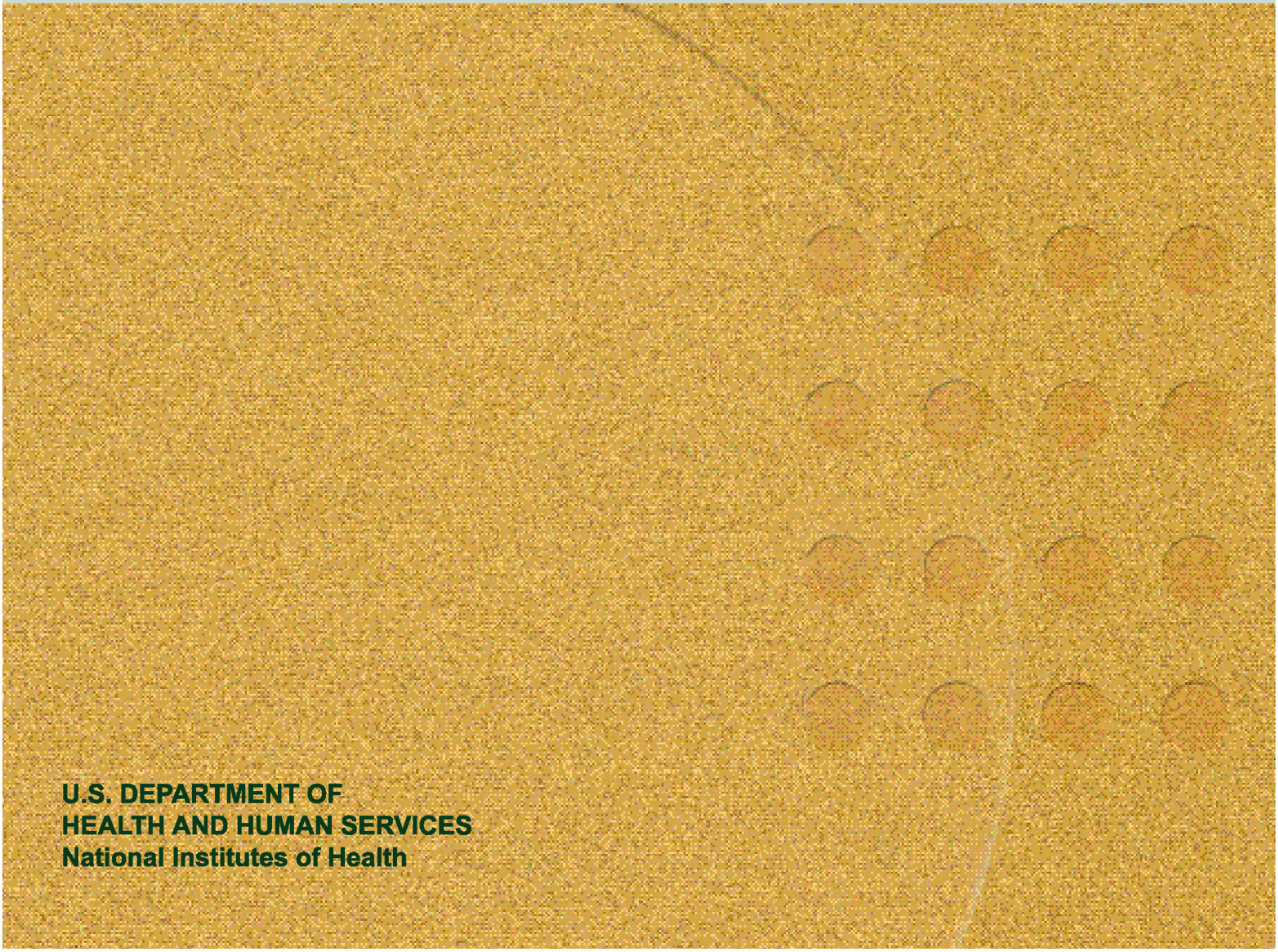
National Cancer Institute

Prostate Cancer Progress Report

Addressing the Recommendations of the Prostate Cancer Progress Review Group

June 2004



U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
National Institutes of Health

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Transmittal Letter From the Working Group

It is our pleasure to submit the *Prostate Cancer Progress Report* to the Director of the National Cancer Institute (NCI). It constitutes the first assessment of progress in addressing the research priorities identified in the 1998 report of the Prostate Cancer Progress Review Group (PRG), entitled *Defeating Prostate Cancer: Crucial Directions for Research*. This progress report characterizes trends in the NCI prostate cancer research portfolio from 1998 to 2002. It presents trends in measures of progress as broad as overall NCI funding levels and as specific as numbers of projects relevant to particular research priorities. In addition to a retrospective view of accomplishments since 1998, the progress report looks forward by providing a bridge to the future NCI efforts described in the *NIH Prostate Cancer Research Plan FY 2003–FY 2008*.

This report is designed to assist the Institute in efforts to accelerate progress against prostate cancer by assessing past research investments and identifying future research needs. It is a unique reference documenting NCI-supported prostate cancer research and the resources available to the prostate cancer research community. We believe that this report will enable readers to better understand the scope of the Institute's prostate cancer research portfolio and identify research and information resources. It will also help to guide implementation of the NCI plans described in the *NIH Prostate Cancer Research Plan FY 2003–FY 2008.*

Respectfully,

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Acknowledgments

The development of this progress report by the NCI Prostate Cancer Working Group would not have been possible without significant contributions from many other individuals. We would especially like to recognize the work of the following individuals and organizations.

- Kevin Callahan, Margaret Ames, and other staff of the NCI Office of Science Planning and Assessment (OSPA) made contributions in a wide variety of areas, including expertise on the PRGs, knowledge of NCI initiatives and programs, development of measures of progress, design of the process for mapping NCI-funded projects to PRG priorities, participation in working group meetings, and review of draft documents.
- Other NCI staff contributed essential data. Brenda Edwards and Lynn Ries of the Surveillance Epidemiology and End Results (SEER) program in the Division of Cancer Control and Population Sciences (DCCPS) provided expertise and data on trends in disease statistics. Lakshmi Grama of the Office of Cancer Information Products and Systems (CIPS) contributed expertise and data on clinical trials. Staff of the Financial Management Branch (FMB) provided information on prostate cancer research funding. Staff in the Division of Extramural Activities (DEA), the Center for Cancer Research (CCR), and the Division of Cancer Epidemiology and Genetics (DCEG) provided data on extramural and intramural NCI-sponsored research projects.
- The staff of Science Applications International Corporation (SAIC) contributed significant technical expertise and dedicated effort to the management, analysis, technical writing, and production of the report. SAIC's efforts were led by Catherine Hall, Sabina Robinson, and Jeff Zalatoris. Significant contributions were made by Eric Levine, Beth Mathews-Bradshaw, Karen Rulli, Maneesha Solanki, Nancy Volkers, Julie Jessup, Jennifer Secula, and their colleagues.
- The staff of the Constella Group, particularly Paul Nedzbala and Jeffrey Morris, assisted in assembling data on the NCI's prostate cancer research portfolio.

Executive Summary

Prostate cancer is the most common cancer (aside from nonmelanoma skin cancer) and the second leading cause of cancer-related death in men in the United States. In 2002, an estimated 189,000 men were diagnosed with, and 30,200 died from, this disease. African American men are more likely than other racial and ethnic populations both to develop and to die from prostate cancer. While recent trends of stabilizing incidence and decreasing mortality rates are encouraging, prostate cancer remains a major health burden for American men and requires continued action.

In 1997, the National Cancer Institute (NCI) convened the Prostate Cancer Progress Review Group (PRG), a multidisciplinary committee of scientists, clinicians, and advocates, to help NCI define a national research agenda for prostate cancer. The Prostate Cancer PRG issued a 1998 report entitled *Defeating Prostate Cancer: Crucial Directions for Research*, which included priority research questions that should be addressed to advance prevention, detection, diagnosis, and treatment of prostate cancer. An internal NCI Prostate Cancer Working Group was recently convened to assess the research progress made since the release of this report. Besides producing the *Prostate Cancer Progress Report*, this working group contributed to the *NIH Prostate Cancer Research Plan FY 2003–FY 2008*.

The NCI *Prostate Cancer Progress Report* documents trends in the NCI prostate cancer research portfolio from 1998 to 2002. Multiple measures of progress are presented at varying levels of specificity, ranging from overall trends in NCI funding, projects, and resulting peer-reviewed publications, to more specific trends in the number of projects relevant to particular research priorities identified by the PRG. Recognizing the evolutionary nature of research, this progress report also relates priority research questions identified by the PRG to the objectives of the more recently released *NIH Prostate Cancer Research Plan FY 2003–FY 2008*.

Between 1998 and 2002, the NCI substantially expanded investments in prostate cancer research as evidenced by:

- tripling of prostate cancer funding from $86.9 million in 1998 to $278.4 million in 2002,
- approximate doubling of the number of relevant projects,
- more than doubling relevant individual training and career development awards,
- expanding ongoing and initiating new programs to sustain and advance both basic and clinical prostate cancer research,
- expanding the prostate Specialized Programs of Research Excellence (SPOREs) network from 3 to 11 sites, and
- expanding collaborative efforts and shared resources to improve the capacity to conduct prostate cancer clinical trials.

Work is under way to translate the discoveries generated by this expanded investment into new prostate cancer prevention, detection, diagnosis, and treatment interventions that will save lives. The following two pages summarize the NCI's investment by research category.

NCI's ability to capitalize on advances in prostate cancer research and care will require continued basic, translational, and clinical research support. This progress report, which documents the NCI's responses to the recommendations of the Prostate Cancer PRG, will help guide efficient and effective implementation of the NCI plans described in the *NIH Prostate Cancer Research Plan FY 2003–FY 2008*.

NCI's Prostate Cancer Research Investment
Increased from $86.9 Million in 1998 to $278.4 Million in 2002

Biology

- Funding increased from $15.2M to $41.7M.
- Number of projects increased from 160 to 302.
- New initiatives included Age-Related Prostate Growth, Role of Hormones and Growth Factors in Prostate Cancer, and Molecular and Cellular Biology of Metastatic Tumor Cells.

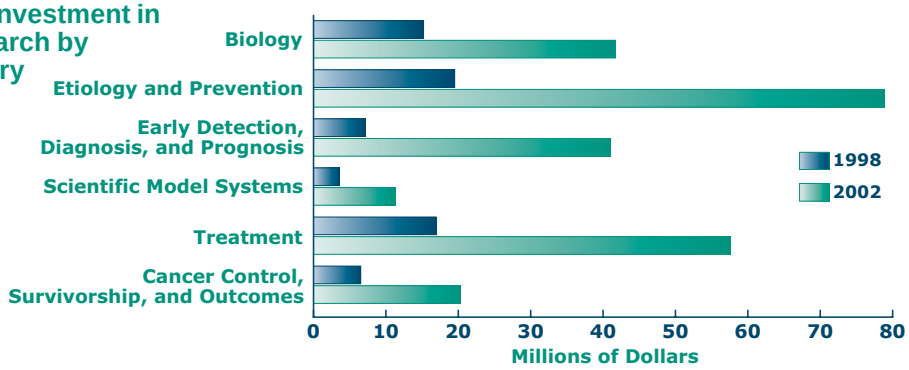
Etiology and Prevention

- Funding increased from $19.5M to $78.9M.
- Number of projects increased from 112 to 203.
- Ongoing clinical trials include the SELECT trial.
- New initiatives included NCI Cohort Consortium, RAPID, and the Small Grants Program for Cancer Epidemiology.

Early Detection, Diagnosis, and Prognosis

- Funding increased from $7.1M to $41.0M.
- Number of projects increased from 58 to 140.
- New initiatives included Clinical Proteomics Program, Director's Challenge, Early Detection Research Network, and Exploratory/Developmental Grants for Diagnostic Cancer Imaging.

Growth of NCI's Investment in Extramural Research by Scientific Category



Scientific Model Systems

- Funding increased from $3.6M to $11.3M.
- Number of projects increased from 40 to 99.
- New initiatives included Mouse Models of Human Cancers Consortium, Cancer Therapy-Related Use of Genetically Engineered Mice, and Competing Supplements for Organotypic Models of Cancer.

Treatment

- Funding increased from $16.9M to $57.6M.
- Number of projects increased from 143 to 277.
- Ongoing clinical trials include the PIVOT study and the Phase III Study of Docetaxel and Estramustine versus Mitoxantrone and Prednisone (SWOG 9916).
- New initiatives included Quick-Trials for Novel Cancer Therapies, Program for Assessment of Clinical Cancer Tests, and National Cooperative Drug Discovery Groups.

Cancer Control, Survivorship, and Outcomes

- Funding increased from $6.5M to $20.3M.
- Number of projects increased from 24 to 48.
- Ongoing clinical trials include the PLCO and PCOS studies.
- New initiatives included Special Populations Networks, Cancer Research Network, Cancer Interventions and Surveillance Modeling Network, Health Communications in Cancer Control, and Cancer Outcomes Measurement Working Group.

Examples of Progress

Resulting from NCI's Prostate Cancer Research Investment

Biology

- Recent advances include identifying molecular mechanisms of cancer initiation, progression, and metastasis; new models of the development of androgen-independent cancers; and growth factor contributions to cancer progression.
- Future investment is needed in new technologies (e.g., proteomics and bioinformatics) and new model systems to advance the study of molecular mechanisms of normal prostate development and cancer progression and the role of tumor microenvironment and macroenvironment.

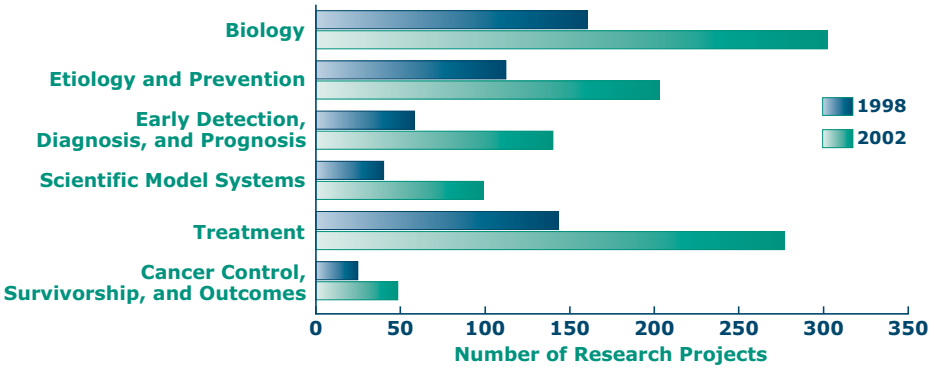
Etiology and Prevention

- Recent advances include finasteride as a chemopreventive agent, diet/nutrient intake and reducing cancer risk, gene–environment associations, and identification of biological factors of cancer.
- Future investment is needed in rapidly initiating and completing prevention trials, refining etiological components of cancer, and validating lifestyle and chemical preventive measures.

Early Detection, Diagnosis, and Prognosis

- Recent advances include biomarker identification, imaging device enhancement, and molecular profiling analyses.
- Future investment is needed in validating and including new biomarkers in trials, further enhancement of noninvasive devices, and better characterization of tumors for predicting clinical behavior.

Growth of NCI's Relevant Prostate Cancer Research by Scientific Category



Scientific Model Systems

- Recent advances include use of the TRAMP mouse model and variants, xenograft mouse models, and metastatic mouse models using gene knockouts.
- Future investment is needed in models covering the natural progression of prostate cancer and evaluating the similarities and differences between models and human disease.

Treatment

- Recent advances in clinical care include hormone therapy as adjuvant with external beam radiation therapy, interstitial brachytherapy for selected patients with localized disease, and zoledronic acid for prevention and treatment of bone metastatic disease.
- Recent advances in research include new chemotherapeutics development and evaluation and surrogate biomarkers in clinical trials.
- Future investment is needed in enhanced capacity in the clinical trials infrastructure, enhanced translational research, and identification and validation of new targets and new interventions.

Cancer Control, Survivorship, and Outcomes

- Recent advances include identifying causes of racial disparities, understanding patient-focused outcomes, and treatment-related complications.
- Future investment is needed in quality-of-life assessments, enhanced surveillance, evaluation of screening and treatment intervention outcomes, biobehavioral research, and dissemination practices.

CHAPTER 1

Prostate Cancer Research: 1998–2002

With an estimated 189,000 new prostate cancer diagnoses and 30,200 prostate cancer deaths in 2002,[1] prostate cancer is a disease that affects many American men and their families. In April 1997, the National Cancer Institute (NCI) convened a multidisciplinary committee of scientists, clinicians, and advocates to review the field of prostate cancer research and make prioritized recommendations concerning the most needed and promising directions for future NCI investment. In August 1998, the Prostate Cancer Progress Review Group (PRG) issued its report *Defeating Prostate Cancer: Crucial Directions for Research*.

In 2001, the NCI established an internal Prostate Cancer Working Group to assist in planning, monitoring, and tracking of progress. This report includes the Prostate Cancer Working Group's findings regarding the NCI's responsiveness to the PRG recommendations, over the years 1998 through 2002.

Since the Prostate Cancer PRG issued its report, the NCI has increased its investment in research relevant to prostate cancer in terms of dollars spent and the number of projects supported. In addition, the monitoring of basic and clinical NCI-supported research has been improved. Numerous resources and programs have been sustained, expanded, and/or developed. Peer-reviewed publications resulting from NCI-sponsored efforts show that much progress has been made in some of the specific topic areas identified as promising by the PRG. Further demonstration of progress can be found in prostate cancer-related patents that have been issued and changes in clinical practice that have been adopted.

We believe that this was, indeed, an opportune time to reassess the Institute's prostate cancer research portfolio and plan a research agenda for prostate cancer that will guide the prostate cancer research field into the next decade.

– Defeating Prostate Cancer: Crucial Directions for Research - Report of the Prostate Cancer Progress Review Group, August 1998.

The Prostate Cancer Burden

Prostate cancer is the most common non-skin cancer in men and second-most common cause of cancer-related death in U.S. men.[2] As shown in Figures 1-1 and 1-2, respectively, prostate cancer diagnosis and death rates increased between 1973 and the early 1990s.[3] Incidence rates, in particular, rose rapidly from the mid-1980s to the early 1990s, following the introduction of prostate-specific antigen (PSA) screening. (See also Figure 5-1, Chapter 5.)

[1] NCI's Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review, 1975–2001.

[2] See Note 1.

[3] The first year in which both incidence and mortality data were collected by the NCI's SEER program for all races, whites, and blacks was 1973. Beginning in the early 1990s, the collected data were expanded to include additional racial/ethnic groups. The most recent year for which analyzed SEER data are available is 2001.

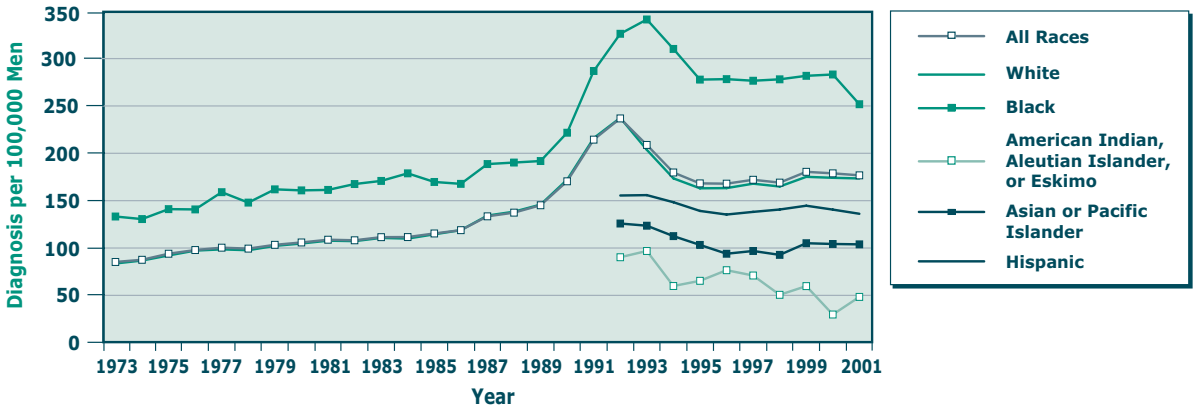


Figure 1-1. Prostate cancer incidence in the United States.

Data derived from NCI's SEER program.

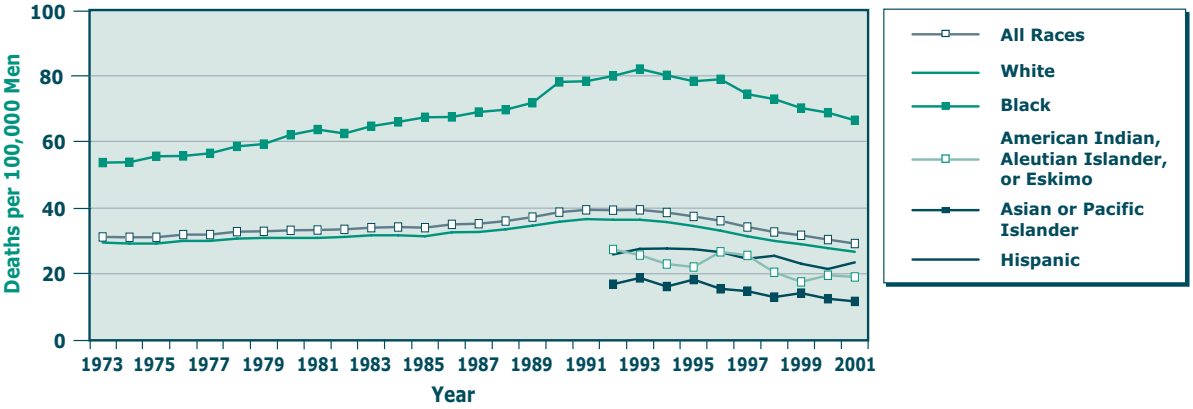


Figure 1-2. Prostate cancer mortality in the United States.

Data derived from NCI's SEER program.

Both incidence and mortality rates began to decrease in the early 1990s. In 2001,[4] the overall incidence rate was similar to the rate in 1990 and the overall mortality rate was nearly the same as that in 1973. Blacks are particularly vulnerable to prostate cancer, with diagnosis and death rates that are considerably higher than those of other racial groups and the overall U.S. population. The 2001 prostate cancer mortality rate for Black men was more than twice that for the overall population.

In addition to premature death, pain, and debilitation, there is a large economic toll associated with prostate cancer. It is estimated that around $4.6 billion is spent in the United States each year on treatment of the disease.[5] There is also the burden of lost productivity and wages.

[4] See Note 1.

[5] In 1996 dollars, as determined by Brown, Riley, Schussler, and Etzioni and reported in the NCI's Cancer Progress Report - 2003 Update.

The Prostate Cancer Progress Review Group

In 1997, the NCI formed two pilot PRGs to help sharpen its focus on research directed at specific cancer sites. The Prostate Cancer PRG was the first PRG to be convened. Consisting of 22 nationally prominent members from academia, industry, nonprofit organizations, and government, with complementary backgrounds in basic, translational, and clinical research and in prostate cancer advocacy issues, the group met periodically from April 1997 to May 1998.

The objectives of the Prostate Cancer PRG were to review the state of the art, receive stakeholder input, assess the existing NCI prostate cancer research portfolio, prioritize key scientific questions, and develop recommendations for action. To ensure that the PRG's understanding of the state of the art in prostate cancer research was both accurate and complete, more than 100 additional scientists, clinicians, and advocates, from throughout the world, participated in a roundtable meeting and in expert panels that addressed the topics of clinical trial design and implementation, prognostic marker validation, radiobiology, screening and early detection, gene technology and gene identification, gene therapy and vaccines, and molecular epidemiology.

In August 1998, the Prostate Cancer PRG published its report, *Defeating Prostate Cancer: Crucial Directions for Research*, which addressed the following eight categories of prostate cancer research:

- Biology, Progression, and Metastasis
- Etiology and Primary Prevention
- Early Detection, Diagnosis, and Prognosis
- Laboratory and Clinical Models
- Staging and Treatment of Localized Prostate Cancer
- Systemic Therapy
- Outcomes Research
- Resources Needed

For each research category, the report includes a synopsis of current status, a statement of the PRG's vision, a discussion of identified challenges and opportunities, and research priorities that are presented in the form of prioritized research questions accompanied by recommended actions.[6]

Five Years of Progress

To implement the PRG's vision for progress, the NCI began to increase its investment in prostate cancer-relevant research and document the progress made in the field. The number of investigator-initiated research projects relevant to prostate cancer increased and specific research initiatives were expanded or implemented. Subsequent to the Prostate Cancer PRG's work, the NCI began tracking its expanding prostate cancer research portfolio according to the Common Scientific Outline (CSO), a research categorization scheme adopted by multiple federal and nonfederal agencies, that is

[6] The Prostate Cancer PRG report identified 156 investigative questions: 48 Priority One (i.e., highest priority), 63 Priority Two, and 45 Priority Three. Accompanying the 48 Priority One investigative questions were 119 recommended actions. The PRG defined Priority One questions as those that addressed critical areas of research that were ready for immediate implementation and/or responded to a recent development or breakthrough. In contrast, the Priority Two questions addressed areas that were less critical or promising, and the Priority Three questions addressed areas that were already being examined or not yet ready for implementation. Although the PRG report included 48 Priority One questions, some had overlapping content. For reporting purposes, the NCI has combined one of the questions with another closely related question (addressed in Chapter 6) and has dropped a second question, which was included, in its entirety, as part of another question (addressed in Chapter 7).

similar, but not identical, to the one used by the Prostate Cancer PRG.[7] The sections that follow provide an overview of:

- The NCI's investment in prostate cancer research, in terms of dollars invested, research projects supported, clinical trials supported, initiatives undertaken, resources developed and maintained, and programs established and expanded
- The return on NCI's investment, in terms of research results obtained and applied

Investment in Prostate Cancer Research

Dollars Invested

NCI's commitment to addressing the identified challenges and opportunities in prostate cancer research is demonstrated by growing investments in relevant activities. Figure 1-3 shows dollar estimates for NCI prostate cancer spending from fiscal year (FY) 1998 through FY 2002. Over the 5-year period, NCI's overall prostate cancer investment increased more than threefold.

The majority of funds devoted to prostate cancer research supported extramural research. Figure 1-4 shows the NCI's dollar investment for prostate cancer-relevant research during FY 1998–2002, with the extramural component, but not the intramural support and contracts component, broken down according to the CSO categorization scheme.

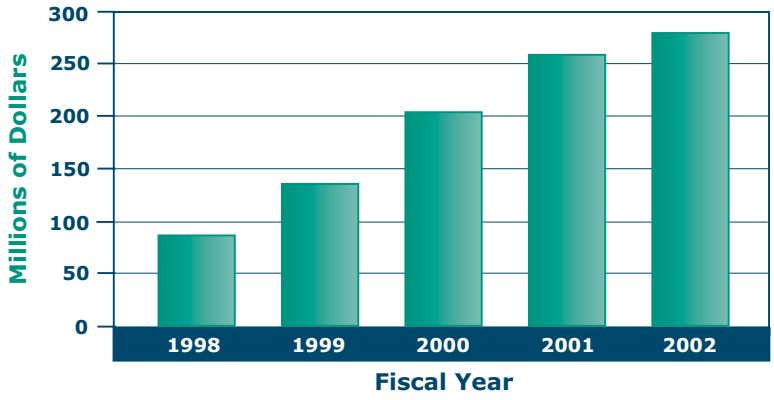


Figure 1-3. Estimate of total NCI dollars for prostate cancer-relevant research.

Values include NCI's total intramural and extramural support for prostate cancer research as reported by the Financial Management Branch of the NCI's Office of Budget and Financial Management (NCI FactBook).

[7] Although the seven research categories of the CSO are similar to the eight categories of the Prostate Cancer PRG report, notable differences include the CSO's separate categories for etiology and prevention, a single treatment category that does not include staging, and division of resources among the other categories. The CSO is described in full at http://researchportfolio.cancer.gov/cso.html.

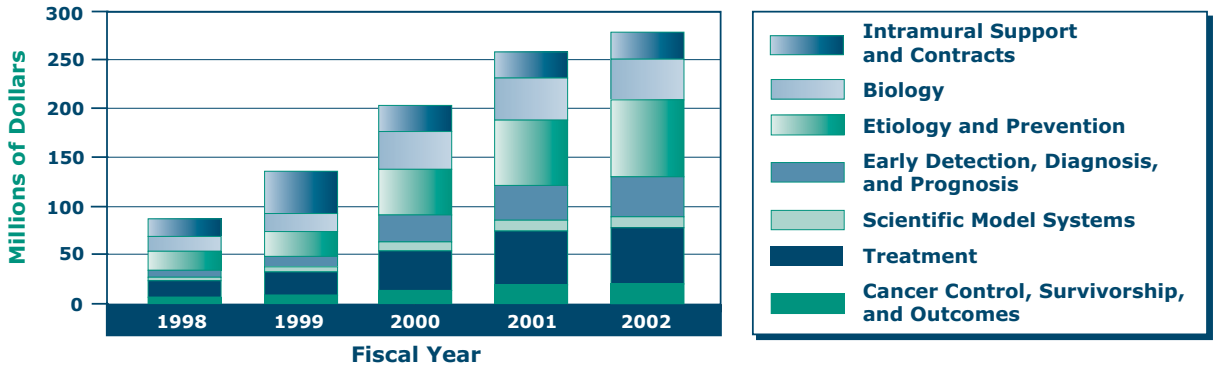


Figure 1-4. Dollar estimates for prostate cancer-relevant research by type of research.

