baylor Prostate Center, Baylor College of Medicine.

Gail S. Prins, Ph.D.: Professor of Physiology, Departments of Urology, Physiology, and Biophysics, University of Illinois at Chicago.

Mack Roach III, M.D.: Associate Professor, Radiation Oncology, Medical Oncology, and Urology, University of California, San Francisco.

William Schwartz: Consumer; President and CEO, FMB Enterprises. Chairman and CEO of the National Prostate Cancer Coalition.

Howard R. Soule, Ph.D.: Executive Vice-President and Chief Science Officer, CapCURE.

Nicholas Vogelzang, M.D.: Fred C. Buffet Professor of Medicine and Surgery (Urology), University of Chicago. Director, Genitourinary Program. Director, University of Chicago Cancer Research Center.

Frederic Waldman, M.D., Ph.D.: Professor, Department of Laboratory Medicine, University of California, San Francisco. Director, DNA Cytometry Service and Director, Molecular, Cytogenetics Core, University of California San Francisco Cancer Center.

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