To derive the values, dollars associated with each funded project were first prorated by estimated prostate cancer relevance, and this portion was then equally distributed among applicable CSO research categories. Dollars directed at resources are included in the values for the research categories.

Research Projects Supported

Between 1998 and 2002, there was a large increase in the number of NCI-sponsored research projects relevant to prostate cancer. Figure 1-5 shows the number of projects with high prostate cancer relevance[8] (i.e., 25% or greater) that were funded by the NCI each year, during FY 1998–2002. Even using these conservative estimates of prostate cancer-relevant projects, there was a substantial increase (85%) in the number of projects. Numbers of funded prostate cancer projects within each research category are shown in Figure 1-6. Details concerning the NCI-sponsored research projects in each category can be found in Chapters 3 through 8 and Appendix B[9] of this report.

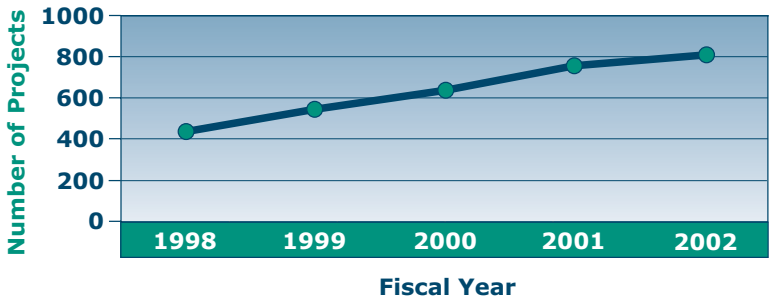


Figure 1-5. Number of research projects relevant to prostate cancer.

Included in the graph are solicited and unsolicited projects and individual training and career development awards, both new and continuing, with prostate cancer relevance values of 25 percent or more. (Solicited projects are those submitted in response to NCI initiatives in targeted topic areas; unsolicited projects are investigator-initiated submissions received by the NCI.)

[8] Quantitative estimates of cancer-site relevance are made by NCI staff based on the proportion of a project considered relevant to particular disease sites. NCI uses relevance values for calculating prorated disease-specific dollar estimates (as in Figure 1-3) and for project tracking.

[9] Appendix B identifies the FY 2002 research projects that were responsive to the Priority One questions of the PRG.

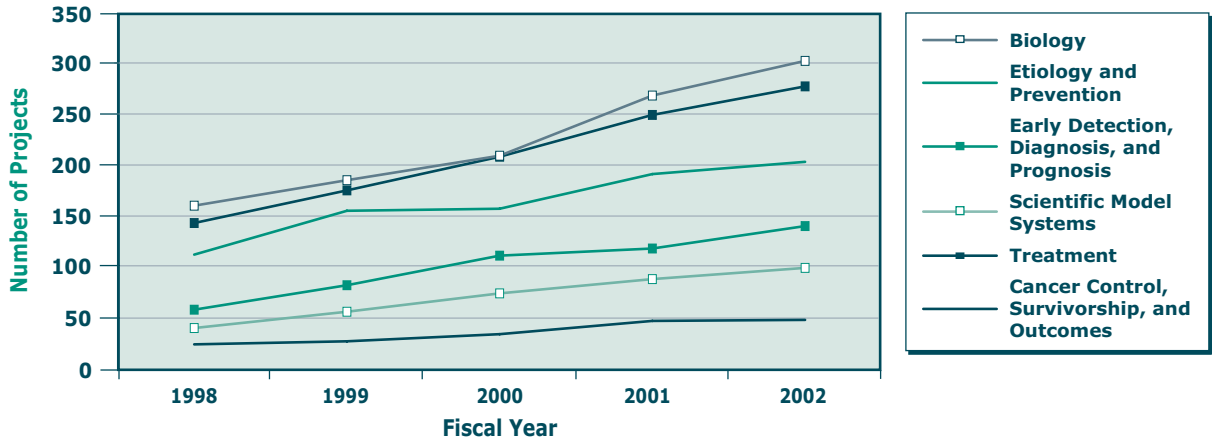


Figure 1-6. Number of prostate cancer-relevant projects addressing each research category.

Each project with 25 percent or greater relevance to prostate cancer was counted once for each category to which it applied. (Category assignment was based on the results of mapping projects to the PRG's Priority One questions and not on original CSO assignments. Projects assigned to more than one research category are included in the data for all appropriate categories.)

Clinical Trials Supported

Between 1998 and 2002, the number of active NCI-sponsored clinical trials relevant to prostate cancer increased. Figure 1-7 shows the increase in the overall number of NCI-sponsored[10] clinical trials relevant to prostate cancer that were active during the calendar years 1998 to 2002. These clinical trials represent research on treatment, prevention, genetics, diagnostics, and supportive care.

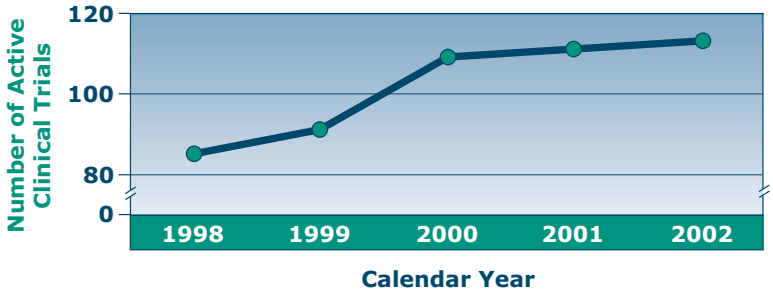


Figure 1-7. Number of NCI–sponsored prostate cancer clinical trials active during calendar years 1998–2002.

These data indicate overall numbers of prostate cancer clinical trials. (Information in the figure is based on a search conducted by staff of the Office of Cancer Information Products and Systems, Office of Communications [in its PDQ Clinical Trials Database] for NCI-sponsored prostate cancer treatment trials active at some time during the timeframe 1998 to 2002. More detailed Information about specific trials is available on NCI's Cancer.gov website at http://www.cancer.gov/clinical_trials.)

[10] An NCI-sponsored clinical trial in Physician Data Query (PDQ) (1) has been reviewed and approved by NCI's CTEP Protocol Review Committee or by an approved NCI-designated Cancer Center Protocol Review and Monitoring System and/or (2) receives support through an NCI grant or cooperative agreement.

Initiatives Undertaken

Between FY 1998 and FY 2002, numerous NCI initiatives stimulated work on the research priorities identified by the Prostate Cancer PRG. The initiatives increased the depth and breadth of the NCI's research on prostate cancer by:

- Encouraging submission of applications for research projects, which are wholly or partially focused on prostate cancer, in targeted topic areas
- Developing and maintaining resources for use by prostate cancer researchers
- Establishing and expanding programs in which research and resources are combined in collaborative pursuit of a common goal

Table 1-1 lists the NCI initiatives that impacted prostate cancer research in FY 1998 through 2002[11] and the chapter of this report in which more detail is provided on the initiative.

Table 1-1. NCI Initiatives Relevant to Prostate Cancer Research: 1998–2002

INITIATIVES FOCUSED ON PROSTATE CANCER
Chapter 2 - General Initiatives
Cooperative Prostate Cancer Tissue Resource (CPCTR) http://www.prostatetissues.org (begun in FY 1999)
Diagnostic Imaging and Guided Therapy in Prostate Cancer CA-99-015 and PAR-99-149 (begun in FY 1999)
Molecular Epidemiology of Prostate Carcinogenesis PA-00-080 (continued in FY 1999 and FY 2000)
Prostate Cancer Intervention Versus Observation Trial (PIVOT) http://www.va.gov/PIVOT/ (ongoing)
Prostate, Lung, Colorectal & Ovarian Cancer Screening Trial (PLCO) http://www3.cancer.gov/prevention/plco/index.html (ongoing)
Prostate Specialized Programs of Research Excellence (SPOREs) http://spores.nci.nih.gov/prostate/prostate.html (expanded in 1999 and 2001)
Chapter 3 - Biology
Age-Related Prostate Growth: Biologic Mechanisms PA-02-116 (begun in FY 2002)
Biology, Development, and Progression of Malignant Prostate Disease PA-99-081 (begun in FY 1999)
Development of Cell-Selective Tools for Studies of the Bladder, Prostate, and Genitourinary Tract PAR-02-143 (begun in FY 2002)
Role of Hormones and Growth Factors in Prostate Cancer RFA-DK-01-008 (begun in 2001)

[11] Initiatives selected for inclusion are those that were begun or continued during FY 1998–2002 that resulted in programs, resources, or research projects relevant to prostate cancer. Also selected for inclusion are NCI intramural initiatives that have a readily identifiable component that is specific to prostate cancer.

Table 1-1. (cont.)

Chapter 4 - Etiology and Prevention
Prostate Cancer Prevention Trial http://www.cancer.gov/pcpt (ongoing)
SELECT Prostate Cancer Prevention Trial http://www.cancer.gov/select (ongoing)
Chapter 7 - Treatment
Quick-Trials for Prostate Cancer Therapy PA-00-047 (begun in FY 1999; replaced by expanded Quick-Trials for Novel Cancer Therapies program in FY 2000)
Chapter 8 - Cancer Control, Survivorship, and Outcomes
Prostate Cancer Outcomes Study (PCOS) http://healthservices.cancer.gov/pcos (ongoing)
INITIATIVES WITH PROSTATE CANCER-RELEVANT COMPONENTS
Chapter 2 - General Initiatives
Applications of Innovative Technologies for the Molecular Analysis of Cancer PAR-01-107 and PAR-01-106 (begun in FY 1999, continued in FY 2001)
Cancer Centers Program http://www3.cancer.gov/cancercenters (ongoing)
Cancer Genome Anatomy Project (CGAP) http://cgap.nci.nih.gov (ongoing)
Cancer Imaging Program (CIP) http://www3.cancer.gov/dip
Cancer Molecular Analysis Project (CMAP) http://cmap.nci.nih.gov (ongoing)
Cancer Prognosis and Prediction PAR-01-062 (begun in FY 2001)
Cancer Research Training, Career Development, and Education Opportunities http://cancertraining.nci.nih.gov (ongoing)
Cancer Therapy-Related Use of Genetically Engineered Mice PAR-02-051 (begun in FY 2002)
Clinical Trials Cooperative Group Program http://ctep.cancer.gov/resources/coop2.html (continued in 1999)
Common Data Elements (CDE) Initiative http://ncicb.nci.nih.gov/CDEBrowser
Community Clinical Oncology Program (CCOP) http://www3.cancer.gov/prevention/ccop (continued in FY 2002)
Cooperative Human Tissue Network (CHTN) http://www-chtn.ims.nci.nih.gov (ongoing)
Director's Challenge: Toward a Molecular Classification of Cancer http://dc.nci.nih.gov (begun in FY 1998)

Table 1-1. (cont.)

Exploratory Grants for Correlative Laboratory Studies and Clinical Trials PA-98-042 (begun in FY 1998)
Flexible System to Advance Innovative Research for Cancer Drug Discovery by Small Businesses (FLAIR) http://dtp.nci.nih.gov/branches/gcob/gcob_web17.html (begun in FY 1998, continued in FY 2000)
Genitourinary Cancers Faculty (http://ccr.cancer.gov/faculties/faculty.asp?facid=131)
Improving DNA, RNA, and Protein Availability in Fixed Tissue PAR-00-079 (begun in FY 2000)
Interdisciplinary Research Teams for Molecular Target Assessment RFA-CA-00-001 (begun in FY 2000)
In Vivo Cellular and Molecular Imaging Centers (ICMICs) http://www3.cancer.gov/bip/ICMICs.htm (begun in FY 1999)
Minority Institution/Cancer Center Partnership (MI/CCP) Program http://minorityopportunities.nci.nih.gov/institutions/faqs.html (begun in FY 2001, continued in FY 2002)
Minority-Based Community Clinical Oncology Program (MBCCOP) http://www3.cancer.gov/prevention/ccop/mbccop.html (begun in FY 2002)
Molecular Profiling Initiative (MPI) http://cgap-mf.nih.gov/ProstateExample/index.html (ongoing)
Molecular Target Drug Discovery for Cancer PAR-01-045 and PAR-01-046 (begun in FY 2000)
NCI Center for Bioinformatics (NCICB) http://ncicb.nci.nih.gov
Program for Assessment of Clinical Cancer Tests (PACCT) http://www.cancerdiagnosis.nci.nih.gov/assessment
Shared Resources for Scientists outside NCI Cancer Centers PAR-99-127 (begun in FY 1999)
Small Animal Imaging Resource Program (SAIRP) RFA-CA-01-012 (begun in FY 1998)
Special Populations Networks (SPNs) http://crchd.nci.nih.gov/spn/index.html (begun in FY 1999)
Specimen Resource Locator http://pluto3.nci.nih.gov/tissue/default.htm (ongoing)
Technologies for Comprehensive, Sensitive, and Quantitative Protein Analysis in Human Tumors: Phased Innovation RFA-CA-01-011 (begun in FY 2001)
Chapter 3 - Biology
Molecular and Cellular Biology of Metastatic Tumor Cells PA-01-020 (begun in FY 2001)
Chapter 4 - Etiology and Prevention
Cancer Genetics Network (CGN) http://epi.grants.cancer.gov/CGN (ongoing)

Table 1-1. (cont.)

Cancer Prevention Research Small Grant Program PAR-00-025 (continued in FY 2000)
Chemoprevention in Genetically Identified High-Risk Groups: Interactive Research and Development Projects RFA-CA-98-012 (begun in FY 1998)
NCI Cohort Consortium http://cancercontrol.cancer.gov/bb/cohort_conso.html (begun in FY 2000)
Rapid Access to Preventive Intervention Development (RAPID) Program http://www3.cancer.gov/prevention/rapid/index.html (begun in FY 2000)
Small Grants Program for Cancer Epidemiology http://epi.grants.cancer.gov/ResPort/grants.html (begun in FY 1998, continued in FY 2001)
Chapter 5 - Early Detection, Diagnosis, and Prognosis
Clinical Proteomics Program http://ncifdaproteomics.com/index.php (begun in FY 1999)
Development of Clinical Imaging Drugs and Enhancers (DCIDE) http://www3.cancer.gov/bip/dcide.htm
Development of Novel Technologies for In Vivo Imaging PAR-01-101 and PAR-01-102 (FY 2001 continuation of Development of Novel Imaging Technologies)
Early Detection Research Network (EDRN) http://www3.cancer.gov/prevention/cbrg/edrn (begun in FY 1998)
Exploratory Studies in Cancer Detection, Prognosis, and Prediction PA-01-010 (begun in FY 2001)
Exploratory Studies in Cancer Diagnostics PA-98-022 (begun in FY 1998)
Exploratory/Developmental Grants for Diagnostic Cancer Imaging PA-01-030 (begun in FY 1998)
Gene Expression Data Portal (GEDP) http://gedp.nci.nih.gov/dc/index.jsp (ongoing)
Innovative Technologies for the Molecular Analysis of Cancer PAR-01-105 and PAR-01-104 (begun in FY 1998, continued in FY 1999 and FY 2001)
Tissue Array Resource Program (TARP) http://ccr.cancer.gov/tech_initiatives/tarp (ongoing)
Chapter 6 - Scientific Model Systems
Competing Supplements for Organotypic Models of Cancer PAR-02-052 (begun in FY 2002)
Mouse Models of Human Cancers Consortium (MMHCC) http://emice.nci.nih.gov (begun in FY 1998)
Chapter 7 - Treatment
Cancer Drug Discovery: Diversity Generation and Smart Assays RFA-CA-98-009 (begun in FY 1998)
Cancer Trials Support Unit http://www.ctsu.org (ongoing)

Table 1-1. (cont.)

Clinical Cancer Therapy Research PA-02-002 (continued in FY 1999)
Development and Application of Imaging in Therapeutic Studies RFA-CA-98-024 (begun in FY 1998)
Expanded Participation Project (EPP) http://spitfire.emmes.com/study/epp (ongoing)
National Cooperative Drug Discovery Groups (NCDDGs) http://dtp.nci.nih.gov/brances/gcob/gcob_web3.html (continued in FY1999)
Quick-Trials for Novel Cancer Therapies PA-00-047 (FY 2000 expansion of the Quick-Trials for Novel Cancer Therapies Program begun in FY 1999)
Rapid Access to Intervention Development (RAID) Program http://dtp.nci.nih.gov/docs/raid/raid_index.html (ongoing)
Therapeutic Modulation of Angiogenesis in Disease PAR-98-096 (begun in FY 1998)
Translational Research Initiative http://ctep.cancer.gov/resources/trf-overview.html
Chapter 8 - Cancer Control, Survivorship, and Outcomes
Cancer Intervention and Surveillance Modeling Network (CISNET) http://cisnet.cancer.gov/about (begun in FY 1999, continued in FY 2002)
Cancer Outcomes Measurement Working Group (COMWG) http://outcomes.cancer.gov/methods/measures/comwg (begun in FY 2001)
Cancer Research Network (CRN) http://cancercontrol.cancer.gov/bb/can_research.html (begun in FY 1998)
Cancer Surveillance Using Health Claims-Based Data System http://dccps.nci.nih.gov/ARP/research/health.asp (continued in FY 1999)
Economic Studies in Cancer Prevention, Screening, and Care http://cancercontrol.cancer.gov/ARP/research/economic.asp (begun in FY 1999, continued in FY 2002)
Exploratory Grants for Behavioral Research in Cancer Control PA-99-163 (begun in FY 1999)
Minority and Underserved Cancer Survivors http://cancercontrol.cancer.gov/ocs/underserved (FY 2001)
SEER–Medicare Linked Database http://healthservices.cancer.gov/seermedicare (ongoing)
SEER Patterns of Care/Quality of Care (POC/QOC) Initiative http://cancercontrol.cancer.gov/bb/seer_pattern.html (expanded in FY 2001)
Small Grants Program for Behavioral Research in Cancer Control http://dccps.nci.nih.gov/smallgrants/index.html (continued in FY 1999)
Surveillance, Epidemiology, and End Results (SEER) http://seer.cancer.gov (expanded in FY 2001)

Resources Developed or Maintained

NCI initiatives have led to increased availability of products, knowledge, services, facilities, and personnel that are critical for advancing prostate cancer research. NCI-funded resources that benefit prostate cancer research include the following:

- Repositories for accessing biological specimens and associated clinical data from patients with prostate cancer and men at risk of developing the disease
- Databases for accessing information that derives from multiple sources
- Animal models that mimic the development and/or progression of prostate cancer
- Forums for communicating research results and stimulating discussion and collaboration among investigators
- Training programs for improving the skills and advancing the careers of young, mid-career, and minority investigators
- Tools for assisting investigators in locating the resources that they require

Examples of NCI initiatives that support development or maintenance of important resources include:

- Cancer Research Training, Career Development, and Education Opportunities
- Cooperative Prostate Cancer Tissue Resource (CPCTR)
- Gene Expression Data Portal (GEDP)
- Mouse Models of Human Cancers Consortium (MMHCC) (which includes a Prostate Cancer Committee)

Most notable among the resulting resources that advance prostate cancer research are the investigators who develop through the Cancer Research Training, Career Development, and Education Opportunities. Through grants awarded to individuals or institutions, the NCI continues to enhance the cadre of prostate cancer investigators.

Programs Established or Expanded

NCI initiatives have established or expanded consortia, collaborative groups, networks, partnerships, and other organized entities that advance prostate cancer research. The programs support the following:

- Rapid development of new technologies
- Conduct of large, multi-institutional clinical trials
- Access to specialized patient populations
- Access to specialized equipment and expertise

Examples of NCI initiatives leading to new or expanded programs include:

- Clinical Trials Cooperative Group Program
- Early Detection Research Network (EDRN) (which includes a Prostate and Other Urologic Cancers Collaborative Group)
- Minority Institution/Cancer Center Partnership (MI/CCP) Program
- Prostate Specialized Programs of Research Excellence (SPOREs)
- Rapid Access to Intervention Development (RAID) Program

Most notable among the NCI-sponsored programs that advance prostate cancer research are the Prostate Specialized Programs of Research Excellence (SPOREs). Individually, and in combination, the Prostate SPOREs provide a comprehensive mix of translational research projects,[12] core resources, and training opportunities. Begun as an experiment in 1992, with a special appropriation from Congress that funded 9 SPOREs for 3 different cancer sites, there are now 49 SPOREs for 14 cancer sites, with 7 additional SPOREs being planned. The NCI's Prostate SPORE Program has grown from 2 SPOREs in 1992 to 11 at the end of 2002; 8 new Prostate SPOREs have been funded since the Prostate Cancer PRG first met.

Research Results Obtained and Applied

Research Results Obtained

The NCI's increased investment in prostate cancer research has increased the rate at which research results are being obtained. Figure 1-8 shows the estimated number of peer-reviewed publications indicating NCI support and relevance to prostate cancer, during calendar years 1998 through 2002. The values in Figure 1-8 should be considered conservative estimates.[13] Among the peer-reviewed publications resulting from NCI-sponsored efforts (1998–2002), 367 derived from the 11 Prostate SPOREs.

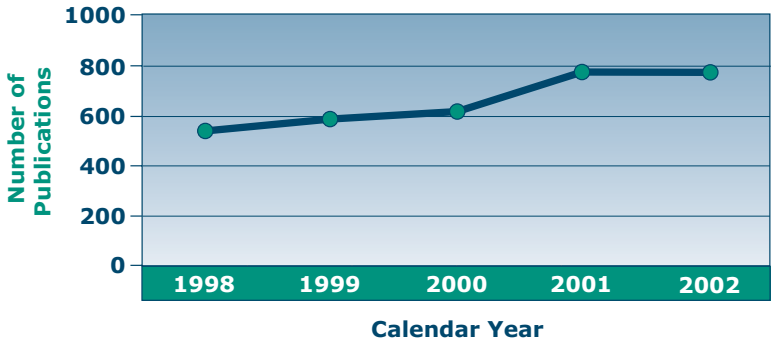


Figure 1-8. Estimated number of peer-reviewed publications on prostate cancer acknowledging NCI support.

Values are the total unique publications identified from MEDLINE and ISI / Web of Science searches. (Both databases were queried using criteria such as (1) terms related to "prostate," (2) presence of an NCI grant number or author address, and (3) limiting to English-language publications in peer-reviewed journals. Both intramural and extramural NCI projects are represented.)

Table 1-2 lists some of the important areas of ongoing NCI-sponsored research that are represented in recent publications. The table also includes the report chapter in which progress in these areas has been highlighted.

[12] Translational research aims to move findings from the basic laboratory into the clinical setting.

[13] Given such factors as less than complete support acknowledgments by authors, inclusion of only the corresponding author's affiliation in MEDLINE, possible typographic errors in reporting grant numbers, possible data entry errors, and journal policies on support acknowledgments, the publication counts reported in Figure 1-8 are no doubt underestimates.

Table 1-2. Recent Progress in Prostate Cancer Research

Areas of Progress	Details
Biology ◆ Early Prostate Cancer - Genetic alterations - Glutathione-s-transferase-1 (GSTP1) gene hypermethylation ◆ Development of hormone-refractory tumors - Androgen receptor (AR) amplification or mutation - AR coactivator overexpression - Other potential pathways ◆ Progression, metastasis, and the role of tumor microenvironment - Transforming growth factor (TGF)-beta - Hepatocyte growth factor ◆ Bone metastasis - Hyaluron synthase (HAS) - Osteomimetic properties of invasive cells - Urokinase-type plasminogen activator (uPA)	**Chapter 3**
Etiology and Prevention ◆ Androgen receptor and androgen metabolism - CAG repeats - PSA gene variants - 3-beta-hydroxysteroid dehydrogenase (HSD3B) - Steroid 5alpha-reductase (SRD5A2) - Cytochrome p450 enzyme - Prostate Cancer Prevention Trial (PCPT) ◆ Insulin-like growth factors ◆ Dietary factors - Fat and branched-chain fatty acids - PhIP (2-amino-1-methyl-6-phenylimidazol[4,5-*b*]pyridine) - Micronutrients (e.g., selenium, lycopene, genistein, and vitamin E) - Alpha-tocopherol beta-carotene cancer prevention trial (ATBC) ◆ Biological agents - Viral infections (herpesvirus and human papillomavirus) - Bacterial infections (gonorrhea and syphilis)	**Chapter 4**

It is difficult to plan for scientific discoveries. However, NCI along with the other NIH Institutes and Centers, can provide the vision, creative environments, and diverse resources needed to facilitate these discoveries and ensure a smooth flow between advances in knowledge and application.

– National Institutes of Health, Prostate Cancer Research Plan for FY 2003–2008.

Table 1-2. (cont.)

Areas of Progress	Details
Early Detection, Diagnosis, and Prognosis ◆ Novel biologic markers - Alpha-methylacyl-CoA racemase (AMACR) - Caveolin-1 (Cav-1) - Ribonuclease L (RNAseL) - Prostate-specific stem cell antigen (PSCA) - Epidermal growth factor receptor (EGFR) - Telomerase reverse transcriptase (TERT) ◆ Imaging technologies - Transrectal ultrasonography (TRUS) - Magnetic resonance imaging (MRI) ◆ Molecular profiling	**Chapter 5**
Scientific Model Systems ◆ Transgenic animal models - Testing of new interventions - New strains ◆ Xenografted animal models ◆ Knockout animal models - Nkx3.1 - PTEN	**Chapter 6**
Treatment ◆ Progress in preclinical models ◆ Early-stage disease - Impact of treatment on survival - Improved prognostic indicators ◆ Biochemical recurrence ◆ Advanced disease - Zoledronic acid - Radiostrontium - Combination chemotherapies	**Chapter 7**
Cancer Control, Survivorship, and Outcomes ◆ Survivorship and outcomes - Complication rates following treatment - Quality of life and patient satisfaction determinations ◆ Statistical trends and surveillance of practice patterns - Declining mortality rates - Racial disparities	**Chapter 8**

Research Results Applied

Clinical practice for treating prostate cancer has been updated on the basis of results from NCI-sponsored research. Sexual potency-sparing interstitial brachytherapy is now considered for certain patients with localized prostate cancer, and hormonal therapy is now considered in addition to external beam radiation for patients with locally advanced disease.[14]

Although not enough evidence has been accumulated to determine whether PSA screening ultimately saves lives,[15] PSA screening has been endorsed by nongovernment organizations and is now frequently performed on men over 50 years of age. Several diagnostic products, which were approved by the U.S. Food and Drug Administration in 1998, have improved the speed and accuracy of measuring serum PSA levels.

U.S. patents issued each year with relevance to prostate cancer show promise for future product development. Investigators supported by the NCI have translated their basic discoveries into advances in technology. Between 1998 and 2002, 69 patents relevant to prostate cancer were awarded or were pending decisions by the U.S. Patent Trademark Office (USPTO).[16] A listing of these patents can be found in Appendix C.

Evolution of the PRG Process

As the first of two pilot PRGs to be convened, the Prostate Cancer PRG helped pave the way for subsequent PRGs. Since 1997, 11 PRGs have been held by the NCI for specific cancer sites or groups of related cancer sites. More recently, other federal agencies have also employed the PRG model (e.g., the Stroke PRG convened by the National Institute of Neurological Disorders and Stroke in 2001 and the Trans-HHS PRG on Cancer Health Disparities convened by the Department of Health and Human Services in 2003).

The NCI has developed strategic plans for addressing the priorities and recommendations of some PRGs. This report represents the NCI's first attempt at reporting research progress in terms of responsiveness to PRG priorities.

Since late 2001, the NCI's *Cancer.gov* website has included web pages that inform prospective investigators of cancer site-relevant funding opportunities.[17] To secure consideration for exception funding, grant applicants are encouraged to list the specific PRG priorities that will be addressed by their proposed research. Research projects funded by the NCI are now coded, tracked, and made accessible to the public[18] according to both cancer site and standardized CSO research category.

[14] NCI Prostate Cancer PDQ Treatment Summary, Version for Healthcare Professionals, National Comprehensive Cancer Network Practice Guidelines in Oncology: Prostate Cancer.

[15] NCI Prostate Cancer PDQ Screening Summary, Version for Healthcare Professionals.

[16] Patents and patent applications were identified by searching the USPTO databases for prostate-relevant terms and then selecting for projects in which the government interests/rights were attributed to grants that included the NCI's Administering Organization Code.

[17] The NCI-sponsored prostate cancer research funding opportunities can be found at the Cancer Research Initiatives website at http://cri.cancer.gov/.

[18] The NCI Cancer Research Portfolio website can be found at http://researchportfolio.cancer.gov.

Looking to the Future

A Strategic Plan

In 2002, the NCI's Prostate Cancer Working Group helped develop the NCI portion of the National Institutes of Health (NIH) Prostate Cancer Research Plan for FY 2003–2008. The plan includes 7 goals and 27 objectives, along with strategies and near-term milestones for achieving the objectives. The research categories in the FY 2003–2008 plan correspond to, but do not exactly match, those of the Prostate Cancer PRG or CSO. Although the plan is based on the recommendations developed by the Prostate Cancer PRG, it also takes into account advances made since completion of the PRG's work.

This Progress Report

This report, which documents the NCI's responsiveness to the recommendations of the Prostate Cancer PRG over the years 1998 through 2002, will be used, by the NCI, for efficient implementation of the FY 2003–2008 prostate cancer research plan. Because the NCI uses the CSO research categorization scheme to track dollar investments, resources, and projects, this report has been organized according to a modified version of the CSO, as follows:

- Initiatives
- Biology
- Etiology and Prevention[19]
- Early Detection, Diagnosis, and Prognosis
- Scientific Model Systems
- Treatment
- Cancer Control, Survivorship, and Outcomes

In Chapter 2, details are provided on broad NCI initiatives that address multiple categories of prostate cancer research, along with the specific programs, resources, and/or research projects that derive from those initiatives. In Chapters 3 through 8, progress is reported for a given research category, as a whole, and for the individual PRG Priority One investigative questions relevant to that category. Quantitative measures are included throughout to demonstrate the extent of the NCI's responsiveness to the PRG research priorities. Consistent with the CSO categorization scheme, investigative questions pertaining to resources needed are addressed in all chapters of this report.

This report addresses only part of the progress made since 1998. First, the content is limited to NCI-sponsored research that is most relevant to prostate cancer. In addition to the NCI, there are other federal and nonfederal agencies that fund research on prostate cancer. Second, human cancers are complex diseases; each cancer site has features that are unique and features that are shared with other cancer sites. It is possible that the solution for preventing prostate cancer or the suffering and death resulting from prostate cancer will ultimately derive from research directed at another cancer site, or even from research directed at a noncancerous disease. Nevertheless, to increase the likelihood that there will be significant breakthroughs in prevention, diagnosis, and treatment, the NCI remains committed to planning, conducting, and assessing research that is directed at prostate cancer.

[19] This chapter combines the separate CSO categories of etiology and prevention.

CHAPTER 2

Initiatives

As the principal federal sponsor of cancer research and research training, the NCI coordinates, conducts, and supports research, training, health information dissemination, and other programs that pertain to development, diagnosis, prevention, and treatment of cancer and the continuing care of cancer patients and their families.

The NCI emphasizes funding of biomedical research through investigator-initiated applications. This paradigm has enabled investigators to ask critical questions, to remain creative in exploring research topics within their scientific expertise, to develop innovative technologies, and to make discoveries that expand the scientific knowledge base.

Progress in prostate cancer is severely impeded by limitations in research funding, policies, and practice.

– Defeating Prostate Cancer: Crucial Directions for Research - Report of the Prostate Cancer Progress Review Group, August 1998.

The investigator-initiated cancer research portfolio extends broadly across research fields; however, limitations of investigator-initiated research include underrepresented research in priority areas and the prohibitive cost of individually maintained resources and advanced technologies. Therefore, research is solicited and resources developed to encourage work in priority areas, to support multidisciplinary research collaborations, and to enable researchers to accelerate the pace of discovery. A recurring theme throughout the 1998 Prostate Cancer PRG report was that ***there are highly promising avenues of prostate cancer research in which progress is being delayed because of limitations in resources, infrastructure, or capacity for conducting the work***. Limitations were identified in areas that included the following:

- Reliable long-term funding at levels sufficient for sustaining progress and motivation
- The number of investigators trained in critical new skills and technologies
- The number of investigators interested in conducting certain types of studies
- Validated models that mimic the natural history and progression of human prostate cancer
- Access to large numbers of well-characterized biological samples
- Access to large numbers of prostate cancer patients or men who are at various levels of risk for developing the disease
- Capability for efficient collection, storage, and analysis of data from large clinical trials
- Standardization of assays and other methodologies

The NCI has responded to the PRG priorities pertaining to needed research areas and resources by expanding its investment in initiatives. Initiatives are used by the NCI to address priorities that might not otherwise be addressed through unsolicited investigator-initiated grant applications. In the broadest sense, initiatives[1] include:

[1] The NCI uses two main funding opportunity mechanisms for soliciting extramural grant proposals in targeted topic areas – Requests for Applications (RFAs) and Program Announcements (PAs). RFAs and PAs are published in the NIH Guide for Grants and Contracts and the NCI's Cancer Research Initiatives website.

- The extramural funding opportunities used for establishing new projects, resources, and programs
- The resources and programs that result from the funding opportunities
- The resources and programs that the NCI establishes within its intramural programs

By expanding ongoing initiatives and introducing new initiatives targeting prioritized research topics, the NCI creates a cadre of researchers focusing on specific questions. By continuing ongoing and creating new initiatives that provide infrastructure and resource support, the NCI facilitates research projects and accelerates research discoveries utilizing centralized, shared resources.

NCI's Investment and Response

In December 1998, the NCI issued *NCI Initiatives Applicable to Prostate Cancer Research*, a notice indicating that the NCI "*intends to increase its support for all forms of research on prostate cancer through the wide range of special mechanisms available*." The purpose of the notice was to bring "*relevant NCI initiatives to the attention of prostate cancer investigators, so that they may effectively capitalize on these opportunities*."

Chapter 1 shows the growth in NCI spending on prostate cancer research (Figure 1-3) and lists the specific initiatives that impacted prostate cancer research (Table 1-1) during the period 1998 through 2002. For each initiative listed in Table 1-1 that affects more than one research category, Table 2-1 provides information on the purpose of the initiative; the research categories affected by the initiative; and the relevant program, resource, and/or research projects that resulted from the initiative. For each initiative in Table 1-1 that applies to a single research category, more detail is provided in the corresponding chapter of this report.

Table 2-1. NCI Initiatives Relevant to Prostate Cancer Research: Initiatives Affecting Multiple Research Categories

INITIATIVES FOCUSED ON PROSTATE CANCER
Cooperative Prostate Cancer Tissue Resource (CPCTR) (http://www.prostatetissues.org) **Objective:** A virtual resource comprising tissue specimens (which remain at the collection site) and a centralized database. **Affected Research Categories:** Biology; Etiology and Prevention; Early Detection, Diagnosis, and Prognosis; Scientific Model Systems; Treatment **Relevant Resource Resulting from This Initiative:** Four institutions provide investigators with primary prostate tissues annotated with data concerning stage of disease, recurrence, vital status, treatment received, histologic type, presence of prostatic intraepithelial neoplasia, availability of normal tissue, Gleason grading, characteristics, and follow-up time.
Diagnostic Imaging and Guided Therapy in Prostate Cancer (PAR-99-149) (RFA-CA-99-015) **Objective:** Support the development, risk assessment, and application of improved imaging methods for the localization, biopsy, and image-guided biopsy or therapy of prostate cancer. **Affected Research Categories:** Early Detection, Diagnosis, and Prognosis; Treatment **Relevant Research Projects Resulting from This PA/RFA:** ◆ Androgen Receptor-Mediated Detection of Prostate ◆ Compton Imaging Probe for the Prostate ◆ Diagnostic Imaging and Guided Therapy in Prostate Cancer ◆ Dosimetric Markers for Image-Guided Radiation Therapy ◆ Dynamic Prostate Brachytherapy

Table 2-1. (cont.)

- Improved Magnetic Resonance Imaging (MRI)/Magnetic Spectroscopic Imaging for Biopsy Guidance of Prostate Cancer
- Interventional MRI/Single Photon Emission Computed Tomography (SPECT)-Guided Prostate Cancer Biopsy and Therapy
- Low-Molecular Weight Ligands for Prostate Cancer
- MR-Guided Focused Ultrasound Ablation of Prostate
- Novel Ultrasonic Imaging of Brachytherapy Seeds
- Precise MRI-Directed Sonic Ablation of Prostate Cancer
- Real-Time Robotic Image-Guided Prostate Brachytherapy
- Ultrasound Image-Guided Stereotactic Navigational System

Molecular Epidemiology of Prostate Carcinogenesis (PA-00-080)

Objective: Stimulate development and application of biological markers of prostate cancer risk and tumor aggressiveness for utilization in chemoprevention studies. Of special interest are studies of markers to elucidate multiethnic differences in prostate cancer susceptibility.

Affected Research Categories: Biology; Etiology and Prevention

Relevant Research Projects Resulting from This PA:

- Analysis of Ras and Rho Activation in Prostate Cancer
- Androgen Pathway Factors and Prostate Cancer
- Androgen Receptor and Prostate Cancer Risk in Chinese
- Effects of Lycopene on High-Risk Prostatic Tissue
- Genetic Epidemiology of Prostate Cancer Aggressiveness
- Genetic Polymorphisms and Prostate Cancer Risk
- IGF-I Levels, IGF-I Genotype, and Prostate Cancer
- Mapping and Cloning Prostate Cancer Predisposition Loci
- Molecular Epidemiology of Prostate Cancer
- Molecular Epidemiology of Prostate Cancer in Tobagonians
- NSAIDs and Other Medications in Prostate Cancer Etiology
- Polymorphisms in Prostate Cancer Carcinogenesis
- Prostate Cancer in Mexican Americans and African Americans
- Risk Factors for Advanced Prostate Cancer
- Signaling in Androgen Refractory Prostate Cancer

Prostate Cancer Intervention Versus Observation Trial (PIVOT) (http://www.va.gov/PIVOT/)

Objective: Randomized trial comparing radical prostatectomy versus expectant management for the treatment of clinically localized prostate cancer.

Affected Research Categories: Early Detection, Diagnosis, and Prognosis; Treatment; Cancer Control, Survivorship, and Outcomes

Relevant Program Relevant to This Initiative: Begun in 1994, the trial is being conducted at over 50 U.S. sites. Enrollment is complete at 731 men who will be followed for 15 years. The Department of Veterans Affairs maintains a PIVOT website that is directed at the public.

Table 2-1. (cont.)

Prostate, Lung, Colorectal & Ovarian Cancer Screening Trial (PLCO) (http://www3.cancer.gov/prevention/plco/index.html)

Objective: A large clinical trial aimed at determining whether cancer screening tests reduce deaths from prostate, lung, colorectal, and ovarian cancer. The study includes questionnaire and biologic sample collections for early marker and etiologic studies of prostate and other cancers.

Affected Research Categories: Early Detection, Diagnosis, and Prognosis; Etiology and Prevention; Treatment; Cancer Control, Survivorship, and Outcomes

Relevant Program Resulting from This Initiative: Publications concerning the PLCO and its initial results can be found at http://www3.cancer.gov/prevention/plco/updates.html.

Prostate Specialized Programs of Research Excellence (SPOREs) (http://spores.nci.nih.gov/prostate/prostate.html)

Objective: Translational research on the prevention, etiology, screening, diagnosis, and treatment of a specific organ-site cancer.

Affected Research Categories: All

Relevant Program Resulting from This Initiative: Eleven current Prostate SPOREs; see Table 2-2 for a listing of projects and core resources associated with each. Yearly meetings are held to facilitate communication among the researchers participating in the Prostate and Genitourinary SPOREs and among the researchers participating in SPOREs for all cancer types.

INITIATIVES WITH PROSTATE CANCER-RELEVANT COMPONENTS

Applications of Innovative Technologies for the Molecular Analysis of Cancer (PAR-01-106) (PAR-01-107)

Objective: Evaluate the utility and pilot the application of molecular analysis technologies in studies relevant to cancer research.

Affected Research Categories: Biology; Early Detection, Diagnosis, and Prognosis; Treatment

Relevant Research Projects Resulting from This PA:

- Analysis of Circulating Cancer Cells Early in Disease
- Development of Bacterial Artificial Chromosome Array Comparative Genomic Hybridization
- Imaging Alternative Splicing during Tumor Progression
- In Vivo Analysis of Tumor Peptide Secretion
- Isolation and Profiling of Circulating Prostate Cancer Cells in Blood
- Molecular Analysis of Cancer—Imaging Mass Spectrometry
- Phage Display and Prostate Neoplasia Progression
- Prognostic Value of Telomere DNA in Prostate Biopsy

Cancer Centers Program (http://www3.cancer.gov/cancercenters)

Objective: Support major academic and research institutions throughout the United States to sustain broad-based, coordinated, interdisciplinary programs in cancer research.

Affected Research Categories : All

Relevant Resource Resulting from This Initiative: Approximately 60 institutions across the United States are being supported as NCI-Designated Cancer Centers. The NCI's Executive Committee has designated 39 of the institutions as Comprehensive Cancer Centers based on the criteria of (1) the Center's breadth, depth, and interactions among basic research, clinical research, and research in prevention, control, and population/behavioral sciences and (2) the Center's public information, education, and outreach activities.

Table 2-1. (cont.)

Cancer Genome Anatomy Project (CGAP) (http://cgap.nci.nih.gov/)

Objective: Collaborative program for determining the gene expression profiles of normal, precancerous, and cancerous cells.

Affected Research Categories: Biology; Etiology and Prevention; Early Detection, Diagnosis, and Prognosis

Relevant Resource Resulting from This Initiative: The program was started in 1996. Through the CGAP website, researchers can access human and mouse genomic data, informatics tools, and information on methods and resources. The database of expressed genes, which includes data from nearly 300 diseased and normal prostate tissue cDNA libraries, currently lists nearly 400 genes uniquely expressed in cancerous or precancerous prostate tissue cDNA libraries.

Cancer Imaging Program (CIP) (http://www3.cancer.gov/dip)

Objective: Promote and support cancer-related basic, translational, and clinical research in imaging sciences and technology; and integration and application of these imaging discoveries and developments to the understanding of cancer biology and to the clinical management of cancer and cancer risk.

Affected Research Categories: Early Detection, Diagnosis, and Prognosis; Scientific Model Systems; Treatment; Biology

Relevant Programs Resulting from This Initiative: Prostate cancer research has been supported through RFAs for the following programs:

- Diagnostic Imaging and Guided Therapy in Prostate Cancer – Phased Innovation Award
- In Vivo Cellular and Molecular Imaging Centers (ICMICs) and the Pre-In Vivo Cellular and Molecular Imaging Centers (Pre-ICMICs)
- Small Animal Imaging Resource Programs

Cancer Molecular Analysis Project (CMAP) (http://cmap.nci.nih.gov)

Objective: Access to molecular data relating to cancer from different frames of reference.

Affected Research Categories: Biology; Etiology and Prevention; Early Detection, Diagnosis, and Prognosis; Treatment

Relevant Resource Resulting from This Initiative: Data can be retrieved from the CMAP website via the key concepts of context (including prostate carcinoma), target, anomaly, profile, agent, and trial.

Cancer Prognosis and Prediction (PAR-01-062)

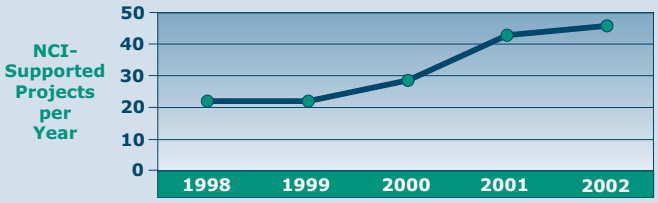
Objective: Develop new strategies for determining prognosis or predicting response to cancer therapy.

Affected Research Categories: Early Detection, Diagnosis, and Prognosis; Treatment

Relevant Programs Resulting from This Initiative: Pending

Cancer Research Training, Career Development, and Education Opportunities (http://cancertraining.nci.nih.gov/)

Objective: Well-trained investigators in the basic, clinical, population, and behavioral sciences, who are prepared to address problems in cancer biology, causation, prevention and control, detection and diagnosis, and treatment and rehabilitation.



Affected Research Categories: All

Relevant Resource Resulting from This Initiative: More than 10 types of awards exist that support predoctoral and postdoctoral training and faculty career development. The number of individual training and career development awards with 25 percent or more relevance to prostate cancer has more than doubled between fiscal year (FY) 1998 and FY 2002.

Table 2-1. (cont.)

Cancer Therapy-Related Use of Genetically Engineered Mice (PAR-02-051)

Objective: Use of genetically engineered mouse cancer models for cancer therapy-related goals.

Affected Research Categories: Scientific Model Systems; Treatment

Relevant Research Projects Resulting from This PA: PI-3 Kinase Therapy in Mouse Tumor Models

Clinical Trials Cooperative Group Program (http://ctep.cancer.gov/resources/coop2.html)

Objective: Support organizations that generate and conduct clinical trials and the developmental efforts that precede them, with emphasis on randomized Phase III trials.

Affected Research Categories: Etiology and Prevention; Early Detection, Diagnosis, and Prognosis; Treatment; Cancer Control, Survivorship, and Outcomes

Relevant Program Resulting from This Initiative: Fourteen member organizations, with nine currently conducting trials on prostate cancer.

Relevant Resource Resulting from This Initiative: Banked tissue resources are available to investigators through each cooperative group.

Common Data Elements (CDE) Initiative (http://ncicb.nci.nih.gov/CDEBrowser)

Objective: Standardize and simplify the collection and reporting of data in NCI-sponsored clinical trials.

Affected Research Categories: Etiology and Prevention; Treatment; Cancer Control, Survivorship, and Outcomes

Relevant Resource Resulting from This Initiative: A set of core and prostate-specific data elements have been developed.

Community Clinical Oncology Program (CCOP) (http://www3.cancer.gov/prevention/ccop)

Objective: Groups of hospitals and private practices that participate in NCI-sponsored clinical trials.

Affected Research Categories: Etiology and Prevention; Treatment; Cancer Control, Survivorship, and Outcomes

Relevant Programs Resulting from This Initiative: Sixty-one CCOPs, including 11 Minority-Based CCOPs, participate in clinical trials with 15 research bases, of which 7 coordinate prostate cancer trials with the CCOPs.

Cooperative Human Tissue Network (CHTN) (http://www-chtn.ims.nci.nih.gov)

Objective: Collect and distribute benign, pre-cancerous, and cancerous human tissue specimens for basic and developmental studies in cancer research.

Affected Research Categories: All

Relevant Resource Resulting from This Initiative: Six member institutions currently coordinate the collection and distribution of specimens that include tissues obtained at surgery and autopsy, serum, and DNA/RNA. In 2002, CHTN delivered 1,285 prostate specimens to investigators.

Director's Challenge: Toward a Molecular Classification of Cancer (http://dc.nci.nih.gov)

Objective: Use of molecular analysis technologies for tumor classification.

Affected Research Categories: Biology; Etiology and Prevention; Early Detection, Diagnosis, and Prognosis

Relevant Program Resulting from This Initiative: The Director's Challenge program website provides researchers with information, tools, and microarray datasets.

Relevant Research Projects Resulting from This Initiative:

- A Cancer Taxonomy Based on Gene Expression Patterns
- Gene Expression Analysis of Cancers of the Prostate and Lung
- Molecular Characterization of Early-Stage Prostate Cancer
- Molecular Classification of Prostate Cancer
- Molecular Reclassification of Prostate Cancer

Table 2-1. (cont.)

Exploratory Grants for Correlative Laboratory Studies and Clinical Trials (PA-98-042)

Objective: Innovative clinical therapy trials or correlative laboratory studies with patient specimens.

Affected Research Categories: Etiology and Prevention; Early Detection, Diagnosis, and Prognosis; Treatment

Relevant Research Projects Resulting from This PA:

- Identification of a Potential Cytogenetic Marker
- Molecular Staging of Lymph Nodes—Outcome of Prostate Cancer
- Monitoring Chemotherapy in Prostate Cancer by Proton Nuclear Magnetic Resonance
- Optimized Cancer Chemotherapy via Pharmacodynamic Models
- Pulse Calcitriol for Prostate Cancer Prevention
- T Cell Signal Transduction in Cancer Immunotherapy

Flexible System to Advance Innovative Research for Cancer Drug Discovery by Small Businesses (FLAIR) (http://dtp.nci.nih.gov/branches/gcob/gcob_web17.html)

Objective: Provide support for the extensive needs of drug and vaccine discovery through proof of principle demonstration in clinical trials.

Affected Research Categories: Etiology and Prevention; Treatment

Relevant Research Projects Resulting from This Initiative:

- Alphavirus Prime-Boost Vaccines for Prostate Cancer
- Complementary Adenoviral Vectors for Treatment of Cancer
- Cytotoxic Gonadotropin Releasing Hormone Derivatives
- Development of DNA Methyltransferase Inhibitors as Anticancer Agents
- Development of a New Antiangiogenic Tumor Blocker SBD 1
- Human Anti-Prostate-Specific Membrane Antigen (PSMA) Antibodies for Prostate Cancer Therapy
- New Target Antigens for Prostate Cancer Vaccines
- Peptide Antagonists of Urokinase Plasminogen Activator

Genitourinary Cancers Faculty (http://ccr.cancer.gov/faculties/faculty.asp?facid=131)

Objective: Develop better methods for prevention, diagnosis, and treatment of genitourinary malignancies through intramural collaborations, interdisciplinary research, and translational (bench-to-bedside) science.

Affected Research Categories: Biology; Etiology and Prevention; Early Detection, Diagnosis, and Prognosis; Treatment

Relevant Resource Resulting from This Intramural Program: Faculty from approximately 20 NCI branches and laboratories participate in a monthly seminar series and annual retreat to facilitate communication and collaborations between laboratories. The faculty members also work together to recruit new urologic and oncology fellows and to plan new research objectives, such as initiating a new molecular imaging study and conducting a trial on seed implantation therapy in prostate cancer.

Improving DNA, RNA, and Protein Availability in Fixed Tissue (PAR-00-079)

Objective: Develop improved methods for fixing tissues and making nucleic acids and proteins more readily accessible from archived specimens.

Affected Research Categories: Biology; Etiology and Prevention; Early Detection, Diagnosis, and Prognosis; Scientific Model Systems; Treatment

Relevant Research Project Resulting from This PA: Fixation of Breast and Prostate Cancer Tissue

Table 2-1. (cont.)

In Vivo Cellular and Molecular Imaging Centers (ICMICs) (http://www3.cancer.gov/bip/ICMICs.htm)

Objective: Capitalize on noninvasive and, in many cases, quantitative imaging methods for studying cancer.

Affected Research Categories: Biology; Etiology and Prevention; Early Detection, Diagnosis, and Prognosis; Scientific Model Systems; Treatment

Relevant Resource Resulting from This Initiative: Seven centers exist, with additional institutions planning to become centers via Planning Grants for Pre-In Vivo Cellular and Molecular Imaging Centers (CA-01-010 and CA-99-002). Examples of research conducted at these centers include (1) the inhibition of cellular growth and angiogenesis factors and (2) the development of functional tracers for molecular targets to be used for imaging primary and metastatic prostate cancer with Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) techniques.

Interdisciplinary Research Teams for Molecular Target Assessment (RFA-CA-00-001)

Objective: Develop methods to assess the effects of interventions directed at specific molecular targets that produce or are associated with the cancer phenotype.

Affected Research Categories: Etiology and Prevention; Treatment

Relevant Research Project Resulting from This PA: Mechanism-Based Evaluations of ErbB Targeted Agents

Minority Institution/Cancer Center Partnership (MI/CCP) Program (http://minorityopportunities.nci.nih.gov/institutions/faqs.html)

Objective: Partnerships between minority-serving institutions and NCI-designated Cancer Centers to increase training and involvement of scientists at minority institutions and develop collaborative projects that address the disproportionate incidence and mortality of cancer in minority populations.

Affected Research Categories: All

Relevant Program Resulting from This Initiative: Twenty current partnerships, including one (University of California Comprehensive Cancer Center/San Francisco State University) that is focused on prostate and one other cancer type.

Minority-Based Community Clinical Oncology Program (MBCCOP) (http://www3.cancer.gov/prevention/ccop/mbccop.html)

Objective: Groups of hospitals and private practices, with extensive minority patient populations, that participate in NCI-sponsored clinical trials.

Affected Research Categories: Etiology and Prevention; Treatment; Cancer Control, Survivorship, and Outcomes

Relevant Program Resulting from This Initiative: Eleven funded groups with eight currently participating in trials on prostate cancer.

Molecular Profiling Initiative (MPI) (http://cgap-mf.nih.gov/ProstateExample/index.html)

Objective: A tissue microdissection-based approach to molecular profiling.

Affected Research Categories: Early Detection, Diagnosis, and Prognosis; Treatment

Relevant Resource Resulting from This Initiative: Prostate Molecular Profiling at NCI, which includes the following:

- 3D Prostate Molecular Model Demo
- Prostate Microreviews

Table 2-1. (cont.)

Molecular Target Drug Discovery for Cancer (PAR-01-045) (PAR-01-046)

Objective: Exploit molecular targets for drug discovery.

Affected Research Categories: Etiology and Prevention; Treatment

Relevant Research Projects Resulting from These PAs:

- Inhibition of Androgen Receptor Activation
- New Triterpenoids for Chemoprevention of Cancer
- Photodynamic Therapy for Prostate Cancer
- Shh Signaling as a Therapeutic Target in Prostate Cancer
- Structure-Based Discovery of AKT Inhibitors
- Targeting Functional Domains in Telomerase

NCI Center for Bioinformatics (NCICB) (http://ncicb.nci.nih.gov)

Objective: Provide bioinformatics support and integrate diverse research initiatives.

Affected Research Categories: All

Relevant Research Projects Resulting from This Initiative: NCICB's Cancer Common Ontologic Reference Environment (caCORE) research information management system backbone software is available to researchers.

Program for the Assessment of Clinical Cancer Tests (PACCT) (http://www.cancerdiagnosis.nci.nih.gov/assessment)

Objective: To maximize the impact of cancer treatments and to ensure translation of new knowledge about cancer into clinical practice.

Affected Research Categories: Biology; Treatment; Early Detection, Diagnosis, and Prognosis

Relevant Programs Resulting from This Initiative: A PACCT Strategy Group was convened in order to develop criteria for assessing which markers are ready for further development.

Relevant Resources Resulting from This Initiative: Several websites help researchers gain access to human specimens:

- NCI Specimen Resource Locator
- Shared Pathology Informatics Network
- Tissue Array Research Program
- Tissue Expediter

Shared Resources for Scientists outside NCI Cancer Centers (PAR-99-127)

Objective: Provide additional shared resource support to institutions that do not have NCI-funded cancer centers or planning grants.

Affected Research Categories: Etiology and Prevention; Early Detection, Diagnosis, and Prognosis; Treatment

Relevant Resource Resulting from This PA: Viral Vector Core Facility

Small Animal Imaging Resource Program (SAIRP) (CA-01-012)

Objective: Support shared imaging research resources to be used by cancer investigators and conduct research related to small animal imaging technology.

Affected Research Categories: Biology; Etiology and Prevention; Early Detection, Diagnosis, and Prognosis; Scientific Model Systems; Treatment

Relevant Programs Resulting from This Initiative: Ten participating institutions provide imaging resources for investigators in their region of the United States. Examples of research conducted at these centers include (1) the inhibition of cellular growth and angiogenesis factors and (2) the development of functional tracers for molecular targets to be used for imaging primary and metastatic prostate cancer with PET and SPECT techniques.

Table 2-1. (cont.)

Special Populations Networks (SPNs) (http://crchd.nci.nih.gov/spn/index.html)

Objective: Establish an infrastructure to promote cancer awareness within minority and medically underserved communities and launch more research and cancer control activities aimed at specific population subgroups.

Affected Research Categories: Etiology and Prevention; Treatment; Cancer Control, Survivorship, and Outcomes

Relevant Programs Resulting from This Initiative:

- Arkansas Special Populations Access Network
- Cancer Awareness and Training Collaboration Coordinated by the Latino Research and Policy Center
- Cancer Awareness Network for Immigrant Minority Populations
- Increasing Access to Clinical and Educational Studies
- National Black Leadership—Cancer Control, Research, and Training Network

Specimen Resource Locator (http://pluto3.nci.nih.gov/tissue/default.htm)

Objective: A database to help researchers locate human specimens for cancer research.

Affected Research Categories: Biology; Etiology and Prevention; Early Detection, Diagnosis, and Prognosis; Scientific Model Systems; Treatment

Relevant Resource Resulting from This Initiative: The Specimen Resource Locator website provides investigators with information and automated tools for identifying tissue procurement systems, including those with samples from normal and diseased prostate.

Technologies for Comprehensive, Sensitive, and Quantitative Protein Analysis in Human Tumors: Phased Innovation (RFA-CA-01-011)

Objective: Develop innovative technologies for the sensitive quantitation of the comprehensive spectrum of proteins present in human tissues.

Affected Research Categories: Biology; Etiology and Prevention; Early Detection, Diagnosis, and Prognosis

Relevant Research Project Resulting from This RFA: Novel Quantitative, Comprehensive Proteomic Technology

Table 2-2 provides more information on the research projects, core resources, training, and other opportunities that are provided by the 11 current Prostate SPOREs.

Table 2-2. Prostate SPOREs

Baylor College of Medicine (funded since September 1992)

Projects:

- Biological Therapy for Prostate Cancer
- Endocrinology and the Role of Stroma Genes in Prostate Cancer
- Gene Therapy for Prostate Cancer
- Markers of Progression and Metastasis
- Physical and Functional Analysis of Prostate Cancer Genes
- Prostate-Specific Gene Expression in Transgenic Animals
- The Role of CDK Inhibitors in Prostate Cancer

Cores: Administrative Core, SPORE Pathology Core, Medical Informatics Core, Transgenic Core, and Microarray Core Facility

Table 2-2. (cont.)

Dana-Farber Cancer Institute (funded since September 1992)

Projects:

- The Androgen Receptor in Hormone Refractory Disease
- Genetic and Serologic Determinants of Prostate Cancer Risk and Progression
- Genomic Expression Analysis of Tumors after Radical Prostatectomy
- PPAR as a Target of Therapy for Prostate Cancer
- Single Nucleotide Repeat Polymorphism Analysis of Recurrent Prostate Cancer after Radiation Therapy

Cores: Administration, Evaluation, and Planning Core; Biostatistics Core; Tissue and Pathology Core; and Genomics Core

Additional: Career Development Project and Developmental Projects Program

The Johns Hopkins School of Medicine (funded since September 1992)

Projects:

- Androgen Receptor Gene Structure and Function in Human Prostate Cancer
- Cellular and Molecular Basis of Prostate Metastasis to Bone
- Down Regulation of Metastasis Suppressor Genes as Diagnostic Methods for Predicting the Biologic Behavior of Histologically Detectable Prostate Cancer
- Gene Therapy for Human Prostate Cancer
- Human Prostate Cancer Nuclei: Abnormalities in Structure and the Development of New Molecular Markers
- Longitudinal Studies of Men with and without Prostate Cancer
- Mechanisms of Sensitivity and Drug Resistance in Prostate Cancer
- Molecular Genetics of Human Prostate Cancer
- Rational Prostate Cancer Prevention Studies
- Search for Hereditary Prostate Cancer Genes Using Linkage Analysis and Positional Cloning
- Transgenic Models of Prostate Cancer and Autoimmunity

Additional:

- Administrative Supplement: SPORE for Developing a Tissue Microarray
- Career Development Project: Determinants of Radiosensitivity in Prostate Cancer Cells
- Career Development Project: New Methods to Determine Tissue Architecture and Chromatin Structure

Mayo Clinic Rochester (funded since August 2001)

Projects:

- Biologic and Clinical Studies of the Overrepresented 8q24 Region Associated with Prostate Cancer Progression
- Gene Therapy of Prostate Cancer Using Radioiodine
- Genetic Susceptibility in Prostate Cancer
- Human Kallikreins as Novel Markers of Prostate Cancer
- An Immune-Based Therapeutic Approach for Prostate Cancer
- Use of Fusogenic Membrane Glycoproteins for Gene Therapy of Prostate Cancer

Cores: Administrative Core, Tissue Procurement Core, Gene Discovery/Bioinformatics Core, Clinical Follow-up Core, and Biostatistics Core

Table 2-2. (cont.)

MD Anderson Cancer Center (funded since June 2001)

Projects:

- The Biology of Human Prostate Cancer Metastasis
- Epidemiologic, Molecular, and Clinical Markers of Prostate Cancer Progression
- Exploring the Molecular Diversity of Blood Vessels for Diagnostic and Therapeutic Targeting in Prostate Cancer
- Targeting Prostate Cancer Bone Metastasis
- Therapeutic Modulation of Apoptosis in Prostate Cancer Patients

Cores: Administrative Core, Biostatistics Core, and Tissue Resource and Pathology Core

Memorial Sloan-Kettering Institute for Cancer Research (funded since September 2001)

Projects:

- The Development of DNA Vaccines against Prostate Cancer with PSMA as a Target
- Mechanism-Based Therapy for Prostate Cancer
- Molecular Analysis of Carcinogenesis in the Mouse and Human Prostate
- Natural History of Prostate Cancer, Prognostic Models, and Decision Making

Cores: Pathology Core, Informatics Core, Animal Models Core, Animal Imaging Core, DNA Array Core, and Administrative Core

Northwestern University (funded since June 2001)

Projects:

- Clinical Trial on Lycopene
- Clusterin as a Negative Prognostic Indicator in Prostate Cancer
- Generation of, and Angiostatin Levels in, Prostate Cancer
- Molecular Mechanisms of Neuropathic Erectile Dysfunction
- QOL Item Banking and Adaptive Testing in Prostate Cancer
- Suppressive Role of Androgen-Response Gene Calreticulin in Prostate Cancer

University of California, Los Angeles (funded since September 2002)

Projects:

- Interactions between Insulin-Like Growth Factor Binding Proteins and Nuclear Receptors in Prostate Cancer
- Prostate Stem Cell Antigen in the Biology and Therapy of Prostate Cancer
- The Role of the Her-Kinase Axis in Emergence of Androgen Independence in Human Prostate Cancer
- The Role of Quantity and Composition of Dietary Fat in the Prevention of Prostate Cancer
- Targeted Therapy of PTEN Null Prostate Cancer

Cores: Administrative Core, Pathology Core, Imaging Core, Animal Models Core, and Biostatistics Core

Maximize the effectiveness and efficiency of prostate cancer scientists by providing them with essential resources and infrastructure for conducting their research.

– National Institutes of Health, Prostate Cancer Research Plan for FY 2003–2008.

Table 2-2. (cont.)

University of California, San Francisco (funded since September 2000)

Projects:

- Anti-CTLA4 Antibody Immunologic Therapy for Prostate Cancer
- Antibody Gene Diversity Libraries and Phage Display to Generate Recombinant Human Antibodies for Prostate Cancer Therapy
- Genomics of Prostate Cancer
- Identification of Prostate Tumor Susceptibility Genes Using Mouse Models for Prostate Cancer
- Mechanisms of Hormone Resistance in Prostate Cancer
- Viral Therapy for Prostate Cancer

Cores: Administrative Core, Tissue Core, Informatics Core, Advocacy Core, Clinical Research Core, and Animal Technology Core

Additional: Developmental Research Program

University of Michigan (funded since September 1995)

Projects:

- Epidemiology of Prostate Cancer in African Americans
- Hereditary Prostate Cancer in African American Families
- Inhibition of Human Prostate Cancer Metastasis
- Rb as a Regulator of Prostate Tumorigenesis
- Vaccinia PSA for Androgen-Modulated, Post-Surgical Recurrence of Prostate Cancer

Cores: Administrative Core, Tissue and Animal Models Core, and Biostatistics Core

University of Washington/Fred Hutchinson Cancer Research Center (funded since September 2002)

Projects:

- Characterization of Anti-Apoptotic Genes Induced during Androgen-Independent Progression and Chemotherapy
- Genomic and Gene Expression Profiling of Disseminated Prostate Cancer
- Molecular Predictors of Prostate Cancer Progression and Mortality
- Transcriptome and Proteome Stratification of Prostate Adenocarcinoma Phenotypes

Cores: Leadership and Administration Core, Specimen and Tissue Core, Biostatistics Core, Informatics and Gene Expression Core, and Clinical Core

Additional: Developmental Research Program and Career Development Program

NCI's Future Investments in Resource and Capacity Building

The NIH Prostate Cancer Research Plan for FY 2003–2008 describes the NCI's planned objectives for each category of prostate cancer research and for resource and capacity building. The FY 2003–2008 objectives for the different categories of prostate cancer research are addressed in Chapters 3–8 of this report. The six FY 2003–2008 objectives for resource and capacity building and their alignment to the PRG priorities for needed resources noted at the beginning of the chapter are summarized in Figure 2-1. Building upon the framework developed by the PRG, the FY 2003–2008 objectives emphasize integration of NCI resources, as well as new opportunities and needs.

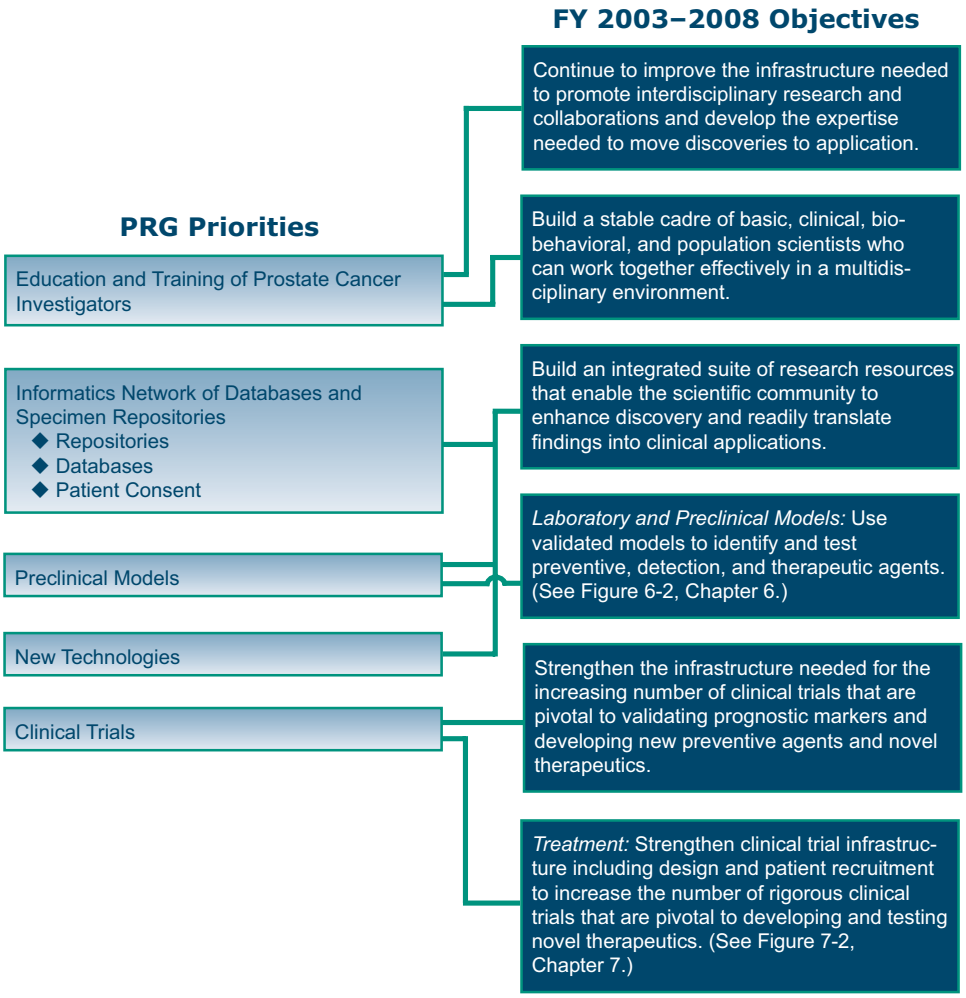


Figure 2-1. NIH's FY 2003–2008 prostate cancer resource and infrastructure objectives build upon PRG priorities.

The NIH Prostate Cancer Research Plan for FY 2003–2008 also describes near-term initiatives for facilitating and stimulating prostate cancer research.

- Under consideration as *new initiatives* are a Comprehensive Protein Fingerprinting Program, a Comprehensive Molecular Technology Program, and a second-round Prostate Cancer Outcomes Study.
- Prostate SPOREs, CGAP, CanCORS,[2] SPNs, and Translating Research into Improved Outcomes (TRIO) were *highlighted for potential expansion.*[3]

Better integration is planned among the various consortia and networks that participate in prostate cancer research.[4]

[2] CanCORS currently focuses on lung and colorectal cancers.

[3] TRIO is focused on breast and cervical cancers.

[4] Toward the goal of better integration, in February 2003, the NCI's P30/P50 Ad Hoc Working Group issued the report *Advancing Translational Cancer Research: A Vision of the Cancer Center and SPORE Programs of the Future.*

CHAPTER 3

Prostate Cancer Biology: NCI's Investment and Recent Progress

To provide a foundation for its applied research on prostate cancer prevention, detection, diagnosis, and treatment, the NCI supports basic research on the biological changes that occur during the development and progression of prostate cancer. Normal, pre-malignant, and malignant prostate tissues, including regional and distant metastases, are characterized for structural and functional differences at tissue, cellular, and molecular levels, with the goal of determining the entire sequence of events in all pathways that lead to or impact progression of prostate malignancy.

In their 1998 report, the Prostate Cancer PRG described the need for continued research on prostate cancer biology, progression, and metastasis. Studies leading to a better understanding of normal prostate development, early prostate cancer, the transition to hormone refractory disease, tumor microenvironment, and bone metastasis are needed to pave the way for improved prevention, detection, and treatment. Specifically, there is a need to identify and characterize the genes and molecular markers that are differentially expressed, the signal transduction pathways that are activated, and the tumor–stromal interactions that take place during the different stages of prostate cancer development and progression.

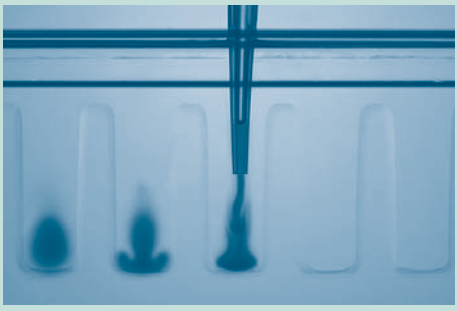
Through dynamic deliberation, the PRG identified 10 Priority One research questions that offered the best opportunities for advancing our understanding of prostate cancer biology. **The NCI has responded to these Priority One questions and their accompanying recommendations.** Significant progress has been made in characterizing the differential expression of specific transcription factors, fatty acid metabolizing enzymes, tumor suppressors, and oncogenes in normal and cancerous prostate tissues. These differences can be leveraged for detection and diagnosis and for targeted destruction of cancerous cells.

New models have been proposed to explain the transition from androgen-dependent to androgen-independent disease—a change that heralds continued progression and poor clinical outcome. Further insight into prostate cancer progression has been gained from identifying and characterizing the specific growth factors and surface proteins of stromal cells, which are, in turn, being applied to investigate metastatic disease, including the invasive mechanism of lymphangiogenesis and the adoption of osteo-mimetic properties by metastatic cells.

The progress made in prostate cancer biology research in recent years has fueled progress in the areas of prevention, detection, diagnosis, and treatment. For a more comprehensive understanding of this progress, readers are urged to see Chapters 4, 5, and 7 of this report.

Understanding prostate cancer biology, progression, and metastasis is fundamental to improving our abilities to successfully prevent, diagnose, and treat human prostate cancer.

– Defeating Prostate Cancer: Crucial Directions for Research - Report of the Prostate Cancer Progress Review Group, August 1998.



NCI's Investment and Response

From fiscal year (FY) 1998 to FY 2002, NCI's extramural investment in research on prostate cancer biology has grown from $15.2 million (M) to $41.7M (Figure 3-1). This increase corresponds to increases in the number of projects that are responsive to PRG priorities in biology. Table 3-1 summarizes NCI's responsiveness to the 10 Prostate Cancer PRG Priority One research questions for biology.

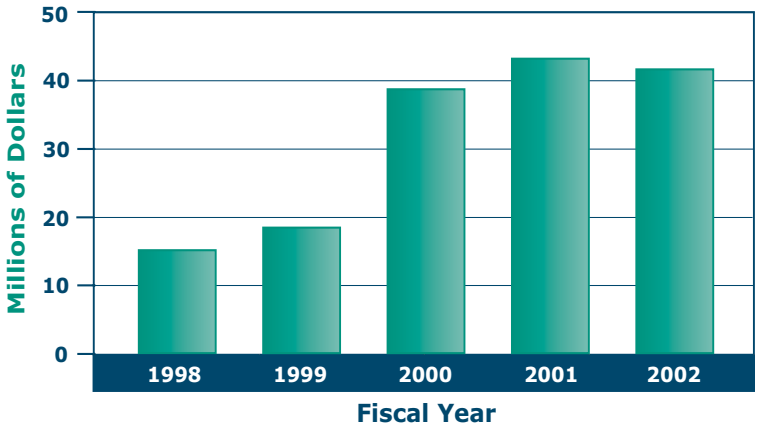
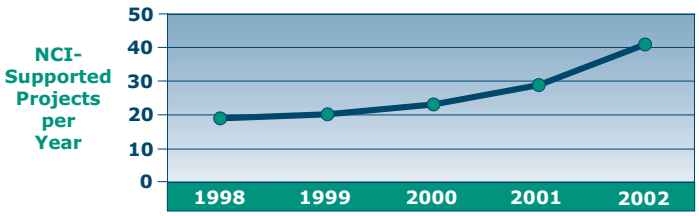


Figure 3-1. NCI's estimated investment in prostate cancer biology, progression, and metastasis extramural research: 1998–2002 (in millions of dollars).

Table 3-1. NCI Efforts Responsive to PRG Priorities in Prostate Cancer Biology[a]

PRG Priority: What are the potential roles of nuclear receptors, their interactive proteins, and ligand-metabolizing enzymes on prostate growth, tissue interactions, and development?



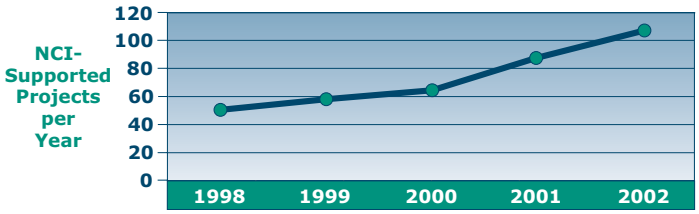
NCI Efforts:

- In FY 2002, active areas of investigation included structural interactions of intracellular receptors and specific ligands, regulation of androgen receptor-mediated transcription of DNA by associated factors, identification of novel proteins that associate with the androgen–androgen receptor complex, and glucocorticoid effects on tumor cells mediated through receptor binding.
- Seven projects addressed the PRG recommendation to expedite structural and pharmacological studies of important nuclear receptors and steroid-metabolizing enzymes.
- NCI initiatives addressing this priority included Age-Related Prostate Growth: Biologic Mechanisms; Prostate Specialized Programs of Research Excellence (SPOREs); Biology, Development, and Progression of Malignant Prostate Disease; and Role of Hormones and Growth Factors in Prostate Cancer.

[a] A given project may map to more than one PRG Priority One question and therefore be represented in more than one figure. Projects active in 2002 are listed by Principal Investigator's name for each PRG Priority One question in Appendix B (Tables B-1–B-11).

Table 3-1. (cont.)

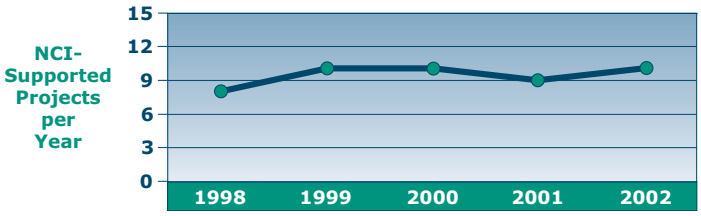
PRG Priority: What are the molecular determinants that govern cancer invasion, migration, and metastasis?



NCI Efforts:

- In FY 2002, active areas of investigation included opposing effects of kinases and phosphatases in cellular invasion, proteases that facilitate tumor growth and metastasis, protease inhibitors that prevent tumor metastasis, identification of specific metastasis-related genes from chromosomal mapping, DNA damage from estrogens and metabolism of estrogens, evaluation of Bcl-2 mutations in mouse models, metastatic potential of the methylated E-cadherin gene, and CXC chemokine dysregulated expression-induced angiogenesis.
- Five projects addressed the PRG recommendation to develop additional models to study cancer metastasis, particularly with respect to skeletal pathophysiology and its associated biochemical characteristics.
- NCI initiatives addressing this priority included Prostate SPOREs; Cancer Molecular Analysis Project (CMAP); Director's Challenge toward a Molecular Classification of Cancer; Biology, Development, and Progression of Malignant Prostate Disease; and Molecular and Cellular Biology of Metastatic Tumor Cells.

PRG Priority: What are the biochemical and molecular events that govern the continuation of prostate development from early embryogenesis to the onset of adulthood, through maturation, aging, and death?

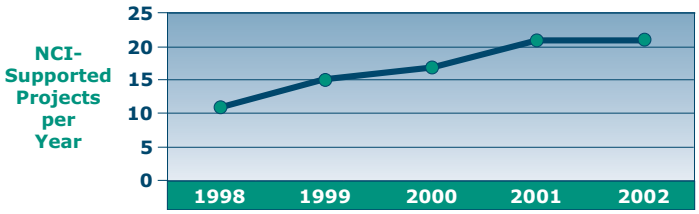


NCI Efforts:

- In FY 2002, active areas of investigation included IGF-I axis in prostate development and carcinogenesis, biochemical analysis and expression analysis of Nkx3.1 in mouse models, EPLIN protein expression and function in embryogenesis and tissue homeostasis, signal transduction processes in normal and dysregulated growth and differentiation, and gonadotrophin-releasing hormone and its receptor in normal and cancerous prostate tissues.
- NCI initiatives addressing this priority included Age-Related Prostate Growth: Biologic Mechanisms; Biology, Development, and Progression of Malignant Prostate Disease; Development of Cell-Selective Tools for Studies of the Bladder, Prostate, and Genitourinary Tract; and Role of Hormones and Growth Factors in Prostate Cancer.

Table 3-1. (cont.)

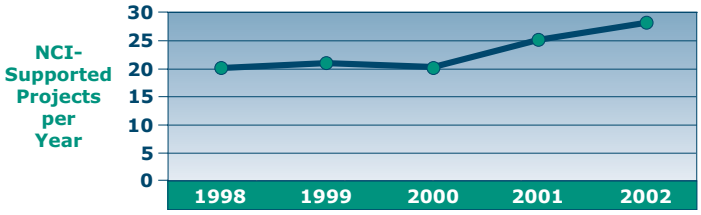
PRG Priority: What are the specific cell–cell interactions between and among developing epithelial cells, stromal cells, endothelial cells, neuroepithelial cells, and inflammatory cells?



NCI Efforts:

- In FY 2002, active areas of investigation included growth factors and receptors identified during tumor induction in epithelial and stromal cells, cell adhesion molecule interacting proteins, epithelial and endothelial cell proliferation regulated by integrin beta1C, and properties of carcinoma-associated fibroblasts that promote tumor progression.
- NCI initiatives addressing this priority included Age-Related Prostate Growth: Biologic Mechanisms; Development of Cell-Selective Tools for Studies of the Bladder, Prostate, and Genitourinary Tract; Prostate SPOREs; and Biology, Development, and Progression of Malignant Prostate Disease.

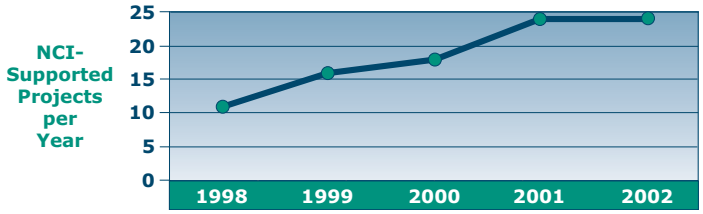
PRG Priority: What are the regulatory effector molecules that control reciprocal interactions between epithelial and stromal cells, among clonal cancer epithelial cells, and between cancer cells and most immune-reactive cells?



NCI Efforts:

- In FY 2002, active areas of investigation included connexin43-mediated gap junction communication, genes expressed in the presence of stromal cells that influence metastasis, age and other effects on tumor microenvironment, mechanisms of smooth muscle interactions with prostate epithelium, and signaling mechanisms that regulate differentiation and secretion of neuroendocrine cells.
- Two projects addressed the PRG recommendation to improve transgenic and other animal systems by introducing factors to the prostate gland in the hope of recapitulating the natural history of prostate development and its neoplastic transformation.
- NCI initiatives addressing this priority included Prostate SPOREs; Biology, Development, and Progression of Malignant Prostate Disease; and Role of Hormones and Growth Factors in Prostate Cancer.

PRG Priority: Are there features of DNA damage, DNA repair, or cell-cycle progression that are novel in prostate cancer cells?

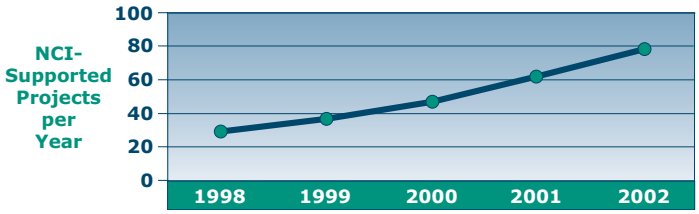


NCI Efforts:

- In FY 2002, active areas of investigation included free-radical scavengers and DNA damage, retinoblastoma-mediated induction of cell death, isopeptidase effects on apoptosis and cell-cycle arrest, BRCA2 and Rad51 mechanisms of DNA repair, TR3/nur77 mediation of cytochrome C release leading to apoptosis, and comparisons of chromosomal instability and DNA repair capacity.
- NCI initiatives addressing this priority included Improving DNA, RNA, and Protein Availability in Fixed Tissue.

Table 3-1. (cont.)

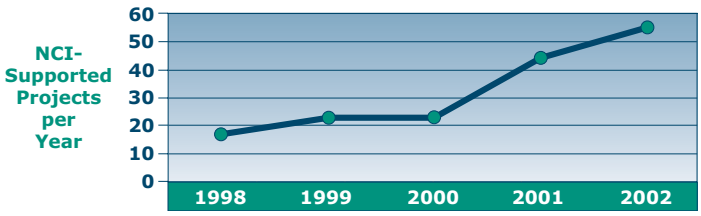
PRG Priority: What are the genetic and epigenetic determinants that affect progression of prostate cancer from the localized to disseminated state? What molecular markers are associated with such progression?



NCI Efforts:

- In FY 2002, active areas of investigation included tumor vasculogenesis, DNA methylation analyses, identification of proliferation-based changes in gene expression by microarray analysis, proteomic-based discovery of stage-specific protein expression, distinct roles of different fibroblast growth factor receptors, and characterization of putative tumor suppressor genes.
- Twenty-six projects addressed the PRG recommendation to validate genetic and epigenetic molecular markers by correlating them with clinical specimens.
- Twelve projects addressed the PRG recommendation to establish powerful methods that will allow "fast-track" discoveries.
- NCI initiatives addressing this priority included Cooperative Prostate Cancer Tissue Resource (CPCTR); Prostate SPOREs; Cancer Genome Anatomy Project (CGAP); CMAP; Director's Challenge: Toward a Molecular Classification of Cancer; Applications of Innovative Technologies for the Molecular Analysis of Cancer; and Biology, Development, and Progression of Malignant Prostate Disease.

PRG Priority: Are there hereditary markers, angiogenesis switches, and/or biochemical and molecular determinants that predict progression?

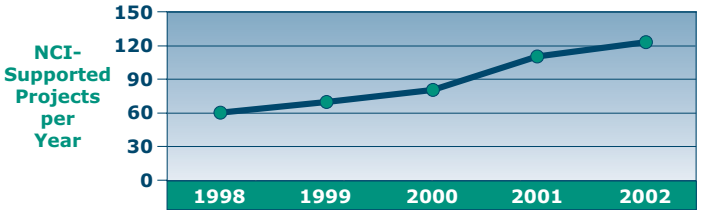


NCI Efforts:

- In FY 2002, active areas of investigation included regulation of parathyroid hormone-related peptide and derived peptides, plasminogen activator inhibitor-I role in angiogenesis, expression and mechanisms of polycomb group proteins (e.g., EZH2) in metastasis, and molecular classification of tumor progression and response to therapy.
- NCI initiatives addressing this priority included Prostate SPOREs; CMAP; CGAP; Director's Challenge: Toward a Molecular Classification of Cancer; Biology, Development, and Progression of Malignant Prostate Disease; and Molecular and Cellular Biology of Metastatic Tumor Cells.

Table 3-1. (cont.)

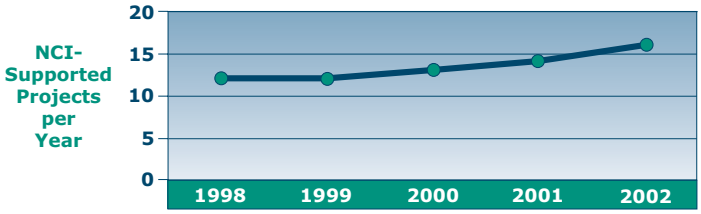
PRG Priority: What are the critical housekeeping and regulatory genes that may be associated with human prostate cancer development and progression?



NCI Efforts:

- In FY 2002, active areas of investigation included bcl-2 protein regulation by Ras, p53, and C/EBP proteins; tumor suppressor functions of proteins, including B-myc and Fez1; interactions and biological effects of kinases and phosphatases; inactivation of glutathione S-transferase P1 by CpG island methylation; signaling pathways in TNF-alpha-mediated apoptosis; and regulation of cell survival, apoptosis, and sensitivity to drugs and radiation by mitochondrial-associated factors.
- Five projects addressed the PRG recommendation to support the collaborative pursuit of discovering novel genes expressed during prostate cancer development and its progression to androgen independence.
- NCI initiatives addressing this priority included Prostate SPOREs; Studies on Breast, Prostate, Ovarian, and Cervical Cancer; CGAP; Applications of Innovative Technologies for the Molecular Analysis of Cancer; CMAP; Director's Challenge: Toward a Molecular Classification of Cancer; and Biology, Development, and Progression of Malignant Prostate Disease.

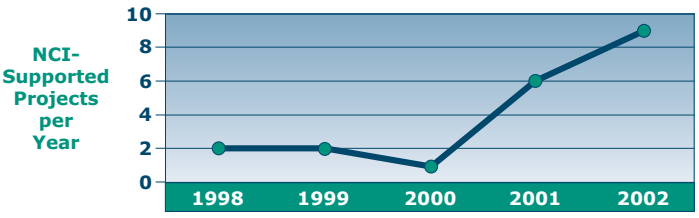
PRG Priority: How do we define genetic susceptibility of individuals to prostate cancer, and how is such susceptibility associated with other forms of malignancies or diseases?



NCI Efforts:

- In FY 2002, active areas of investigation included genetic map construction of chromosome region 8p21; functional roles of BRCA2, p21, and p53 as susceptibility genes; distribution and linkage of androgen and estrogen metabolizing enzyme polymorphisms; and linkage analysis of previously identified and novel genetic loci.
- NCI initiatives addressing this priority included Prostate SPOREs and Molecular Epidemiology of Prostate Carcinogenesis.

Additional prostate cancer biology projects that did not address the PRG priority questions in this table.



NCI Efforts:

- In FY 2002, active areas of investigation included intracellular calcium modulation associated with apoptosis, structural characterization of Akt kinase, NF-kB transcription factor correlation with cellular oxidative stress, and bioavailability and biotransformation of isoflavonoids.

Much of the NCI's responsiveness to PRG recommendations has been through initiatives soliciting new projects on prostate cancer biology. The initiatives relevant to research on prostate cancer biology between 1998 and 2002 include the following list of general initiatives that are described in Table 2-1[1] (Chapter 2) and the category-specific initiatives that are listed and described in Table 3-2:[2]

- Applications of Innovative Technologies for the Molecular Analysis of Cancer
- Cancer Centers Program
- Cancer Genome Anatomy Project (CGAP)
- Cancer Imaging Program
- Cancer Molecular Analysis Project (CMAP)
- Cancer Research Training, Career Development, and Education Opportunities
- Cooperative Human Tissue Network (CHTN)
- Cooperative Prostate Cancer Tissue Resource (CPCTR)
- Director's Challenge: Toward a Molecular Classification of Cancer
- Improving DNA, RNA, and Protein Availability in Fixed Tissue
- In Vivo Cellular and Molecular Imaging Centers (ICMICs)
- Minority Institution/Cancer Center Partnership (MI/CCP) Program
- Molecular Epidemiology of Prostate Carcinogenesis
- NCI Center for Bioinformatics
- Program for the Assessment of Clinical Cancer Tests (PACCT)
- Prostate Specialized Programs of Research Excellence (SPOREs)
- Small Animal Imaging Resource Program (SAIRP)
- Specimen Resource Locator
- Technologies for Comprehensive, Sensitive, and Quantitative Protein Analysis in Human Tumors: Phased Innovation

[1] Initiatives that impact multiple categories of prostate cancer research.

[2] Initiatives unique to the biology research category.

Table 3-2. NCI Initiatives Relevant to Prostate Cancer Research: Biology

INITIATIVES FOCUSED ON PROSTATE CANCER

Age-Related Prostate Growth: Biologic Mechanisms (PA-02-116)

Objective: Explore biologic mechanisms of initiation and progression of age-related development and pathophysiologic processes.

Relevant Research Programs Resulting from This Program Announcement (PA): Pending

Biology, Development, and Progression of Malignant Prostate Disease (PA-99-081)

Objective: Study the biology underlying the development and progression of malignant prostatic disease.

Relevant Research Projects Resulting from This PA:

- Androgen-Independent Prostate Cancer: Mechanisms and Treatment
- Angiopoietins in Prostate Biology and Disease
- Apoptosis Regulation by Lipid Signals in Prostate Cancer
- Beta Catenin in Prostate Cancer
- Cyclin D1 Function in Prostate Cancer
- Death Receptors in Prostate Cancer Biology and Apoptosis
- Ebp1 Control of Prostate Cancer Cell Growth
- Endothelial Growth Factor in Prostate Cancer Metastasis
- EphA2 Agonists as Novel Inhibitors of Tumor Progression
- Fibroblast Growth Factor Receptor Signaling in Prostate Development and Cancer
- Functional Analysis of the PTEN Tumor Suppressor Protein
- Gene Expression in Diet-Induced Prostate Cancer
- Growth Control of Prostate Cancer Cells by Plant Phenols
- GSTP1 Gene Repression in Prostate Cancer
- Host/Tumor Interactions in Immunotherapy of Prostate Cancer
- Integrin Signaling Pathways in Prostate Cancer
- Mechanism of Apoptosis by Par4
- Mechanisms of Metastasis in Experimental Prostate Cancer
- Modes of Prostate Cancer Progression—Role of p53 Pathway
- Molecular Dissection of 13q14 in Prostate Cancer
- Molecular Regulation of Androgen Receptor Activation
- Neutral Endopeptidase Inactivation in Advanced Prostate Cancer
- Progression/Oncogene Induced Prostate Cancer
- Prostate Cancer, Bone Metastasis, and Metalloproteinases
- Prostate Cancer Metastatic Colonization—Role of MKK4
- Prostate Carcinogensis and PKC Signaling
- Prostatic Vasculogenic Mimicry: A New Metastatic Pathway
- Repressors in Prostate Cancer
- Role of a New Ets Factor, PDEF, in Prostate Cancer
- Serine Proteases in Prostate Cancer Metastasis
- Testing of Novel Apoptotic Agents in Prostate Cancer
- TGF-Beta/Smads and Androgen Signaling in Prostate Cancer
- TNF-Alpha-Mediated Apoptosis in Prostate Cancer
- Tumor Suppressor Gene at 13q21 in Prostate Cancer

Table 3-2. (cont.)

Development of Cell-Selective Tools for Studies of the Bladder, Prostate, and Genitourinary Tract (PAR-02-143)

Objective: Develop new, cell-selective research tools and methods that apply to studies of the bladder, prostate, and other organs of the genitourinary tract.

Relevant Research Projects Resulting from This PA: Pending

Role of Hormones and Growth Factors in Prostate Cancer (RFA-DK-01-008)

Objective: Explore the underlying mechanisms of action of hormones and growth factors in regulating prostate development, growth, and tumorigenesis.

Relevant Research Projects Resulting from This Request for Applications (RFA):

- Calcitonin in Prostate Growth and Neoplasia
- Eph Kinase Signaling in Prostate Cancer

INITIATIVES WITH PROSTATE CANCER-RELEVANT COMPONENTS

Molecular and Cellular Biology of Metastatic Tumor Cells (PA-01-020)

Objective: Study the molecular and cellular biology of metastatic tumor cells through collaborations that facilitate scientific interchange between investigators with experience in the biology of metastasis and in more basic scientific disciplines such as molecular or cellular biology, or biochemistry.

Relevant Research Project Resulting from This PA: Prostate Cancer Metastasis to Bone

Ongoing NCI Research: Recent Progress in Prostate Cancer Biology

Early Prostate Cancer

Prostate cancer development proceeds through a series of defined states, including preinvasive disease or prostatic intraepithelial neoplasia, androgen-dependent cancer, and eventually androgen-independent metastasis. Studies using rodent models and human tumor samples have contributed significantly toward a better understanding of early prostate carcinogenesis.

Molecular genetic studies of prostate cancer have identified mutations, deletions, or loss of expression of tumor suppressor genes (e.g., Nkx3.1, p53, and PTEN) as well as overexpression or amplification of oncogenes (e.g., c-MYC, HER2, and BCL-2) in subsets of tumors (Abate-Shen and Shen, 2000; Moul et al., 2002). Due to the heterogeneity of prostate cancer itself and the focal nature of oncogene/tumor suppressor gene alterations, the role of these genes in prostate cancer onset and the diagnostic and/or prognostic value of such gene alterations remain uncertain. Molecular genetic alterations that are present in a homogeneous manner and with high frequency in prostate cancer are being discovered through unbiased genome scanning or global gene expression profiling approaches. Some of the more common prostate cancer-associated genetic alterations now include loss of glutathione S-transferase-pi expression, overexpression of HEPSIN and alpha-methylacyl-CoA racemase, and consistent loss or gain of specific chromosomal hot spots.

Analysis of genome alterations in prostate cancer cells has revealed that somatic inactivation of GSTP1, which encodes the carcinogen-detoxifying enzyme glutathione S-transferase-pi, may serve as an initiating genome lesion for prostatic carcinogenesis (Nelson et al., 2001). The loss of GSTP1 leaves cells vulnerable to damage, increasing the chances of further genetic mutation that could lead to malignant transformation. The inactivation of this gene occurs by a mechanism of gene silencing termed

hypermethylation (Lin X et al., 2001) and is detected in up to 90 percent of prostate cancers (Lee et al., 1994). There is an association between hypermethylation and loss of GSTP1 protein expression in men with prostate cancer (Song et al., 2002), and NCI-supported work has shown that it may be possible to screen for GSTP1 levels in urine (Gonzolgo et al., 2003).

Development of Hormone-Refractory Tumors

Standard therapy for prostate cancer relies on blocking or removing hormones called androgens, which are necessary for normal prostate growth. While most tumors initially respond to this therapy, the tumor may become resistant (refractory), resulting in disease progression. Recent research has shown that, perhaps counterintuitively, the androgen receptor (AR) has a functional role in androgen-refractory prostate cancer (Zegarra-Moro et al., 2002). Data from several laboratories have resulted in the elucidation of multiple mechanisms behind the transformation of a tumor from androgen dependence to androgen independence (Grossmann et al., 2001).

- Amplification of the AR gene may increase the sensitivity of tumor cells to the remaining androgens in the body (Grossmann et al., 2001; Zegarra-Moro et al., 2002). The AR gene is rarely amplified in primary prostate but is amplified in up to 30 percent of androgen-refractory prostate tumors. AR gene amplification also has been associated with p53 mutations.
- Mutations in the AR gene may make the AR more sensitive to androgens or allow it to bind to other steroids, adrenal androgens, or even anti-androgens (Grossmann et al., 2001; Zegarra-Moro et al., 2002).
- Overexpression of AR coactivators, or reduced expression of AR corepressors, could lead to activation of the AR by other hormones or even by anti-androgens. AR coactivators may also stimulate the transcription of AR in the presence of low levels of androgens or other steroids and activate pathways downstream of the AR (Grossmann et al., 2001; Zegarra-Moro et al., 2002).
- Tumor cells may bypass the AR pathway altogether in their transformation to androgen independence. Possible mechanisms include neuroendocrine cell differentiation, activation of PI3 kinase and related pathways, and loss of *PTEN* function (Grossmann et al., 2001).

Progression, Metastasis, and the Role of Tumor Microenvironment

A growing body of evidence indicates that the microenvironment in which tumors develop profoundly affects the many steps of tumor progression. Results from experimental tumor models emphasize the contribution of stromal components within this microenvironment in shaping several aspects of tumor formation, including growth efficiency, growth rate, ability to metastasize, and extent of invasiveness. For example, NCI-supported investigators have demonstrated that prostate tumor growth in vivo could be accelerated by co-culture with cancer-associated fibroblasts, but not by benign tissue-associated fibroblasts (Olumi et al., 1998). These effects are mediated in part by paracrine signaling mechanisms between tumor cells and neighboring stromal fibroblasts, leading to the generation of a reactive stromal environment that, in turn, promotes tumorigenesis. This reciprocal interaction has been described as causing a “vicious cycle” between stromal and tumor cell components within the prostate and may contribute to prostate cancer progression.

One mechanism by which this “vicious cycle” is activated is through the secretion of cytokines, growth factors, and/or extracellular matrix components by the tumor. These factors may alter the morphology and gene expression of surrounding stroma such that it reciprocally induces the growth and gene expression of tumor epithelium. For example, recent NCI-supported research has shown that a soluble protein termed transforming growth factor-beta (TGF-beta) stimulates the switch of prostate stromal fibroblasts located near the tumor to a reactive state, in which they display a myofibroblast phenotype and express tenascin (Tuxhorn et al., 2002). TGF-beta was also shown to regulate the stroma’s ability to initiate and promote angiogenesis and tumor growth. In one experiment, prostate tumors were

generated in the presence of reactive stroma and a TGF-beta inhibitor. The resulting tumors had fewer blood vessels than control tumors and were nearly half the size of control tumors (Tuxhorn et al., 2001). Thus, it is evident that TGF-beta plays an important role in prostate cancer progression.

A second paracrine signaling loop that is active in prostate cancer progression involves the soluble protein hepatocyte growth factor (HGF) and its cognate ligand c-Met. NCI-funded researchers recently reported that the addition of prostate-derived stromal cells to prostate tumor cells significantly enhanced the growth of the tumor cells in nude mice (Nakashiro et al., 2000). In vitro studies revealed that HGF was the molecule responsible for this effect and that HGF secreted by the stromal cells directly stimulates the growth of prostate carcinoma cells by binding to c-Met receptors expressed on the surface of those cells (Nakashiro et al., 2000). Furthermore, these researchers determined that expression of c-Met on the tumor cells increases with stage of prostate cancer progression (Nakashiro et al., 2003).

In addition to paracrine-mediated mechanisms of tumor progression, autocrine signaling and genetic instability may also contribute to the "vicious cycle" of prostate cancer progression. NCI-supported research has shown that soluble factors such as Nox1 and vascular endothelial growth factor are secreted by the tumor cells themselves and can promote further tumor growth (Arbiser et al., 2002). Chromosomal loss or gain in prostate tumor cells can be exacerbated by the interaction of tumor cells with stromal components (Rhee et al., 2001; Tlsty, 2001). The extent to which each of these mechanisms contributes to prostate tumor progression and metastasis is a continuing area of research.

Bone Metastasis

A major contribution to our understanding of the process of bone metastasis has been the demonstration that the bone microenvironment critically influences the behavior of cancer cells that metastasize to bone by altering the phenotype of the metastatic tumor cells. Furthermore, some of the molecular mechanisms responsible for the bi-directional interaction between bone and tumor cells in vivo have been recently identified. A few examples are briefly described.

Hyaluronan synthase (HAS, the enzyme used to produce hyaluronan) is necessary for bone metastasis. Increased expression of hyaluronan synthase by prostate tumor cells triggers adhesion of the tumor cells to bone marrow endothelial cells, allowing the tumor cells to spread to bone (Simpson et al., 2001; Simpson et al., 2002a). When HAS synthesis was inhibited in prostate cancer cells injected into mice, the resulting tumors were smaller and had up to an 80 percent reduction in vascularization compared with controls (Simpson et al., 2002b). Conversely, when tumor cells were transfected with the gene for HAS3 (one of three forms of the enzyme), they grew at a faster rate in cell culture and formed larger tumors than control cells when injected into mice (Liu et al., 2001).

As prostate cancer cells become more aggressive, they exhibit osteo-mimetic properties such as the inappropriate expression of osteoblast-specific genes and proteins, which can stimulate the formation of osteoblastic lesions in the bone. For example, the osteotropic prostate cancer cell line C4-2B, but not its non-skeletal metastatic parent cell line LNCaP, induces bone mineralization through the release of factors such as osteocalcin, alkaline phosphatase, and osteonectin (Lin DL et al., 2001). The production of these proteins by prostate carcinoma cells illustrates potential mechanisms by which metastatic skeletal lesions are formed that characterize advanced prostate cancer (Keller et al., 2001).

The role of proteases in prostate cancer metastasis is another active area of interest. Urokinase-type plasminogen activator (uPA) is a protease that is normally expressed in the bone and stimulates the natural turnover of bone cells. This enzyme is also expressed by metastatic prostate cancer cells that spread to the bone. Increased expression of uPA by tumor cells in the bone contributes to the proteolytic remodeling of the bone matrix, resulting in increased survival for tumor cells in the bone microenvironment (Goltzman, 1997). Maspin is a potent inhibitor of uPA that is expressed by normal prostate cells but not highly invasive prostate cancer cells. Recent work has shown that tumor cells engineered to express maspin cannot form invasive tumors in the bone. Such maspin-containing cells can neither degrade bone

nor induce blood vessel formation and remain enmeshed in calcified extracellular matrix (Cher et al., 2003). Thus, maspin presents an exciting therapeutic potential to treat and prevent bone metastasis in prostate cancer.

Continuing Needs and Evolution

Recent research on the biology of prostate cancer has opened many doors. The advent of microarray technology will facilitate the analysis of hundreds of tumors and thousands of genes and is already helping illuminate the complex web of biological changes that leads to prostate cancer. For example, microarray analysis of metastatic prostate cancer tissue versus localized prostate cancer tissue showed greater upregulation of neural cell adhesion molecule (N-CAM) in the nerves of metastatic tissue, implicating N-CAM in neural invasion and metastasis (Li et al., 2003a). Recently, published microarray studies have implicated altered expression of NAG-1, ASCT2, ZnT4, 5-alpha-reductase-2, protein kinase C-mu, and many others in prostate cancer initiation and/or progression (Iczkowski and Pantazis, 2003; Li et al., 2003b; Henshall et al., 2003; Luo et al., 2003; Jaggi et al., 2003).

We are beginning to define the intracellular mechanisms responsible for malignant transformation and cancer progression, as well as the interactions between the cancer cell and its environment that influence organ invasion, metastases, hormone-independent growth, and resistance to cell death.

– National Institutes of Health, Prostate Cancer Research Plan for FY 2003–2008.

For biological knowledge to translate into clinical practices that can reduce the burden of prostate cancer, research must continue to examine and understand the biology of the normal prostate, especially as it relates to the earliest stages of malignant transformation. Studies on cell–cell and cell–matrix communication will further the understanding of carcinogenesis and lead to treatments targeting both the tumor and its microenvironment. The discovery of tumor markers, as well as markers of progression and of response to treatment, will allow for earlier diagnosis and targeted treatment of a disease that continues to be the most commonly diagnosed cancer and the second-leading cause of cancer death in U.S. men.

NCI's Future Investment in Prostate Cancer Biology

The NIH Prostate Cancer Research Plan for FY 2003–2008 describes the NCI's planned objectives for research on the biology, progression, and metastasis of prostate cancer. The objectives are based on the priorities identified by the PRG and the advances that have taken place since completion of the PRG's work. The five FY 2003–2008 objectives and their alignment to the ten PRG priorities are shown in Figure 3-2.

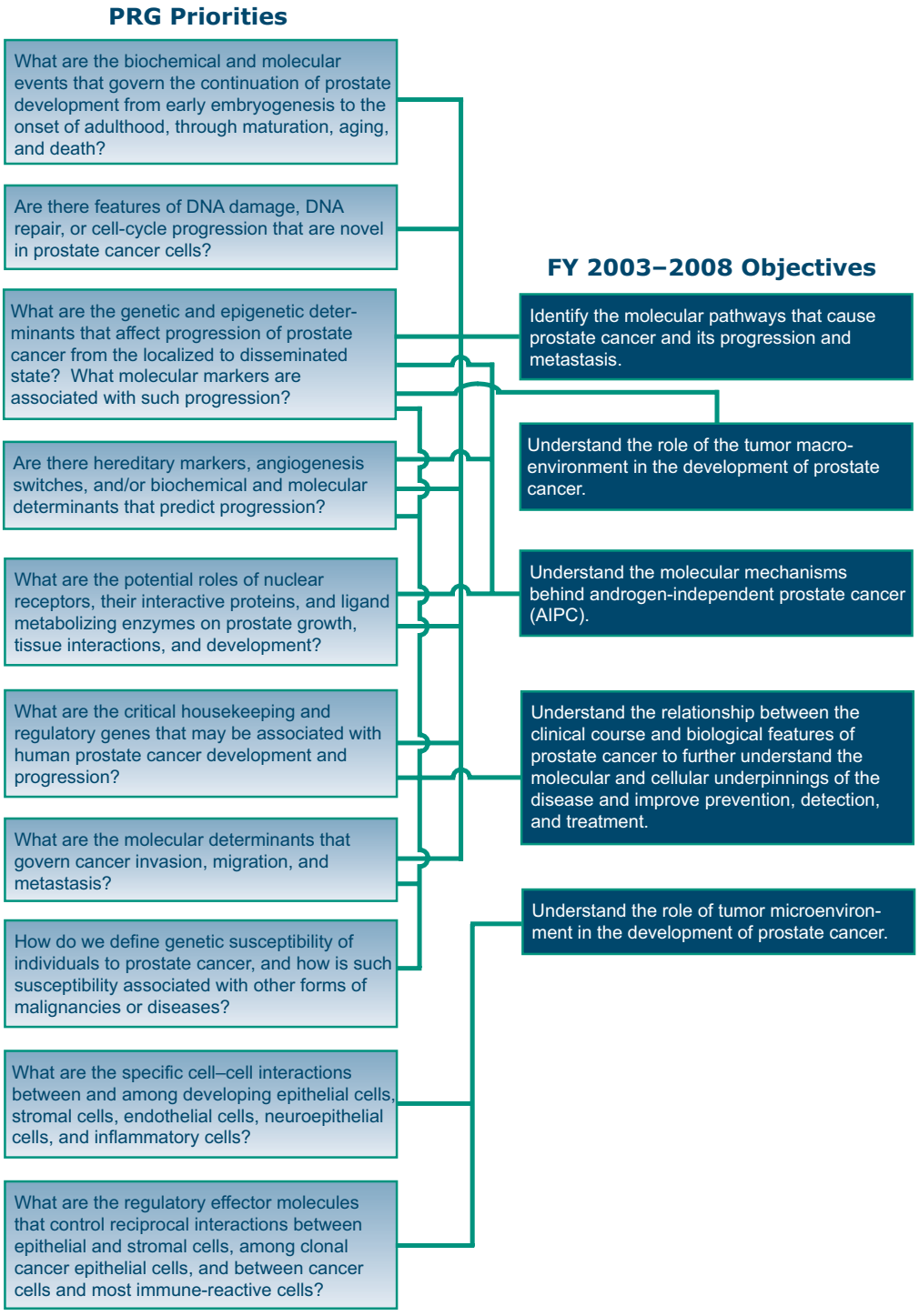


Figure 3-2. NIH's FY 2003–2008 prostate cancer biology research objectives build upon the 1998 PRG priorities.

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CHAPTER 4

Etiology and Prevention of Prostate Cancer: NCI's Investment and Recent Progress

By pursuing research on the direct causes and modulators of prostate cancer, the NCI has opened the door to the possibility of prostate cancer prevention. Genetic, dietary, lifestyle, and environmental factors are being examined for their impact on prostate cancer risk. In addition, the biologic pathways leading to the onset of prostate cancer or the progression of an otherwise indolent prostate cancer are being characterized. These endeavors have led to behavioral and drug-based strategies for reducing risk and blocking the cellular and molecular events that are required for tumor formation.

In their 1998 report, the Prostate Cancer PRG described the continuing challenge of determining prostate cancer risk factors and enabling the development of preventive agents. The report indicated that, while prevention is an appealing approach to controlling prostate cancer, classic epidemiologic studies have revealed few indisputable risk factors to pinpoint exact causes. Studies have documented the risk factors of age, family history, race/ethnicity, and nationality, but this documentation has not identified the biological, environmental, and lifestyle causes of prostate cancer or the interactions of these factors. The lack of established risk factors limits preventive efforts and highlights the need to better understand the biology of both normal and malignant prostate cells and tissues. In addition, a better understanding of how genetic predisposition and exogenous factors interact to determine prostate cancer susceptibility is needed to design effective prevention strategies. Beyond identifying prevention strategies, this approach will facilitate the development of methods to aggressively control progression of the disease and reduce mortality.

An important goal in prostate cancer prevention is to identify men at high risk of developing life-shortening forms of the disease, and to understand how lifestyle characteristics and exogenous exposures influence this risk. This understanding will allow the development of effective prevention strategies.

– Defeating Prostate Cancer: Crucial Directions for Research - Report of the Prostate Cancer Progress Review Group, August 1998.

NCI has been responsive to the eight PRG Priority One questions related to prostate cancer etiology and prevention. The questions and accompanying recommendations in the 1998 report addressed the priorities for identifying genetic, dietary, environmental, and other risk factors to develop a sound knowledge base. Corresponding with this line of research, NCI-sponsored investigators have been working to determine which of these risk factors are due to racial differences; whether there are genetic and/or environmental interactions that modify risk; and the identity of promising preventive agents and activities. Biological studies of carcinogenesis and clinical studies on higher risk cohorts have accelerated the discovery of important biological mechanisms of prostate cancer and the identification of how different etiologic variables interact and contribute to the onset and progression of disease.

NCI's Investment and Response

From fiscal year (FY) 1998 to FY 2002, the NCI investment for extramural prostate cancer etiology and prevention research grew from $19.5 million (M) to $78.9M (Figure 4-1).

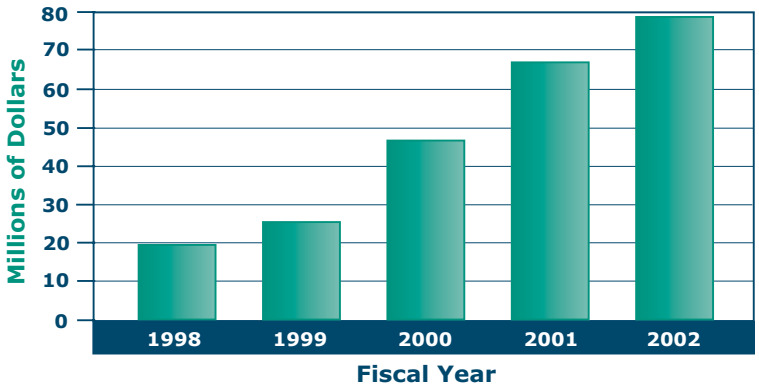
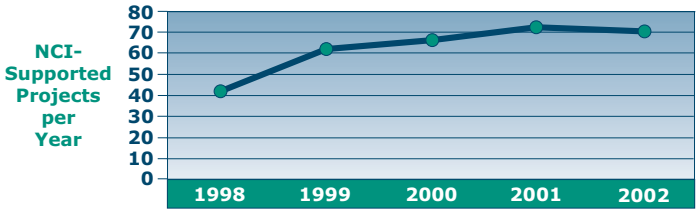


Figure 4-1. NCI's extramural investment in prostate cancer etiology and prevention research: 1998–2002 (in millions of dollars).

NCI's response to the eight Prostate Cancer PRG Priority One research questions for etiology and prevention is summarized in Table 4-1.

Table 4-1. NCI Efforts Responsive to PRG Priorities in Prostate Cancer Etiology and Prevention[a]

PRG Priority: What genes are important in the etiology of prostate cancer? What fraction of familial prostate cancer is monogenic with Mendelian inheritance of susceptibility alleles? What is the function of such genes?



NCI Efforts:

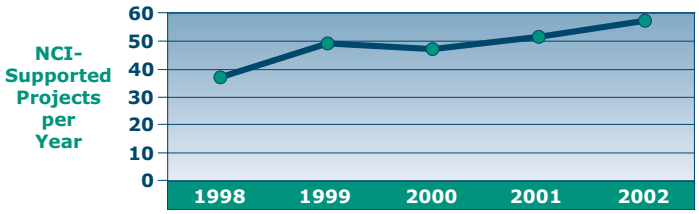
- In FY 2002, active areas of investigation included linkage analysis of previously identified and novel genetic loci, association of genetic polymorphisms (e.g., androgen receptor and insulin-like growth factor [IGF] pathway genes, and drug metabolizing genes) and prostate cancer risk and carcinogenesis, genetic studies in Chinese and Israeli men, prostate epithelial cell transformation, genetic analysis of hereditary prostate cancer, genetics of prostate susceptibility, and BRCA1 as a prostate tumor suppressor gene.
- The feasibility of accruing prostate cancer patient–sibling pairs is being assessed for the clinical trial *Genetic Mapping of Interactive Susceptibility Loci in Patients and Siblings with Breast, Colon, Lung, or Prostate Cancer (E-1Y97)*.
- Eighteen projects addressed the PRG recommendation that families with multiple cases of prostate cancer be studied to identify hereditary factors.
- The PRG recommended genetic factors be studied:
  - Fourteen projects addressed the recommendation that factors involved in testosterone synthesis, function, and degradation be examined.
  - Forty-one projects addressed the association of genetic polymorphisms and prostate cancer.
  - Three projects addressed the development of transgenic or gene knockout mice to validate the role of genes associated with prostate cancer.

[a] A given project may map to more than one PRG Priority One question and therefore be represented in more than one figure. Projects active in 2002 are listed by Principal Investigator's name for each PRG Priority One question in Appendix B (Tables B-12–B-20).

Table 4-1. (cont.)

- In 2000, NCI sponsored a workshop on Emerging Opportunities in Cancer Epidemiology; and in 2001, NCI and the Office of Rare Diseases sponsored a workshop on Genetic Susceptibility to Prostate Cancer.
- NCI initiatives addressing this priority included Prostate Specialized Programs of Research Excellence (SPOREs), Molecular Epidemiology of Prostate Carcinogenesis, Cancer Genetics Network (CGN), and Small Grants Program for Cancer Epidemiology.

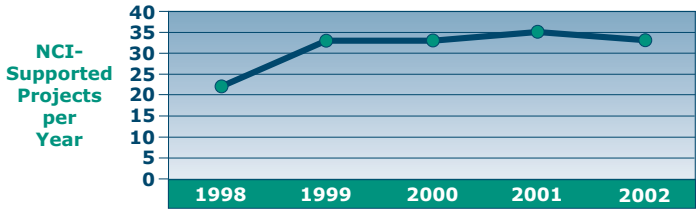
PRG Priority: Which dietary nutrients affect risk of prostate cancer (e.g., fat, phytoestrogens, and micronutrients)? What are the mechanisms by which these nutrients alter risk?



NCI Efforts:

- In FY 2002, active areas of investigation included genes expressed in diet-induced cancer, molecular epidemiology of dietary prevention, diet and multiethnic populations and cancer, carcinogenicity of heterocyclic amines, and prevention and cancer control through various dietary components/supplements (e.g., lycopene, selenium, flaxseed, beta-carotene, and alpha-tocopherol).
- The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is projected to complete the accrual of 32,400 men by summer 2004 to determine if dietary selenium and/or vitamin E are beneficial in reducing prostate cancer risk.
- Examples of additional clinical trials addressing this priority include the following:
  - *Phase I Study of Lycopene for the Chemoprevention of Prostate Cancer* (NCI-P00-0143)
  - *Phase II Randomized Study of Dietary Soy in Patients with Elevated PSA Levels* (NCI-P02-0207)
  - *Phase II Randomized Study of the Effects of a Low-Fat, High-Fiber Diet on Serum Factors in Patients with Prostate Cancer* (NCI-G01-1973)
- The PRG recommended that the role of nutrients be examined in large-scale investigations. Twenty-four projects addressed the recommendation to initiate long-term nutritional science and epidemiologic studies and to attach dietary measurement studies to ongoing clinical trials.
- The PRG recommended specific studies of the biochemistry of nutrients:
  - Nine projects addressed the role of nutrients in androgen production and prostate physiology.
  - Fifteen projects addressed the genetic factors regulating metabolism and transport of specific nutrients.
- NCI initiatives addressing this priority included Molecular Epidemiology of Prostate Carcinogenesis, Prostate SPOREs, Cancer Prevention Research Small Grant Program, and Small Grants Program for Cancer Epidemiology.

PRG Priority: What other exogenous risk factors are involved in prostate cancer (e.g., viral, exercise, vasectomy, and sexual factors)?

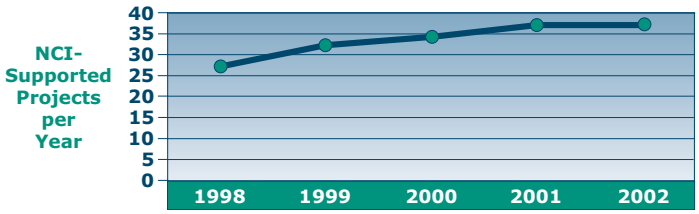


NCI Efforts:

- In FY 2002, active areas of investigation included biostatistics and epidemiology, metals and carcinogenesis, role of viruses (e.g., herpesviruses), effects of medications (e.g., NSAIDs), and occupational exposures.
- NCI initiatives addressing this priority included the Small Grants Program for Cancer Epidemiology.

Table 4-1. (cont.)

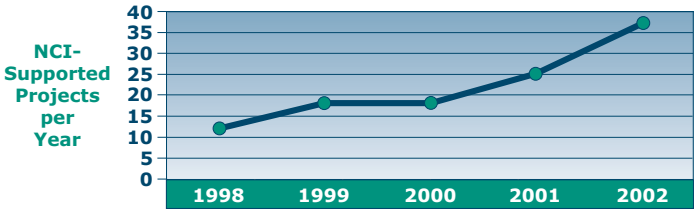
PRG Priority: Which genetic and exogenous risk factors account for differences in incidence and mortality among African American, Caucasian, Hispanic, and Asian American populations?



NCI Efforts:

- In FY 2002, active areas of investigation included susceptibility genes in African and Hispanic Americans, genetic polymorphisms in different populations, epidemiology outside the United States (e.g., Shanghai and Africa), and epidemiology in rural areas of the United States.
- Thirty-six projects addressed the PRG recommendation to establish cohorts of African American, Hispanic American, and Asian American men to study genetic and lifestyle factors in different populations.
- NCI initiatives addressing this priority included Molecular Epidemiology of Prostate Carcinogenesis, the NCI Cohort Consortium, and the Small Grants Program for Cancer Epidemiology.

PRG Priority: Are there genetic or exogenous factors associated with prostate cancer progression, as opposed to its incidence?

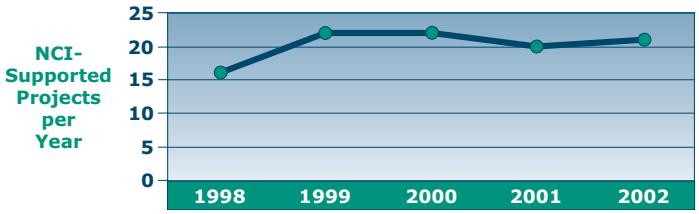


NCI Efforts:

- In FY 2002, active areas of investigation included physical changes of prostate correlated to molecular changes, PSA level and PSA glycosylation correlated to patient clinical status, endogenous sex hormone levels, polymorphisms of susceptibility genes including metabolism and transport genes, stage-specific gene expression libraries, and reactive oxygen damage to DNA.
- Examples of clinical trials addressing this priority include the following:
  - *Phase II Randomized Prevention Study of Fat- and/or Flaxseed-Modified Diets in Patients with Newly Diagnosed Prostate Cancer* (NCI-P02-0235)
  - *Phase II Randomized Study of Dietary Soy in Patients with Elevated PSA Levels* (NCI-P02-0207)
  - *Phase II Randomized Study of the Effects of a Low-Fat, High-Fiber Diet on Serum Factors in Patients with Prostate Cancer* (NCI-G01-1973)
  - *Phase II Randomized Study of Doxercalciferol in Patients with Localized Prostate Cancer* (NCI-N01-CN-95130)
  - *Phase II Randomized Study of Toremifene Followed by Radical Prostatectomy in Patients with Stage I or II Adenocarcinoma of the Prostate* (NCI-P01-0181)
  - *Phase II Clinical Trial of Soy Isoflavones prior to Radical Prostatectomy*
  - *Phase II Chemoprevention Trial of Selenium and Prostate Cancer (Watchful Waiting with Selenium Trial)*
  - *Phase III Trial of Selenium for Prostate Cancer Prevention (Negative Biopsy Trial)*
  - *Phase III Randomized Study of Selenium as Chemoprevention of Prostate Cancer in Patients with High-Grade Prostatic Intraepithelial Neoplasia* (NCI-P02-0203)
  - *Randomized Study of Flutamide for Prostate Cancer Prevention in Patients with High-Grade Prostatic Intraepithelial Neoplasia (* NCI-P00-0156)
  - *Randomized Study of Isoflavones in Reducing Risk Factors in Patients with Stage I or II Prostate Cancer* (NCI-4031)
- Twelve projects addressed the PRG recommendation that prospective cohort studies be used to evaluate risk of recurrence, metastasis, and/or death.
- NCI initiatives addressing this priority included Molecular Epidemiology of Prostate Carcinogenesis, Prostate SPOREs, the Clinical Trials Cooperative Group Program, Exploratory Grants for Correlative Laboratory Studies and Clinical Trials, and the Minority-Based Community Clinical Oncology Program (MBCCOP).

Table 4-1. (cont.)

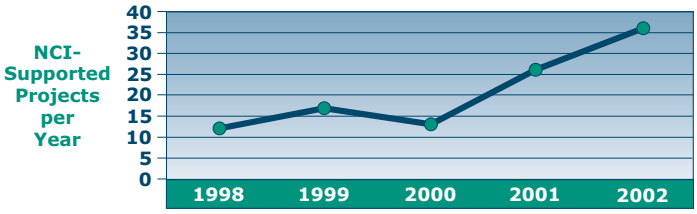
PRG Priority: Are there interactions between genetic predisposition and exogenous exposures?



NCI Efforts:

- In FY 2002, active areas of investigation included pharmacogenetics of metabolizing enzymes; correlation of selenium, beta-carotene, and IGF-1 gene variants to clinical disease; international studies of cancer epidemiology; and risks attributed to herbicide exposure.
- Thirteen projects addressed the PRG recommendation to support studies that evaluate gene–environment interactions.
- NCI initiatives addressing this priority included Prostate SPOREs, the NCI Cohort Consortium, and the Small Grants Program for Cancer Epidemiology.

PRG Priority: What interventions can alter the underlying etiology of prostate cancer? What are the most promising potential preventive agents and activities?



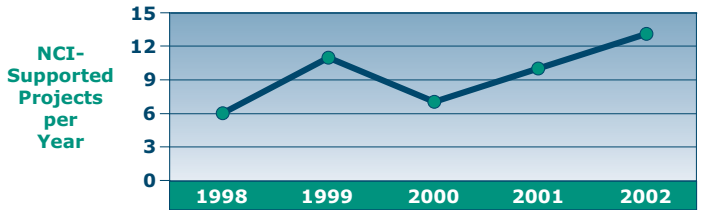
NCI Efforts:

- In FY 2002, active areas of investigation included biological mechanisms of chemoprotection by cottonseed oil, retinoids, isoflavones, and sanguinarine; proliferative inflammatory atrophy as a target for preventive therapy; bioavailability of tea polyphenols; and plant engineering for new dietary sources of selenium.
- In addition to the dietary intervention clinical trials, listed for a priority described earlier, the following trials address this priority: *Prostate Cancer Prevention Trial* (NCI-P93-0049) and *Phase IIB Randomized Chemoprevention Study of Eflornithine (DFMO) in Patients at High Genetic Risk for Prostate Cancer* (NCI-P00-0164).
- Sixteen projects addressed the PRG recommendation to investigate mechanisms of potential chemopreventive interventions.
- The PRG recommended that the design of chemoprevention trials be examined to make the process more efficient:
  - Eleven projects addressed the development of endpoint or surrogate endpoint markers for chemoprevention trials.
  - Three projects addressed efficient and appropriate design of new prevention trials.
- In August 1999, the NCI sponsored the workshop *Strategies for New Clinical Trials for Prostate Cancer Chemoprevention*. The Proceedings of the workshop were published in the April 2001 Supplement to *Urology*.[b]
- NCI initiatives addressing this priority included Molecular Epidemiology of Prostate Carcinogenesis, Prostate SPOREs, the Clinical Trials Cooperative Group Program, MBCCOP, Molecular Target Drug Discovery for Cancer, the Cancer Prevention Research Small Grant Program, Chemoprevention in Genetically Identified High-Risk Groups: Interactive Research and Development Projects, and Rapid Access to Preventive Intervention Development (RAPID) Program.

[b] *Urology* 57 Issue 4 (Supplement 1).

Table 4-1. (cont.)

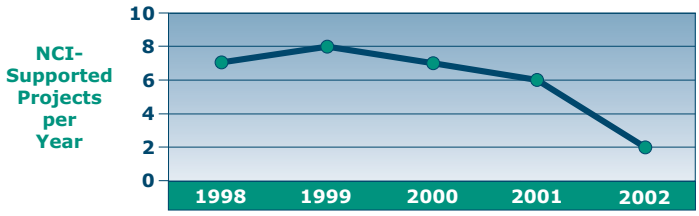
PRG Priority: What is the potential of new animal models for testing of potential chemopreventive agents?



NCI Efforts:

- In FY 2002, active areas of investigation included mechanisms of dietary protection in lac transgenic mice and rats, hormone treatments and caloric restriction in mice with or without specific tumor suppressors, dihydroxyvitamin D mechanisms of prevention in mice with human prostate tumor xenografts, preventive effects of plant phenols on mice, and selecting chemopreventive agents using the transgenic adenocarcinoma mouse prostate model.
- NCI initiatives addressing this priority included Prostate SPOREs.

Additional etiology and prevention projects that did not address the PRG priority questions in this table.



NCI Efforts:

- In FY 2002, active areas of investigation included general demographic analysis and developing isoflavone-fortified foods.

A portion of the NCI's responsiveness to PRG priorities and recommended actions consisted of clinical trials. In addition to the compounds in clinical trials listed in Table 4-1, the following compounds have been recently examined for effectiveness at reducing the risk of prostate cancer development or progression: Exisulind, Celecoxib, Acapodene (GTx-006), Casodex, vitamin C, and multivitamins.

The initiatives relevant to research on prostate cancer etiology and prevention between FY 1998 and 2002 include the following list of general initiatives that are described in Table 2-1[1] (Chapter 2) and the category-specific initiatives that are listed and described in Table 4-2:[2]

- Cancer Centers Program
- Cancer Genome Anatomy Project (CGAP)
- Cancer Molecular Analysis Project (CMAP)
- Cancer Research Training, Career Development, and Education Opportunities
- Clinical Trials Cooperative Group Program
- Common Data Elements (CDE) Initiative

[1] Initiatives that impact multiple categories of prostate cancer research.

[2] Initiatives unique to the research category of *Etiology and Prevention*.

- Community Clinical Oncology Program (CCOP)
- Cooperative Human Tissue Network (CHTN)
- Cooperative Prostate Cancer Tissue Resource (CPTCR)
- Director's Challenge: Toward a Molecular Classification of Cancer
- Exploratory Grants for Correlative Laboratory Studies and Clinical Trials
- Flexible System to Advance Innovative Research for Cancer Drug Discovery by Small Businesses
- Improving DNA, RNA, and Protein Availability in Fixed Tissue
- Interdisciplinary Research Teams for Molecular Target Assessment
- In Vivo Cellular and Molecular Imaging Centers (ICMICs)
- Minority Institution/Cancer Center Partnership (MI/CCP) Program
- Minority-Based Community Clinical Oncology Program (MBCCOP)
- Molecular Epidemiology of Prostate Carcinogenesis
- Molecular Target Drug Discovery for Cancer
- NCI Center for Bioinformatics
- Program for the Assessment of Clinical Cancer Tests (PACCT)
- Prostate, Lung, Colorectal & Ovarian Cancer Screening Trial (PLCO)
- Prostate Specialized Programs of Research Excellence (SPOREs)
- Shared Resources for Scientists outside NCI Cancer Centers
- Small Animal Imaging Resource Program (SAIRP)
- Special Populations Networks (SPNs)
- Specimen Resource Locator
- Technologies for Comprehensive, Sensitive, and Quantitative Protein Analysis in Human Tumors: Phased Innovation

Table 4-2. NCI Initiatives Relevant to Prostate Cancer Research: Etiology and Prevention

INITIATIVES FOCUSED ON PROSTATE CANCER
Prostate Cancer Prevention Trial (PCPT) (http://www.cancer.gov/pcpt) **Objective:** Randomized trial to evaluate whether the drug finasteride (Proscar) could prevent prostate cancer in men ages 55 and over. **Relevant Program Resulting from This Initiative:** Enrollment in PCPT began in 1993, and nearly 19,000 men participated in the trial. PCPT was concluded early due to the finding that finasteride reduced the incidence of prostate cancer by 25 percent; however, men taking finasteride were more likely to have higher grade tumors.
SELECT Prostate Cancer Prevention Trial (http://www.cancer.gov/select) **Objective:** Prospective trial in 32,400 healthy men to determine whether selenium and vitamin E are effective at preventing prostate cancer. **Relevant Program Resulting from This Initiative:** Recruitment for the *Selenium and Vitamin E Cancer Prevention Trial* began in August 2001 and is expected to be completed in summer 2004. The SELECT homepage provides additional information for SELECT investigators and participants.

Table 4-2. (cont.)

INITIATIVES WITH PROSTATE CANCER-RELEVANT COMPONENTS
Cancer Genetics Network (CGN) (http://epi.grants.cancer.gov/CGN/) **Objective:** A national network of centers specializing in the study of inherited predisposition to cancer. **Relevant Resources Resulting from This Initiative:** There are currently nine participating centers. Among the ongoing CGN studies, one is specific to prostate cancer: Recruitment of Families with Prostate Cancer.
Cancer Prevention Research Small Grant Program (PAR-00-025) **Objective:** Developmental research in chemoprevention agent development, biomarkers, early detection, and nutrition science. **Relevant Research Projects Resulting from This Program Announcement:** ◆ Bioavailability of Tea Polyphenols in Prostate Cancer ◆ Cancer-Relevant Proteins in the Human Prostate Proteome ◆ Chemoprevention of Prostate Cancer by Sanguinarine ◆ Chemopreventive Action of Human Selenium Binding Protein ◆ Chemopreventive Effects of Dietary Cottonseed Oil ◆ Dietary Isoflavone-Regulated Genes in Prostate Cancer ◆ Dietary Soy Effects on Markers of Prostate Cancer ◆ DNA Methylation in Early Detection of Prostate Cancer ◆ Efficacy of Prostate-Specific Antigen (PSA) Screening and Prostate Cancer Mortality ◆ Inhibition of Prostate Carcinogenesis by Apigenin ◆ Prostate Cancer Chemoprevention by Apigenin ◆ Prostate Cancer Chemoprevention by COX 2 Inhibition ◆ Tea Targeting Proteasome—A Role in Cancer Prevention
Chemoprevention in Genetically Identified High-Risk Groups: Interactive Research and Development Projects (RFA-CA-98-012) **Objective:** Integrated, multidisciplinary research programs that define and evaluate chemopreventive strategies in asymptomatic subjects at high risk for cancer. **Relevant Research Project Resulting from This Request for Applications (RFA):** Chemoprevention of Familial Prostate Cancer
NCI Cohort Consortium (http://cancercontrol.cancer.gov/bb/cohort_conso.html) **Objective:** Support multicohort investigations of cancer etiology. Large-scale epidemiologic investigations are needed to verify preliminary epidemiologic findings from smaller studies and to elucidate genetic and environmental interrelationships in cancer causation. **Relevant Resource Resulting from This Initiative:** The NCI Cohort Consortium supports investigators leading 23 U.S. and international cohort studies of cancer etiology, with exposure data and biologic specimens for 700,000 study participants. Initial investigations on prostate cancer etiology, including more than 5,000 prostate cancer cases, are focusing on the genetics of hormonal and growth factor determinants of this disease.
Rapid Access to Preventive Intervention Development (RAPID) Program (http://www3.cancer.gov/prevention/rapid/index.html) **Objective:** Movement of novel molecules and concepts from the laboratory to the clinic for clinical trials of efficacy. **Relevant Research Project Resulting from This Initiative:** Preclinical Development of Four Flavonoids from *Broussonetia Papyrifera*

Table 4-2. (cont.)

Small Grants Program for Cancer Epidemiology (http://epi.grants.cancer.gov/ResPort/grants.html)

Objective: Build relationships between large research institutions and community-based programs and address cancer burden in minority communities.

Relevant Research Projects Resulting from This Initiative:

- Androgen Pathway and Genetic Risk of Prostate Cancer
- Androgens Regulate IGF Pathway and Prostate Diseases
- Beta 2 Adrenergic Receptors and Prostate Cancer Risk
- Calcidiol Therapy for Prostate Cancer
- Development and Evaluation of a Soyfood Questionnaire
- Epidemiology of Cancer Mortality in Chicago Heart Association Detection Project
- Epidemiology of Prostate Cancer—Ornithine Decarboxylase and Androgen Receptor (AR) Genotypes
- Feasibility of New Prostate Cancer Molecular Genetic Technology
- Genetics of Prostate Cancer in an African American Population
- Markov Chain Monte Carlo for Very Large Pedigrees
- Meta Analysis of Risk Factors for Prostate Cancer
- Modifiable Risk Factors for Prostate Cancer
- Molecular Biomarkers for Prostate Cancer Susceptibility
- Oncogenic Human Papillomaviruses and Prostate Cancer Risk
- Postmortem PSA: Role in Epidemiology of Prostate Cancer
- Prostate Cancer Morbidity and Metal Working Fluids
- Tissue Vitamin E Levels and Prostate Cancer Risk
- Variation of the HSD17B3 Gene and Prostate Cancer

Ongoing NCI Research: Recent Progress in Prostate Cancer Etiology and Prevention

Risks for prostate cancer are approximately doubled among men who have a family history of this disease compared to men with no family history. Genome-wide analysis of large multiple-case prostate cancer families has identified several chromosomal regions potentially linked to this disease; however, the prostate cancer inheritance pattern is genetically complex (Easton et al., 2003), with several candidate genes identified in high-risk families, including RNAseL (Carpten et al., 2002), ELAC2 (Tavtigian et al., 2001), and MSR1 (Xu et al., 2002a).

Androgen Receptor and Androgen Metabolism

While testosterone and its more potent metabolite dihydrotestosterone (DHT) are necessary for normal prostate development, these hormones have also been linked to prostate cancer. Additionally, androgen deprivation leads to physiological changes in the prostate, which result in clinical responses in prostate cancer patients. Investigators are examining androgen-associated cellular and genetic factors in the etiology of prostate cancer.

Prostate cancer susceptibility is being investigated at the genetic level by examining the AR gene and genes regulated by AR. Within the AR gene, there is a region in which the codon CAG is repeated multiple times, and the number of repeats can vary in different men. In multiple studies, men having AR genes with fewer CAG repeats were associated with a higher risk for prostate cancer, regardless of their racial/ethnic background. The presence of fewer repeats was found significantly more often in the higher

risk African American population than in lower risk Asian populations (Irvine et al., 1995; Bennett et al., 2002). The functional relevance of this repeat polymorphism has been examined by studying the interaction of the AR variants with variants of the PSA gene, which is regulated by AR. A comparison of the AR and PSA genotypes indicated that men with the higher risk types of both genes had 5 times the risk for all prostate cancer and 10 times the risk for advanced prostate cancer (Xue et al., 2000).

Researchers have investigated the possibility that genes encoding androgen metabolizing enzymes may be prostate cancer susceptibility genes. At least two enzymes of the 3-beta-hydroxysteroid dehydrogenase (HSD3B) family are involved in androgen biosynthesis and are expressed in prostate tissue. Variations in these genes were found significantly more often in men with prostate cancer than in men without cancer, and this effect was more pronounced in men with a hereditary form of cancer (Chang et al., 2002). Steroid 5-alpha reductase (SRD5A2) is the enzyme responsible for the metabolic conversion of testosterone to DHT. A genetic variant of *SRD5A2* was associated with sevenfold and fourfold increases in the risk of clinically significant prostate cancer in African American and Hispanic men, respectively (Makridakis et al., 1999; Jaffe et al., 2000). A case-control study analyzed genetic variants of the cytochrome p450 enzyme CYP17, which is involved in testosterone biosynthesis. One variant of *CYP17* was associated with prostate cancer risk in white men with a family history of the disease (Stanford et al., 2002).

The NCI's Prostate Cancer Prevention Trial (PCPT), a randomized, double-blind, placebo-controlled trial, investigated the prevention potential of 7 years of finasteride treatment. This drug acts to decrease the amount of DHT by blocking 5-alpha reductase. Almost 19,000 healthy men ages 55 and older participated in the nationwide study. The PCPT was concluded early when findings revealed that finasteride results in a 25 percent reduction in the incidence of prostate cancer; however, it was also found that men taking finasteride had higher grade tumors than their placebo counterparts (Thompson et al., 2003) (NCI-P93-0049).

Insulin-Like Growth Factors

IGF factors are important for regulation of prostate cell proliferation, differentiation, apoptosis, and tumorigenesis. Epidemiologic investigations suggest that IGF-1 and its major binding protein, IGFBP-3, are related to prostate cancer risk (Li et al., 2003). The underlying genetics of the IGF pathway and its interrelationship with dietary and other factors in prostate cancer development are under current investigation.

Dietary Factors

While numerous epidemiologic studies have associated a lower energy diet, especially a diet low in animal fats, with a slightly reduced risk for prostate cancer, mechanisms of carcinogenesis due to high-fat diets have been explored recently. Prostate cancer risk has been associated with total energy intake, and the risk for regional/distant prostate cancer has been associated with dietary fat and calcium (Kristal et al., 2002). Red meat and dairy products are major sources of branched-chain fatty acids that are metabolized by the enzyme alpha-methylacyl-CoA-racemase (AMACR). Genetic variants of AMACR have been identified, some of which significantly associate with prostate cancer risk (Zheng et al., 2002). Studies investigating the preparation of foods have generally associated meats prepared by grilling or frying with a greater risk than other means of cooking. A byproduct of grilling meat is the heterocyclic amine, PhIP (2-amino-1-methyl-6-phenylimidazol[4,5-*b*]pyridine); PhIP is a putative carcinogen of the rat prostate (Archer et al., 2000). N-acetyltransferases (NAT)-1 and -2 are the enzymes principally responsible for the metabolic inactivation of PhIP. Genetic variants of *NAT1* and *NAT2* have been associated with a significantly increased risk for prostate cancer (Hein et al., 2002).

A diet high in meats and dairy products typically will be lower in vegetables and fruits that are associated with lower risk for prostate cancer. Specific micronutrients (e.g., selenium, lycopene, genistein, and vitamin E) have been associated with a reduced risk for prostate cancer. Lycopene, a carotenoid antioxidant found in tomatoes and other red fruits, has been consistently associated with reduced risk for cancer (Gann et al., 1999). Mechanistically, dietary antioxidants have been hypothesized to detoxify reactive oxygen species (ROS), which are DNA-damaging molecules. However, enzymes exist that can repair DNA damaged by ROS. Certain DNA repair enzymes are being investigated as potential prostate cancer susceptibility genes, including *BRCA*, *ERCC*, and *hOGG*, and genetic variants of the *hOGG1* gene have been associated with hereditary prostate cancer (Xu et al., 2002b).

Prevention Trials

Recent results from NCI-sponsored research have increased the understanding of risk factors and prevention methods. Findings from the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, conducted by the NCI in collaboration with the National Public Health Institute of Finland, indicate that daily use of a modest-dose of alpha-tocopherol (a form of Vitamin E) can lead to a striking reduction in prostate cancer incidence (Heinonen et al., 1998). Based on this knowledge, a similar study revealed that long-term alpha-tocopherol supplementation decreased serum androgen concentrations thought to contribute to the incidence and mortality of prostate cancer (Hartman et al., 2001).

Sexually Transmitted Diseases

Prostate tissues can be infected by pathogens, including viral and bacterial agents of sexually transmitted diseases. Although oncogenic strains of human herpesvirus and human papillomavirus have been identified in prostatic tissues, multiple studies have not established their association with prostate cancer. Past incidence of gonorrhea has been associated with prostate cancer, and the risk appears to increase with increasing occurrences of gonorrhea and syphilis (Rosenblatt et al., 2001; Hayes et al., 2000). Pathologic underpinnings linking infectious agents and prostate inflammatory pathways are under investigation (DeMarzo et al., 2003).

Continuing Needs and Evolution

The use of genes and specific genotype patterns associated with increased risk for prostate cancer to develop prevention, screening, and prognostic applications is currently limited by the scope of the genetic studies. For some of the genes that appear associated with the risk of prostate cancer development or progression, the small scale of the studies has led to contradictory results among different research groups. Large-scale, multi-institutional studies are being conducted to validate the association and causation of putative susceptibility genes with prostate cancer risk, incorporating advanced genomic analyses by haplotyping and genomic scans, to address the complexities of genetic and environmental interrelationships. Genetic etiology studies are collecting and analyzing data on other lifestyle and environmental factors to ascertain any specific linkages between certain genes and the environment. The development of nationwide and international cohorts requires a standardized mechanism for collecting, analyzing, and reporting data and enhanced resources to support these studies.

We have made significant strides in detecting, diagnosing, and treating prostate cancer, but a fuller understanding of the genetic, biochemical, and environmental risk factors that contribute to its development and progression is key to effective prevention.

– National Institutes of Health, Prostate Cancer Research Plan for FY 2003-2008.

Prostate cancer prevention studies have followed significant advances in dietary and androgen metabolism research. Predominantly, specific micronutrients from dietary sources are being investigated for their potential to reduce the progression of cancer from localized to disseminated disease. As indicated earlier,

selenium, soy isoflavones, and other micronutrients are being examined prospectively in clinical trials to validate results. Within the last 4 years, nearly 10 such prevention studies were initiated. Additionally, as the biological etiology of prostate cancer is continually refined, new targets for preventive interventions will need to be rapidly validated, and interventions will need to be prospectively examined in clinical trials.

NCI's Future Investment in Prostate Cancer Etiology and Prevention

The NIH Prostate Cancer Research Plan for FY 2003–2008 describes the NCI's planned objectives for research on prostate cancer etiology and prevention. The plans are based on the priorities that were identified by the PRG and the advances that have taken place since completion of the PRG's work. The three FY 2003–2008 objectives and their alignment to the eight PRG priorities are summarized in Figure 4-2. In addition, there is one PRG priority in etiology and prevention that also aligns with an FY 2003–2008 objective in the category of laboratory and preclinical models.

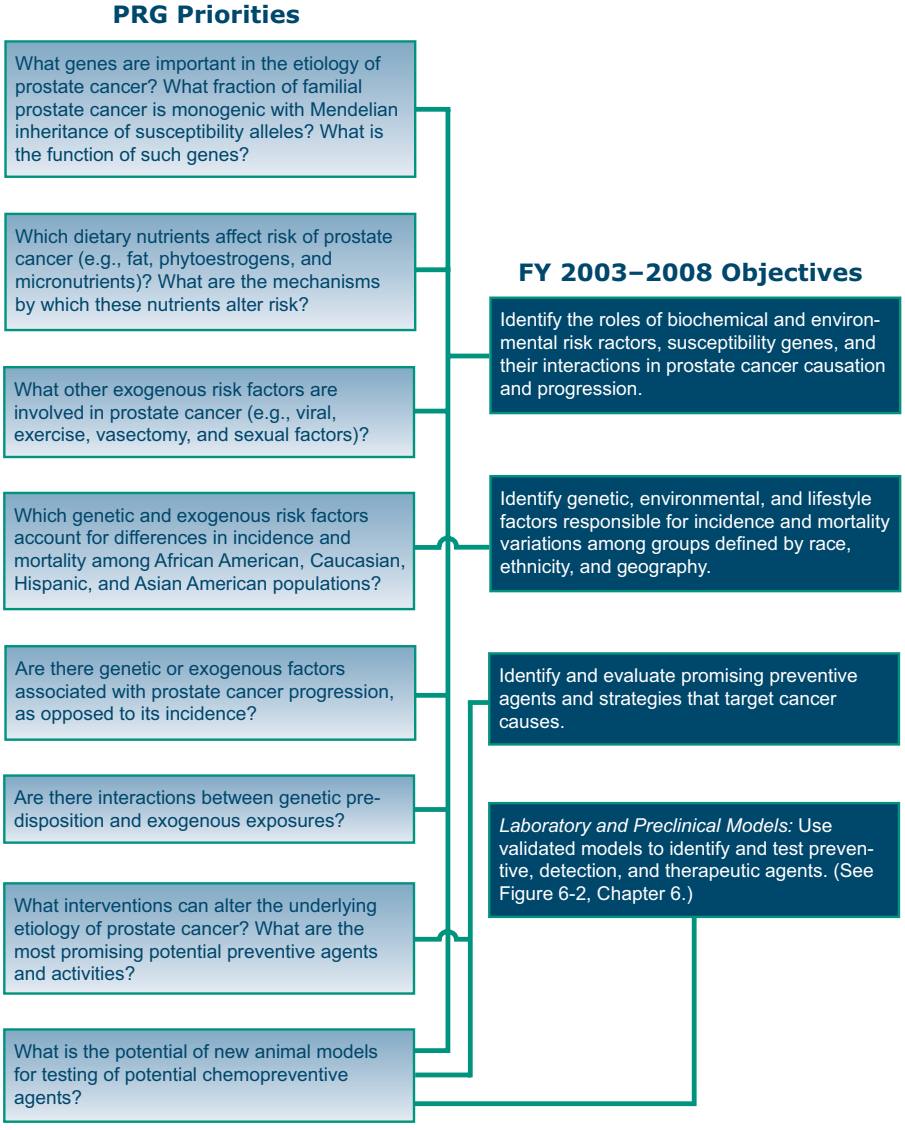


Figure 4-2. NIH's FY 2003–2008 prostate cancer etiology and prevention objectives build upon the 1998 PRG priorities.

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CHAPTER 5

Prostate Cancer Early Detection, Diagnosis, and Prognosis: NCI's Investment and Recent Progress

Management of cancer begins with the early detection of disease. For men in whom cancer has been detected, the disease can be most successfully controlled when diagnostic and prognostic measures accurately predict the course of disease progression and the most suitable treatment interventions. Research in early detection, diagnosis, and prognosis is aimed at enhancing diagnostic specificity and selectivity with noninvasive techniques.

From the late 1980s through the early 1990s, the incidence rates for prostate cancer increased (Figure 1-1 [Chapter 1] and Figure 5-1). This increase corresponded with the widespread adoption of prostate specific antigen (PSA) testing, which received Food and Drug Administration approval in 1986. In the 1990s, there was a decrease in the rate (Figure 5-1) and absolute number of new prostate cancer diagnoses in which cancer was found to have already spread to sites distant from the prostate.

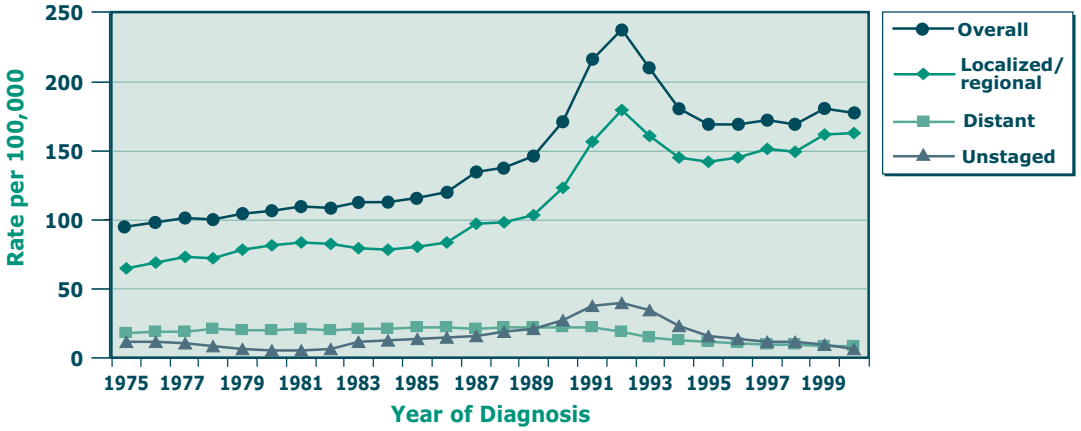


Figure 5-1. U.S. prostate cancer incidence rates by stage.

Data derived from NCI's Surveillance, Epidemiology, and End Results (SEER) Program.
Rates are per 100,000 men and age-adjusted to the 2000 U.S. standard.

In their 1998 report, the Prostate Cancer PRG described pivotal needs in early detection, diagnosis, and prognosis research for better management of localized disease. The report emphasized the importance of both early detection of prostate cancer and predicting the clinical course of tumors for individual patients. While early detection, particularly through the use of PSA screening, has led to an increase in the number of early-stage prostate cancer diagnoses, not all clinically significant tumors detected by PSA screening are life threatening. Since many of the definitive therapies for prostate cancer can have a significant impact on quality of life, patients face difficult decisions

The primary problem remains our inability to distinguish between "indolent" and "aggressive" carcinomas.

– Defeating Prostate Cancer: Crucial Directions for Research - Report of the Prostate Cancer Progress Review Group, August 1998.

when choosing among different types of therapies. Therefore, the identification of additional diagnostic and prognostic markers that can distinguish indolent (i.e., slow-growing) from aggressive prostate carcinomas was, and still is, considered of critical importance.

The Prostate Cancer PRG identified several areas that offered the best opportunities to advance prostate cancer research for early detection, diagnosis, and prognosis. Specifically, the natural history of prostate cancer was considered a major knowledge gap; more information was needed on all the biological steps from the onset of prostate cancer through advanced, metastatic disease. Better definitions of steps in the natural history of prostate cancer will enable researchers and clinicians to differentiate indolent from aggressive carcinomas. Fortunately, in the late 1990s new prostate cancer models and molecular technologies were developed that could be harnessed to accelerate future research. The PRG recommended emphasizing the development, validation, and application of biologic determinants that can provide reliable prognostic information and serve as surrogate markers for assessing the response to treatment. Areas of particular interest that were identified included molecular assays to replace tissue-based assays, computer and mathematical-modeling techniques, improved body-imaging techniques, and computer-assisted image analysis.

The NCI has responded to the five PRG Priority One questions and recommendations. Multiple initiatives support research to develop molecular profiles of cancer and novel imaging techniques. Significant progress has been made, particularly in the area of identifying new markers. New biologic markers will improve our ability to screen for and detect prostate cancer in its early stage and predict which therapy, if any, is optimal for individual patients.

NCI's Investment and Response

From fiscal year (FY) 1998 to FY 2002, NCI's investment in early detection, diagnosis, and prognosis prostate cancer extramural research has grown from $7.1 million (M) to $41.0M (Figure 5-2). Much of this investment was made in the form of increases in the number of projects that respond to PRG Priority One questions. Table 5-1 summarizes NCI's responsiveness to the five Prostate Cancer PRG Priority One research questions for prostate cancer early detection, diagnosis, and prognosis.

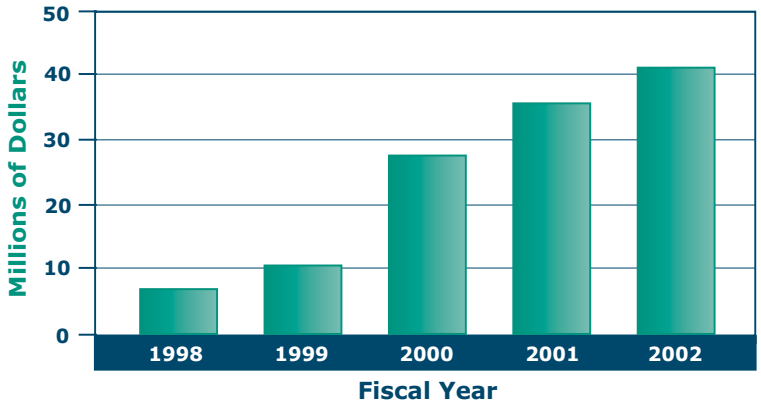
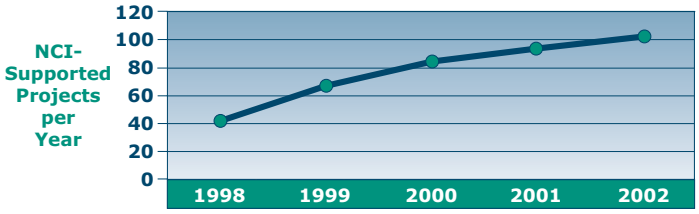


Figure 5-2. NCI's investment in prostate cancer early detection, diagnosis, and prognosis extramural research: 1998–2002 (in millions of dollars).

Table 5-1. NCI Efforts Responsive to PRG Priorities in Prostate Cancer Early Detection, Diagnosis, and Prognosis Research[a]

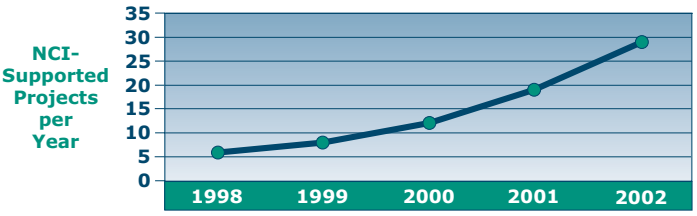
PRG Priority: What biologic determinants, independent of stage, can provide a better definition of the malignant phenotype, natural history, and prognosis with various therapeutic interventions?



NCI Efforts:

- In FY 2002, active areas of investigation included novel biologic markers, molecular staging of prostate cancer, translating basic research studies on potential markers into clinical studies that evaluate their potential utility, nuclear magnetic resonance (NMR) to define prostate differentiation, prostate cancer characterization with ultrasonic imaging, and examination of micrometastases. In accordance with the PRG's recommendation, most of the projects on this list involve noninvasive diagnosis and less-invasive prognostics.
- Nine 2002 projects addressed the PRG recommendation to characterize prostatic intraepithelial neoplasia (PIN) and prostate tumor heterogeneity.
- This priority was addressed by the NCI-sponsored workshop Applications of Bioinformatics in Cancer Detection (ABCD), which was held on August 6–7, 2002.
- NCI initiatives addressing this priority included Cooperative Prostate Cancer Tissue Resource (CPCTR), Prostate Specialized Programs of Research Excellence (SPOREs), Cancer Genome Anatomy Project (CGAP), Clinical Proteomics Program, Director's Challenge: Toward a Molecular Classification of Cancer, and Tissue Array Resource Program (TARP).

PRG Priority: How should prognostic markers be validated?



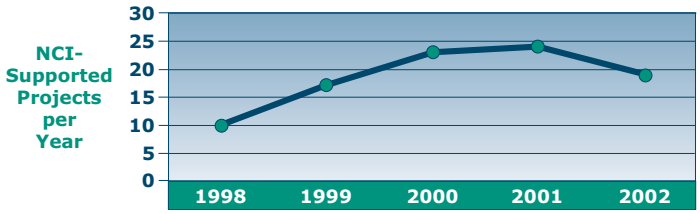
NCI Efforts:

- In FY 2002, active areas of investigation included validating novel biologic markers, validating intermediate markers for intervention studies, developing statistical methods, and developing a cancer taxonomy based on gene expression.
- NCI initiatives that supported the PRG recommendation that a consortium be developed to evaluate and validate prognostic markers included the Early Detection Research Network's Prostate and Other Urologic Cancers Collaborative Group and the 11 Prostate SPOREs.
- Additional NCI initiatives addressing this priority included Director's Challenge: Toward a Molecular Classification of Cancer and the Clinical Proteomics Program.

[a] A given project may map to more than one PRG Priority One question and therefore be represented in more than one figure. Projects active in 2002 are listed by Principal Investigator's name for each PRG Priority One question in Appendix B (Tables B-21–B-26).

Table 5-1. (cont.)

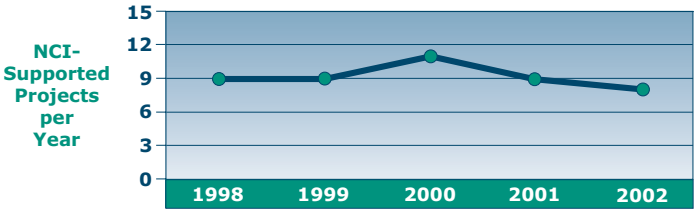
PRG Priority: What biologic determinants characterize the growth rate and/or tumor-doubling time during the progression of prostate cancer?



NCI Efforts:

- In FY 2002, active areas of investigation included studying biologic markers, including HK2 and the androgen receptor, molecular profiling analysis, new tools to predict tumor growth and metastatic potential, and utilizing cytogenetics.
- NCI initiatives addressing this priority included Prostate SPOREs.

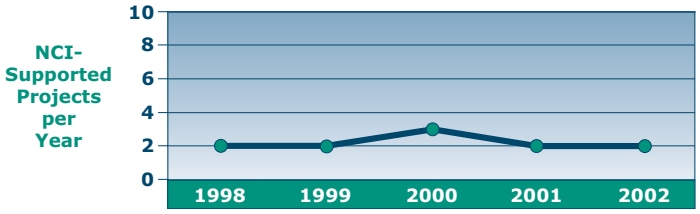
PRG Priority: Does early detection change mortality from prostate cancer?[b]



NCI Efforts:

- In FY 2002, active areas of investigation included the impact of PSA screening on prostate cancer mortality, U.S. prostate cancer trends, approaches to modeling and predicting therapeutic benefit of surveillance, and correlation of telomere DNA content assay results to patient survival.
- NCI initiatives addressing this priority included Prostate Cancer Intervention Versus Observation Trial (PIVOT) and Prostate, Lung, Colorectal & Ovarian (PLCO) Cancer Screening Trial.

PRG Priority: What are the effects of early detection on morbidity and quality of life?[b]



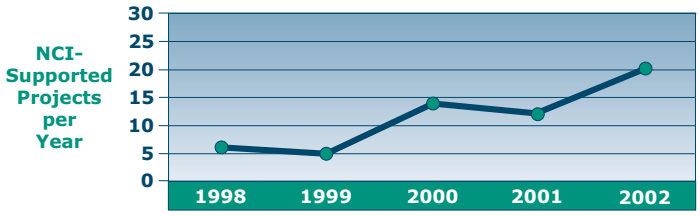
NCI Efforts:

- In FY 2002, active areas of investigation included assessing the impact of PSA screening on prostate cancer incidence and mortality.
- NCI initiatives addressing this priority included PIVOT and PLCO Cancer Screening Trial.

[b] See p. 8-3 for related priority "What is the impact of early detection and screening on outcomes?"

Table 5-1. (cont.)

Additional early detection, diagnosis, and prognosis projects that did not address the PRG priority questions already listed in this table.



NCI Efforts:

- In FY 2002, active areas of investigation included developing and refining imaging technologies such as magnetic resonance imaging (MRI), gamma probes, and spectroscopy; measurement of seminal zinc as a cancer detection tool; and development of prodrugs to release probes as diagnostic agents.

The initiatives relevant to research on prostate cancer early detection, diagnosis, and prognosis between FY 1998 and FY 2002 include the following list of general initiatives that are described in Table 2-1[1] (Chapter 2) and the category-specific initiatives that are listed and described in Table 5-2:[2]

- Applications of Innovative Technologies for the Molecular Analysis of Cancer
- Cancer Genome Anatomy Project (CGAP)
- Cancer Imaging Program (CIP)
- Cancer Molecular Analysis Project (CMAP)
- Cancer Prognosis and Prediction
- Cancer Research Training, Career Development, and Education Opportunities
- Clinical Trials Cooperative Group Program
- Cooperative Human Tissue Network (CHTN)
- Cooperative Prostate Cancer Tissue Resource (CPCTR)
- Diagnostic Imaging and Guided Therapy in Prostate Cancer
- Director's Challenge: Toward a Molecular Classification of Cancer
- Exploratory Grants for Correlative Laboratory Studies and Clinical Trials
- Improving DNA, RNA, and Protein Availability in Fixed Tissue
- In Vivo Cellular and Molecular Imaging Centers (ICMICs)
- Minority Institution/Cancer Center Partnership (MI/CCP) Program
- Molecular Profiling Initiative (MPI)
- NCI Center for Bioinformatics (NCICB)
- Program for the Assessment of Clinical Cancer Tests (PACCT)
- Prostate Cancer Intervention Versus Observation Trial (PIVOT)
- Prostate, Lung, Colorectal & Ovarian (PLCO) Cancer Screening Trial
- Prostate Specialized Programs of Research Excellence (SPOREs)
- Shared Resources for Scientists outside NCI Cancer Centers
- Specimen Resource Locator

[1] Initiatives that impact multiple categories of prostate cancer research.

[2] Initiatives unique to the research category of early detection, diagnosis, and prognosis.

Table 5-2. NCI Initiatives Relevant to Prostate Cancer Research: Early Detection, Diagnosis, and Prognosis

INITIATIVES WITH PROSTATE CANCER-RELEVANT COMPONENTS
Clinical Proteomics Program (http://ncifdaproteomics.com/index.php) **Objective:** A collaboration between the NCI and the Food and Drug Administration for providing access to raw proteomics data and models. **Relevant Resource Resulting from This Initiative:** Prostate spectra available for download derived from 322 samples categorized according to disease status and PSA levels.
Development of Clinical Imaging Drugs and Enhancers (DCIDE) (http://www3.cancer.gov/bip/dcide.htm) **Objective:** Facilitate promising investigational imaging enhancers (contrast agents) or molecular probes from the laboratory to Investigational New Drug status. **Relevant Program, Resource, and/or Research Projects Resulting from This Initiative:** Pending
Development of Novel Technologies for In Vivo Imaging (PAR-01-101) (PAR-01-102) **Objective:** Develop and evaluate feasibility of novel image acquisition or enhancement methods. **Relevant Research Project Resulting from this PA:** NMR Imaging of Prostate Cancer Using Ligands
Early Detection Research Network (EDRN) (http://www3.cancer.gov/prevention/cbrg/edrn/) **Objective:** Collaborative development and testing of promising biomarkers or technologies, with rapid dissemination of results. **Relevant Program Resulting from This PA:** A consortium that currently includes 18 biomarker development laboratories (3 address prostate cancer); 3 biomarker validation laboratories; 9 clinical and epidemiologic centers (2 address prostate cancer); and 1 data management coordinating center.
Exploratory Studies in Cancer Detection, Prognosis, and Prediction (PA-01-010) **Objective:** Innovative strategies for the early detection, assessment of prognosis, or prediction of response to cancer treatment. **Relevant Research Projects Resulting from This PA:** ◆ Human Kallikrein 4 (hK4): A New Prostatic Biomarker? ◆ Human RNA Binding Protein as a Cancer Marker ◆ Neural Network Prediction of Prostate Cancer Progression ◆ Proteomic Study of Androgen Independent Prostate Cancer
Exploratory Studies in Diagnostics (PA-98-022) **Objective:** Novel studies in cancer diagnostics. **Relevant Research Projects Resulting from This PA:** ◆ Characterization of Prostate Cancer with HRMAS 1HMRS ◆ hTERT Expression as a Marker for Early Cancer Detection ◆ Molecular Markers for Prostate Cancer ◆ Molecular Markers for Prostate Cancer Detection

Table 5-2. (cont.)

Exploratory/Developmental Grants for Diagnostic Cancer Imaging (PA-01-030)

Objective: Highly innovative research concepts in diagnostic cancer imaging.

Relevant Research Projects Resulting from This PA:

- Aptamers as Cellular Targeting Agents
- Diagnostic Freehand Elastographic Imaging of Cancer
- High Spectral and Spatial Resolution MRI of Rodent Tumors
- Improved Prostate Cancer Staging with Dual Mode Imaging
- NMR Detection of Prostate Tumor Differentiation
- Prostate Cancer and BPH Ablation Using HIFU Waveguide
- Seed Localizer for Image-Guided Prostate Brachytherapy
- Sodium MRI for Assessing Early Chemotherapy Response

Gene Expression Data Portal (GEDP) (http://gedp.nci.nih.gov/dc/index.jsp)

Objective: A public source of microarray research that also provides online data annotation and analysis tools.

Relevant Data Generated by the Following Research Projects:

- Alterations in Gene Expression Profiles during Prostate Cancer Progression
- Comprehensive Gene Expression Analysis of Prostate Cancer Reveals Distinct Transcriptional Programs Associated with Metastatic Disease
- Gene Expression Correlates of Clinical Prostate Cancer Behavior
- Molecular Classification of Prostate Cancer

Innovative Technologies for the Molecular Analysis of Cancer (PAR-01-104) (PAR-01-105)

Objective: Develop novel technologies that will support the molecular analysis of cancers and their host environment in support of basic, clinical, and epidemiological research.

Relevant Research Projects Resulting from These PAs:

- Androgen Receptor Biochip—Prostate Cancer Management
- Messenger RNA Profiling by Single Molecule Counting
- Imaging Alternative Splicing during Tumor Progression
- In Vivo Analysis of Tumor Peptide Secretion
- Live Sensors for Molecular Profiling in Prostate Cancer
- Optomechanical Chips for Molecular Profiling of Cancer
- Phosphoinositide 3-Kinase Assays in Cancer Diagnosis
- Technology to Detect Genome-Wide DNA Methylation Changes

Tissue Arrray Resource Program (TARP) (http://ccr.cancer.gov/tech_initiatives/tarp/)

Objective: Develop and disseminate multi-tumor tissue microarray slides and related technology to cancer research investigators.

Relevant Resource Resulting from This Initiative: The fifth-generation prostate cancer slide includes 79 samples of prostatic adenocarcinoma.

Ongoing NCI Research: Recent Progress in Prostate Cancer Early Detection, Diagnosis, and Prognosis

Novel Biologic Markers

Through the use of new technologies, the rate at which new biologic markers are being identified has significantly increased. New biologic markers have been identified in human serum, urine, prostatic fluid, and tissue samples. Over the last 3 years, the result has been the identification of scores of novel prostate cancer markers. Through NCI initiatives such as CGAP, numerous genes that are unique to prostate cancer and pre-cancerous prostate have been identified. Many of these genes are being further investigated to determine if they can be used as markers or therapeutic targets for prostate cancer. The following NCI-supported research represents examples of recently identified biologic markers for prostate cancer that may become clinically useful.

- Alpha-Methylacyl-CoA Racemase (AMACR) is an enzyme that normally functions in a digestive system pathway; AMACR is required for bile acid synthesis and breaking down complex fatty acids, such as those found in dairy products and beef. Increased expression of AMACR has been observed in prostate cancer tissues compared to normal prostate or benign prostatic hyperplasia (BPH) (Luo et al., 2002; Rubin et al., 2002). In two studies, samples representing different stages of prostate cancer progression were analyzed. No correlation was observed between AMACR and stage, grade, tumor size, or surgical margin status. However, high-grade prostatic intraepithelial neoplasia (HGPIN) had increased levels of AMACR. This suggests AMACR may be a valuable marker for early detection of prostate cancer.
- Caveolin-1 (Cav-1) is a protein that plays an important role in communication within a cell in both signal transduction pathways and lipid transport. In some studies, increased levels of Cav-1 have been associated with prostate cancer metastasis, biochemical recurrence after radical prostatectomy, and androgen insensitivity (Yang et al., 1999; Li et al., 2001). Additionally, some preliminary results suggest that differences in Cav-1 expression may underlie the observed difference in the virulence of prostate cancer in African American versus white patients (Yang et al., 2000). To serve as an effective marker or prognostic indicator, it is important to understand how Cav-1 functions. Recent investigations have clarified how the Cav-1 gene is turned on and, once the protein is produced, what downstream effects are mediated by Cav-1 (Cui et al., 2001; Tahir et al., 2001). While still being developed, Cav-1 shows promise as a marker for detection and prognosis and as a target for therapeutic interventions.
- Ribonuclease L (RNAseL) normally functions as a regulator in cell growth and cell death pathways. Recently, the RNAseL gene has been identified as a candidate gene for a form of familial prostate cancer (Carpten et al., 2002). Two different mutations have been identified that were previously linked to a chromosome 1 gene, known as the hereditary prostate cancer 1 locus. The role of RNAseL in prostate cancer was further supported by a second study on noninherited forms of prostate cancer (Casey et al., 2002). This analysis implicated a third variant of RNAseL as a contributing factor in as many as 13 percent of prostate cancer cases. Men with a specific variant of the RNAseL gene had two to four times the risk of developing prostate cancer compared to individuals without the variant. Thus, RNAseL shows the potential for use as a genetic and diagnostic marker for prostate cancer and a potential target for therapeutic interventions.
- Prostate-Specific Stem Cell Antigen (PSCA) is a protein that is found on cell surfaces, is predominantly expressed in prostate cells, and may play a role in the normal development of the prostate gland (Reiter et al., 1998). Published studies have shown a high correlation (64%–94%) between increased PSCA expression and prostate cancer. The protein is also expressed in HGPIN and BPH. PSCA expression is maintained in androgen-independent prostate cancer and is highly

expressed in metastatic disease (Gu et al., 2000). In a recent study, anti-PSCA monoclonal antibodies have been shown to inhibit tumor growth and metastasis formation in mouse models of prostate cancer (Ross et al., 2002). Thus, PSCA shows promise as both a diagnostic/prognostic marker for prostate cancer and a potential therapeutic target.

- Epidermal Growth Factor Receptor (EGFR) is a protein involved in cell growth and differentiation signaling. Using immunohistochemical studies, EGFR expression appeared to be increased in androgen-insensitive prostate cancer and in some prostate cells in advanced disease (Sherwood et al., 1998; Leav et al., 1998). Since the expression of EGFR is deregulated in advanced disease, several research groups are examining EGFR inhibitors as potential therapeutic agents. EGFR is inhibited by a number of agents including C225 (cetuximab), which blocks the ligand-binding domain of EGFR. OSI774, ZD1839 (Iressa), PKI166, and CI1033 prevent the protein from performing its enzymatic functions by inhibiting the EGFR tyrosine kinase (Sirotnak et al., 2000; Karashima et al., 2002). Selection of treatment with any of these agents would follow pretreatment analysis of samples to determine the extent of EGFR expression and determine whether treatment with any of these agents would be efficacious. Several NCI-sponsored trials to determine the efficacy of EGFR pathway inhibitors are currently under way.
- The Telomerase Reverse-Transcriptase (TERT) gene encodes the protein component of telomerase, the ribonucleoprotein that maintains the telomeric ends of chromosomes. Published reports demonstrate TERT activity levels in most prostate cancers and in some cases of high-grade PIN (HGPIN) and that TERT is consistently absent from normal prostate tissues (Sommerfield et al., 1996; Koeneman et al., 1998). The process of cancer development from normal cells through precancerous cells appears to be correlated to the shortening of telomeres (Meeker et al., 2002), the stimulation of TERT expression (Guo et al., 2003; Moore et al., 2003), and the maintenance of cellular longevity by active telomerase. Further evaluation of TERT expression following telomere shortening may reveal a niche for its use as a supplement to diagnostic PSA testing.

Imaging Technologies

Transrectal ultrasonography (TRUS) became a standard technique for imaging the prostate by the late 1980s. As tests that detect elevated PSA became commonly employed, cancers could be detected below the limit of sensitivity of TRUS. In the past decade, the sensitivity and specificity of detecting prostate cancers by TRUS have been significantly enhanced with three-dimensional Doppler imaging, spectral analysis, and computer-aided image analysis (Moskalik et al., 2001; Balaji et al., 2002).

Research in magnetic resonance imaging (MRI) is also enhancing the potential for noninvasive cancer detection. Advances in equipment design and newer analytic methods are being examined in animal models. In addition, novel contrast agents and molecular probes are being examined to enhance the specificity and selectively of MRI to detect prostate cancers and to differentiate metastatic from nonmetastatic tumors (Karczmar et al., 2000; Fan et al., 2001). MRI is also being employed to detect the uptake of drugs, which will enhance the ability to predict drug effectiveness (Artemov et al., 2001).

Molecular Profiling

Molecular profiling involves determination of an individual tumor's gene and protein expression patterns through the use of technologies such as cDNA microarray and proteomic analyses. These high-throughput techniques have only been developed in the past decade and are still being optimized. Gene expression microarray and proteomic approaches have been examined as complementary techniques to study androgen-induced prostate cancer gene expression and protein level changes (Nelson et al., 2000; Nelson et al., 2002). In evaluating normal,

The challenge will be to select the most promising markers and to determine how to validate and develop them into diagnostic tests.

- National Institutes of Health, Prostate Cancer Research Plan for FY 2003–2008

BPH, PIN, and carcinoma cell lines, cancer stage-specific gene expression patterns have been detected, and both novel genes and previously characterized proteins have been identified from these analyses (Chakrabarti et al., 2002). Patterns of multiple proteins detected by mass spectrometry have proven more selective and specific in identifying prostate cancers than the measurement of any single protein (Cazares et al., 2002). Novel bioinformatics algorithms are being coupled to the newer mass spectrometry techniques to optimize the selective identification of cancer cells versus non-cancer cells derived from microdissected tissues or serum (Petricoin et al., 2002; Qu et al., 2002; Yasui et al., 2003). In the future, molecular profiles will be used to classify tumors and define subsets of patients so that treatment can be tailored for individuals.

Continuing Needs and Evolution

The development of comprehensive approaches to molecular analysis and the validation of prostate cancer markers remain high priorities. Currently, there are several new markers whose potential utility must be validated in large clinical studies. NCI's current investments will provide a foundation and the infrastructure to support large validation studies. Multi-institutional studies will be required to accumulate adequate sample sizes, and appropriate controls will be necessary along with standardization procedures that will eliminate site-to-site differences in assay results. Future studies will likely include a focus on early disease detection, prognosis of disease course, prediction of response to treatment, or other parameters such as risk of disease recurrences or overall disease-free survival.

NCI's Future Investment in Prostate Cancer Early Detection, Diagnosis, and Prognosis

The NIH Prostate Cancer Research Plan for FY 2003–2008 describes the NCI's planned objectives for early detection, diagnosis, and prognosis research pertaining to prostate cancer. The evolving nature of science and NCI's adaptations to changing needs are evident when the 1998 PRG report is compared to the FY 2003–2008 Research Plan. The three FY 2003–2008 early detection, diagnosis, and prognosis objectives and their alignment to the PRG priorities are summarized in Figure 5-3. Figure 5-3 also shows how two PRG priorities in early detection, diagnosis, and prognosis align with an FY 2003–2008 objective under the category of cancer control, survivorship, and outcomes.

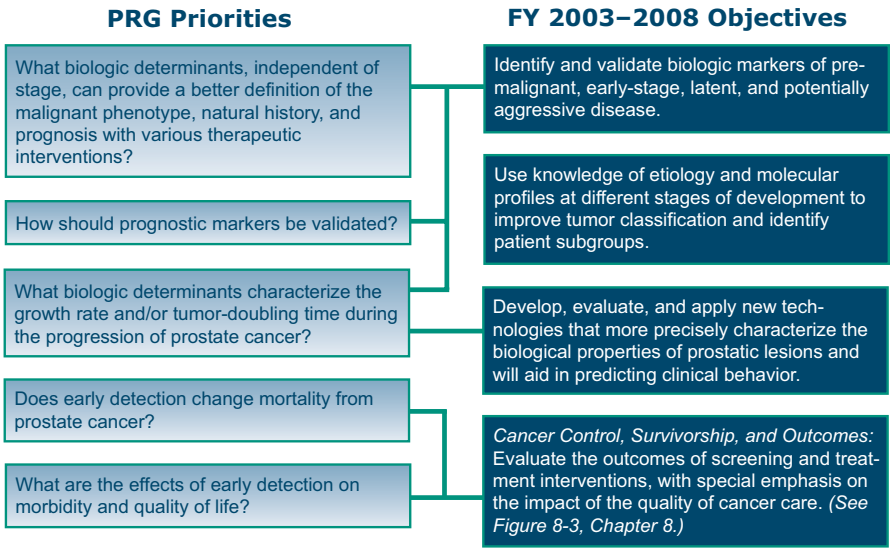


Figure 5-3. NIH's FY 2003–2008 prostate cancer early detection, diagnosis, and prognosis research objectives build upon the 1998 PRG priorities.

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CHAPTER 6

Scientific Model Systems for Prostate Cancer: NCI's Investment and Recent Progress

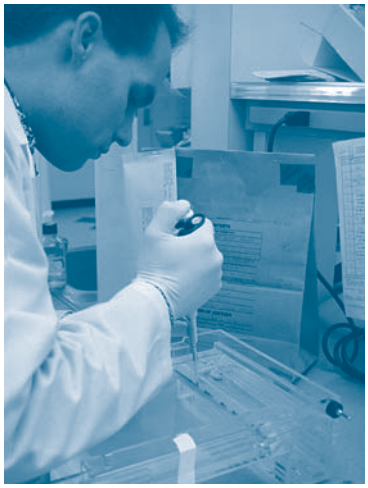
The NCI supports utilization of various cell, organ, animal, and mathematical models for studying mechanisms of prostate cancer development and progression along with testing prevention and treatment strategies. To maximize utility for prostate cancer research, a scientific model needs to be fully characterized, validated for both consistency and applicability to human disease, and readily available to researchers.

In their 1998 report, the Prostate Cancer PRG described the advantages and limitations of existing models for research on prostate cancer and the need for additional models. Although there are a variety of models that mimic one or more aspects of prostate cancer in humans, there is no single model that replicates the full spectrum of human disease development and progression. Furthermore, our limited understanding of prostate cancer etiology, progression, and metastasis complicates the validation of existing models and development of new models.

A laboratory model ideally simulates all of the properties of prostate cancer in humans, but this is difficult to achieve in practice.

– Defeating Prostate Cancer: Crucial Directions for Research - Report of the Prostate Cancer Progress Review Group, August 1998.

The Prostate Cancer PRG identified four[1] Priority One research questions that apply to the category of scientific model systems. The questions and their accompanying recommendations addressed the need for models that better simulate important aspects of human prostate cancer (e.g., progression to androgen independence and affinity for bone) and models that are better suited for testing new therapies, including the novel and targeted therapies that are currently being pursued (e.g., gene and immunologic therapies and other biologics).



The NCI has been responsive to the PRG's recommendations. Model development, validation, and access have been addressed by a major new initiative—the Mouse Models of Human Cancers Consortium (MMHCC)—and supplements to existing NCI grants. Since 1998, emphasis has also been placed on the use of models to study specific genes and pathways that are thought to play a role in prostate cancer development and progression and to develop interventions directed at these genes and their gene products.

[1] Although the *Laboratory and Clinical Models* section of the PRG report actually included five questions, one of the questions (*Can models of human prostate cancer metastases be developed to mimic the affinity of human prostate cancer for bone marrow?)* has been combined with a second related question (*Can models be designed to display the carcinogenic characteristics of human prostate cancer [i.e., its genetic characteristics, host–tumor interactions, micro-environment, angiogenesis, and progression]?).*

NCI's Investment and Response

From fiscal year (FY) 1998 to FY 2002, NCI's extramural investment in scientific model systems relevant to prostate cancer has increased from $3.6 million (M) to $11.3M (Figure 6-1).

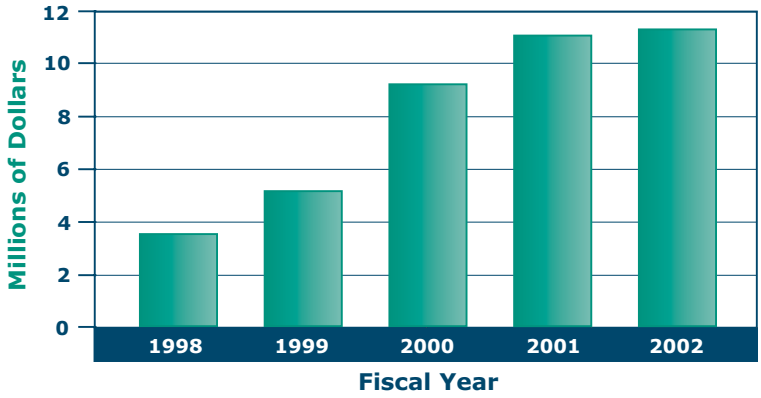
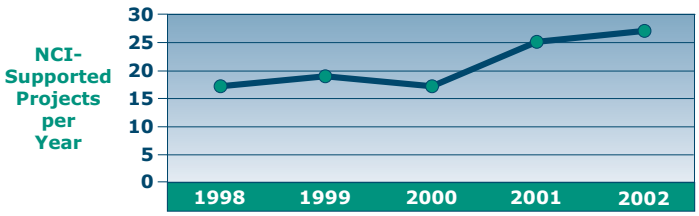


Figure 6-1. NCI's extramural investment in scientific model systems pertaining to prostate cancer: 1998–2002 (in millions of dollars).

NCI's responsiveness is summarized in Table 6-1 for the four Prostate Cancer PRG Priority One research questions pertaining to scientific model systems.

Table 6-1. NCI Efforts Responsive to PRG Priorities in Scientific Model Systems of Prostate Cancer[a]

PRG Priority: Can models be designed to display the carcinogenic characteristics of human prostate cancer (i.e., genetics, host–tumor interactions, micro-environment, angiogenesis, and progression)? Importantly, can models that mimic bone marrow metastases be developed?



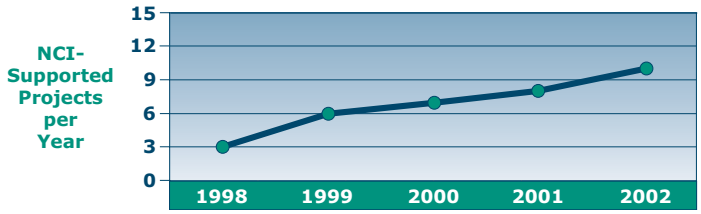
NCI Efforts:

- In FY 2002, active areas of investigation included keratinocyte growth factor and fibroblast growth factor receptors in the transgenic adenocarcinoma of the mouse prostate (TRAMP) and derived cell lines, transgenic mouse models that closely mimic human progression using different genes, identity of stage-specific gene expression patterns in mice, early prostate cancer events and progression in Nkx3.1 mutant mice, role of integrins in bone metastasis, and bone effects in promoting growth of metastatic tumors.
- The NCI portfolio addressed the following recommended actions to improve prostate cancer models:
  - Six projects to identify genes that drive the initiation process of prostate cancer development
  - Three projects to develop new prostate cancer cell lines
  - Nineteen projects to develop new animal models, including four projects specifically developing models that mimic prostate metastasis to bone
  - Two projects to study the interaction of bone cells and prostate cells
- NCI initiatives addressing this priority included Prostate Specialized Programs of Research Excellence (SPOREs), MMHCC, and Competing Supplements for Organotypic Models of Cancer.

[a] A given project may map to more than one PRG Priority One question and therefore be represented in more than one figure. Projects active in 2002 are listed by Principal Investigator's name for each PRG Priority One question in Appendix B (Tables B-27–B-31).

Table 6-1. (cont.)

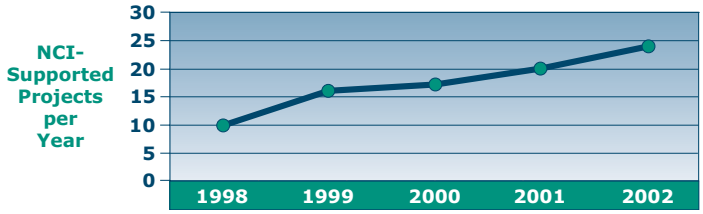
PRG Priority: Can models be designed to display the hormone responsiveness of human prostate cancer and its progression to hormone independence?



NCI Efforts:

- In FY 2002, active areas of investigation included hormone effects in an early prostate cancer mouse model, estradiol-17-beta and testosterone mechanisms of tumor progression, inhibitors of androgen receptor and androgen metabolizing enzymes, and hormone-induced carcinogenesis and cancer progression in retinoblastoma (Rb)-knockout and conditionally Rb-deleted mice.
- Five projects addressed the PRG recommendation to study the mechanism of hormone action in prostate cell lines and animal models.
- Three projects addressed the PRG recommendation to study the mechanism by which prostate cancer cells become refractory to androgens.
- NCI initiatives addressing this priority included Prostate SPOREs and MMHCC.

PRG Priority: Can laboratory models be used to screen potential chemotherapeutic agents, clarify dose/response relationships, and understand chemotherapy resistance and mechanisms of therapeutic response?



NCI Efforts:

- In FY 2002, active areas of investigation included topoisomerase I inhibitors, mechanisms of anti-tubulin and anti-phosphatase agents, anti-cancer properties of natural products and their derivatives, preclinical and clinical evaluation of peptides against angiogenesis and metastasis, thermal-sensitive liposomal drug delivery, and green fluorescent protein-tagged proteins in rodent model transplants to examine metastasis and angiogenesis.
- NCI initiatives addressing this priority included Cancer Therapy-Related Use of Genetically Engineered Mice, Prostate SPOREs, and MMHCC.

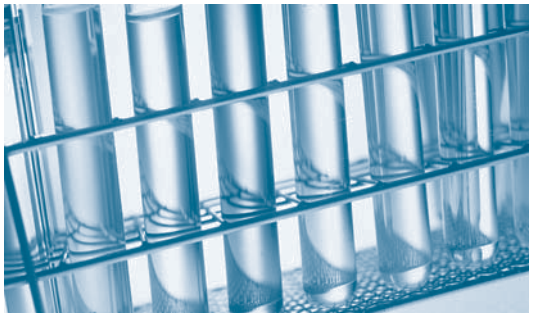
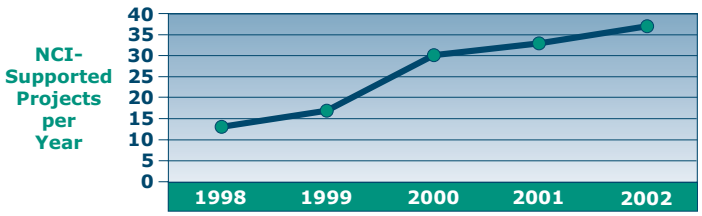


Table 6-1. (cont.)

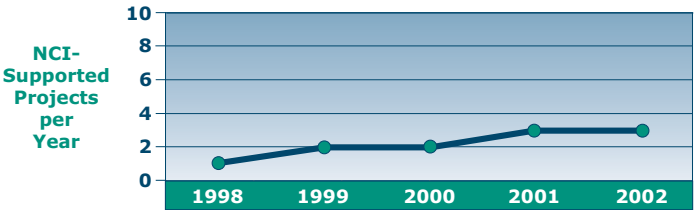
PRG Priority: Can models be used to test novel therapeutic approaches (e.g., cancer vaccines, gene therapy, and immunological therapies)?



NCI Efforts:

- In FY 2002, active areas of investigation included T-cell-stimulated cytotoxic response, anti-angiogenesis antibodies in combination with conventional chemotherapy or hormonal therapy, immunization of TRAMP mice with tumor-associated antigen, immunization of transgenic models with peptides of human telomerase, gene therapy vector delivery, and herpes simplex virus thymidine kinase gene therapy with valacyclovir or ganciclovir.
- Eight projects addressed the PRG recommendation to develop vectors for gene therapy.
- Three projects addressed the PRG recommendation to define the immune components of prostate cancer cells.
- Twenty-three projects addressed the PRG recommendation to test novel therapeutic approaches in animal models.
- NCI initiatives addressing this priority included Cancer Therapy-Related Use of Genetically Engineered Mice, Prostate SPOREs, and MMHCC.

Additional scientific model systems projects that did not address the PRG priority questions in this table.

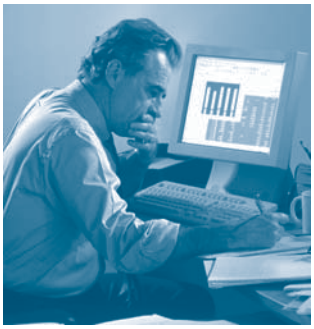


NCI Efforts:

- In FY 2002, active areas of investigation included evaluation of dietary carcinogens; development, validation, and dissemination of TRAMP and other mouse models; and mouse models used to develop positron emission tomography imaging techniques.

The initiatives relevant to research on prostate cancer scientific model systems between FY 1998 and FY 2002 include the following list of general initiatives that are described in Table 2-1[2] (Chapter 2) and the category-specific initiatives that are listed and described in Table 6-2:[3]

- Cancer Research Training, Career Development, and Education Opportunities
- Cancer Therapy-Related Use of Genetically Engineered Mice
- Cooperative Prostate Cancer Tissue Resource (CPCTR)
- Improving DNA, RNA, and Protein Availability in Fixed Tissue



[2] Initiatives that impact multiple categories of prostate cancer research.

[3] Initiatives that are unique to the scientific model systems research category.

- In Vivo Cellular and Molecular Imaging Centers (ICMICs)
- Prostate Specialized Programs of Research Excellence (SPOREs)
- Specimen Resource Locator

Table 6-2. NCI Initiatives Relevant to Prostate Cancer Research: Scientific Model Systems

INITIATIVES WITH PROSTATE CANCER-RELEVANT COMPONENTS
Competing Supplements for Organotypic Models of Cancer (PAR-02-052) **Objective:** Development and use of alternate model systems that more closely resemble normal tissue or emerging tumors than do dispersed cells cultured on plastic. **Relevant Research Projects Resulting from This Program Announcement:** ◆ Cathepsin B and Tumor Invasion ◆ Cell Motility in Prostate Tumor Invasion
Mouse Models of Human Cancers Consortium (MMHCC) (http://emice.nci.nih.gov/) **Objective:** Accelerate the pace at which mice with heritable malignancies that are accurate, reproducible models of human cancers are made available to the research community. **Relevant Research Project Resulting from This Initiative:** A collaborative project that makes information and tools available to the public via its eMICE website, which includes a section on Prostate Cancer Models and a Mouse Tumor Biology Database. The consortium includes a Prostate Cancer Committee that is charged with developing mouse models of prostate cancer that faithfully simulate the human disease. In addition, there are four strains of mice specific to prostate cancer and one specific to both prostate and breast cancer* that can be ordered for use in research: ◆ *C3(1)/Tag (FVB-Tg(C3-1-TAg)cJeg) ◆ Nkx3.1 null (B6.129-*Nkx3-1tm1Mms*) ◆ Nkx3.1 null (FVB.129-*Nkx3-1tm1Mms*) ◆ PB-Cre4 (B6;D2-Tg(PB-Cre)4Prb) ◆ TRAMP (C57BL/6-Tg(TRAMP)8247Ng) **Additional Relevant Research Projects Resulting from This Initiative:** ◆ Mouse Cancer Models by Regulated Inactivation of Tumor Suppressors ◆ Mouse Cancer Models via TGF-Beta RII Loss ◆ A Mouse Model for Prostate Cancer ◆ Mouse Models for Prostate Cancer ◆ Transgenic Mouse Models of Prostate Cancer

Ongoing NCI Research: Recent Progress in Scientific Model Systems

Transgenic Animal Models

In recent years, notable advances have been made in utilizing existing and developing new transgenic, xenograft, and knockout models. The TRAMP model was first described in 1995 (Greenberg et al., 1995). Recently, it has been used for preclinical testing of therapeutic strategies (Shariat et al., 2001; Arap et al., 2002) and chemopreventive agents (Gupta et al., 2000) and for studying the events that lead to androgen independence at the molecular level (Buchanan et al., 2001; Han et al., 2001).

Prior to development of the TRAMP model, transgenic animals designed as models of prostate cancer developed tumors at sites other than (Schaffner et al., 1995) or in addition to (Maroulakou et al., 1994) the prostate. The TRAMP model is the first to consistently develop prostate cancer. It is based on inclusion of gene sequences not normally present in the mouse—the overlapping large T and small t antigen-coding sequences (Tag sequences) of the SV40 simian virus and the promoter region of the rat probasin gene, a gene that is specific to prostate epithelial cells and regulated by androgen. The transgene sequences affect mouse prostate epithelial cells by blocking transcription of the normally expressed mouse p53 and Rb tumor suppressor genes (via the expressed large T SV40 antigen) and inactivating the MAP kinase pathway enzyme protein phosphatase 2A (via the expressed small t SV40 antigen). This results in mice that consistently display pathological changes leading to high-grade prostatic intraepithelial neoplasia (PIN), adenocarcinoma (by 12 weeks of age), and metastasis (by 30 weeks of age) (Gingrich et al., 1999). The TRAMP mice develop metastases to the regional lymph nodes and lungs and infrequently develop skeletal metastasis. Studies have shown that the prostate tumors that spontaneously develop in TRAMP mice progress to androgen independence and that one or more mutations can be found in the androgen receptor gene sequences of each mouse that has become androgen independent (Han et al., 2001).

New transgenic strains that are variants of the TRAMP model have been developed and characterized in recent years. The LADY model, which is under rat probasin promoter control but fails to express the small t SV40 antigen, develops prostate cancers that are less aggressive than those in TRAMP (Kasper et al., 1998; Masumori et al., 2001). While these mice develop low- and high-grade PIN lesions and adenocarcinoma, progression to distant metastases is rarely observed. However, following androgen deprivation therapy, the tumors in LADY mice initially regress but then grow further and progress to metastatic disease.

Transgenic strains that rely on other insertional elements, including the rat probasin promoter and mouse androgen receptor gene (Stanbrough et al., 2001), have also been recently developed. These strains develop hyperplasia and low-grade PIN, but do not progress to prostatic adenocarcinoma.

Xenografted Animal Models

Xenografted mouse models, in which characterized human prostate cancer cell lines are implanted subcutaneously or intra-prostatically (orthotopically) in immunodeficient animals, such as nude mice, were first described in the mid-1970s (Schroeder et al., 1976). Numerous human prostate cancer cell lines (e.g., LNCaP, LuCAP, CWR22, DU145, and PC-3) derived from different sources ranging from primary tumors to distant site metastases have been used for this purpose. These cell lines display different genetic backgrounds, androgen sensitivities, and metastatic potential. Further influencing the behavior of the cells is the site of implantation. PC-3 cells lead to metastases following orthotopic placement in the prostate but not following subcutaneous implantation (Glinskii et al., 2003).

Xenografted animals have recently been used to study inducers of apoptosis (Dhanalakshmi et al., 2003; Xiao et al., 2003) and other therapeutic interventions (Denmeade et al., 2003). They have also been employed in microarray analysis of gene expression in normal versus diseased prostate (Glinsky et al., 2003).

In its quest to rapidly advance prostate cancer research, NCI is committed to develop more accurate models of prostate cancer.

– National Institutes of Health, Prostate Cancer Research Plan for FY 2003–2008.

The drawbacks of xenograft models include the absence of bone metastasis (although tumors can appear in bone following direct implantation) and the internal milieu of immunodeficient animals, which is different from that of wild-type animals and the vast majority of men who develop prostate cancer. Furthermore, because the cell lines used in implantation are already malignant, xenografted models are not suitable for studying the initiating events in prostate carcinogenesis.

Knockout Animal Models

Knockout mouse models, in which a specific gene has been inactivated due to deletion or other mutation, have been developed for studying the involvement of specific gene products and regulator sequences in prostate cancer development and progression (Ruan et al., 1999; Kim et al., 2002). An important feature of knockout models is that they provide a tailored environment for testing targeted gene therapies and other therapies based on gene product replacement.

Knockout models based on the tumor suppressor Nkx3.1 and/or Pten genes have been found to display prostatic abnormalities such as hyperplasia, PIN, and, when the two deletions are combined, possible progression to adenocarcinoma (Di Cristofano et al., 1998; Bhatia-Gaur et al., 1999; Kim et al., 2002; Park et al., 2002; Abate-Shen et al., 2003). A recent study has shown that the high-grade PIN lesions removed from Nkx3.1/Pten compound knockout mice result in adenocarcinoma and lymph node metastases following transplantation into immunodeficient animals (Abate-Shen et al., 2003).

Another recent study has shown that when Pten is preferentially deleted from prostate epithelial cells, the PIN lesions are followed by progression to invasive carcinoma and subsequent metastasis in the regional lymph nodes and lungs. These metastases were androgen receptor positive. This is the first animal model in which deletion of an endogenous gene leads to metastatic prostate cancer. Since the initiating oncogenic event is androgen independent, the Pten conditional deletion mice may provide a unique opportunity to address the mechanisms of resistance to androgen ablation therapy (Wang et al., 2003).

Continuing Needs and Evolution

A continuing need in the area of scientific model systems is model validation (1) to determine the extent to which scientific model systems are similar to and different from the human disease state and (2) to understand the significance of these similarities and differences for preclinical assessment of pathways/mechanisms and preventive and therapeutic interventions. Proteomic analysis has shown that there are substantive differences between (1) prostate tumor cells obtained via laser capture micro-dissection and (2) both commonly used and same patient-derived cell lines that are maintained in vitro (Ornstein et al., 2000).

NCI's Future Investment in Scientific Model Systems

The NIH Prostate Cancer Research Plan for FY 2003–2008 describes the NCI's planned objectives for research on scientific model systems of prostate cancer. The objectives are based on the priorities identified by the PRG and advances that have taken place since completion of the PRG's work. The three FY 2003–2008 objectives and their alignment to the four PRG priorities in the area of scientific model systems and additional PRG priorities in the areas of resources needed, and etiology and prevention are summarized in Figure 6-2.

One of the FY 2003–2008 objectives, which does not align with any of the five PRG priorities, recognizes an advancement in the area—the ability to leverage mouse and other models to refine knowledge of molecular and cellular processes initially gleaned from human subjects and patients. Key to this objective is the NCI initiative that supports disease site-specific model development (i.e., the MMHCC).

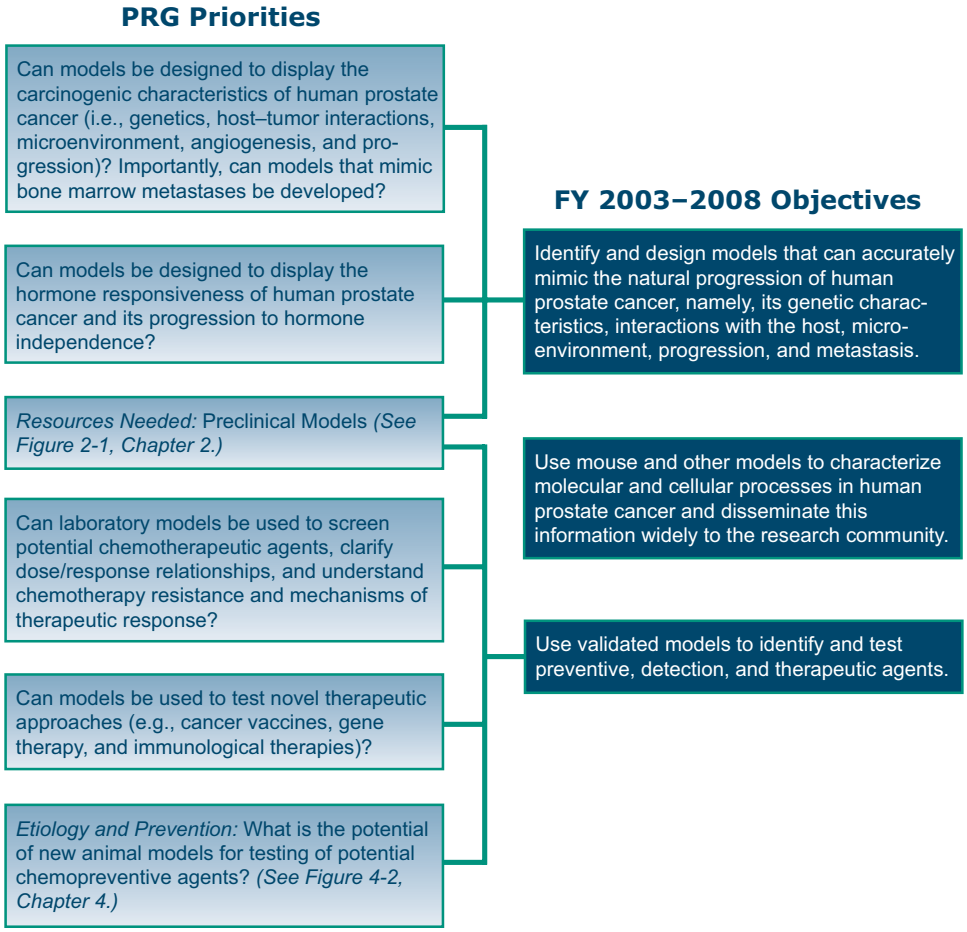


Figure 6-2. NIH's FY 2003–2008 prostate cancer scientific model systems research objectives build and expand upon the 1998 PRG priorities.

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CHAPTER 7

Prostate Cancer Treatment: NCI's Investment and Recent Progress

Research leading to improved cancer treatment plays a prominent role in NCI's cancer portfolio. It spans a spectrum of activities ranging from synthesis and discovery on the benchtop, to preclinical testing of safety and efficacy in animal models, and ultimately, to clinical trials in increasing numbers of cancer patients.

In their 1998 report, the Prostate Cancer PRG described promising directions and unmet needs for staging and treatment of localized prostate cancer and for systemic treatment of prostate cancer that cannot be cured by localized treatment modalities.[1] For both localized and advanced prostate cancer, the PRG stressed the importance of developing the following:

- Technologies for more precise disease staging, treatment selection, and treatment optimization
- Targeted therapies, especially gene and cellular therapies

The ultimate goal of prostate cancer treatment is to reduce prostate cancer-specific mortality.

– Defeating Prostate Cancer: Crucial Directions for Research - Report of the Prostate Cancer Progress Review Group, August 1998.

Existing limitations on the ability to accurately assess disease stage and treatment response have resulted in some patients being "undertreated" for tumors that will ultimately advance or recur and "overtreated" for tumors that will remain indolent. Additionally, treatments for localized prostate cancer are not always effective, nor are they free from side effects. Therefore, research is needed to develop optimal treatments for patients at different stages of prostate cancer.

The Prostate Cancer PRG identified 11 Priority One research questions that apply to the category of treatment: Four that pertain to staging and treatment of localized prostate cancer and seven that pertain to systemic therapy.[2] The questions and their accompanying recommendations addressed the need for improving existing approaches and the potential promise of novel approaches.

The NCI's broad approach to conducting and sponsoring research on treatment for prostate cancer is responsive to these recommendations. This approach includes the following:

- Developing novel agents based on mechanism of action
- Developing molecularly targeted agents that influence key pathways implicated in prostate cancer progression
- Optimizing promising hormonal and chemotherapeutic regimens

[1] Although staging and treatment of localized prostate cancer and systemic therapy were addressed as two discrete categories of research in the PRG report, this report addresses both under the single category entitled treatment. This approach is consistent with the Common Scientific Outline (CSO) research categorization scheme that was adopted by the NCI for tracking dollar investments, resources, and projects. (See discussion in Chapter 1.)

[2] Although the PRG report actually included eight questions pertaining to the category of systemic therapy, one of the questions (*How can new targets be identified?)* was also part of a second question (*How can new targets be identified and what is the role of novel therapeutic agents directed at these targets?).*

- Pursuing multidisciplinary approaches
- Developing new functional imaging tools
- Incorporating new technology
- Training new multidisciplinary investigators

NCI's Investment and Response

From Fiscal Year (FY) 1998 to FY 2002, NCI's extramural investment in research for prostate cancer treatment grew from $16.9 million (M) to $57.6M (Figure 7-1). Much of this investment was made in the form of increases in the number of projects that respond to PRG Priority One questions.

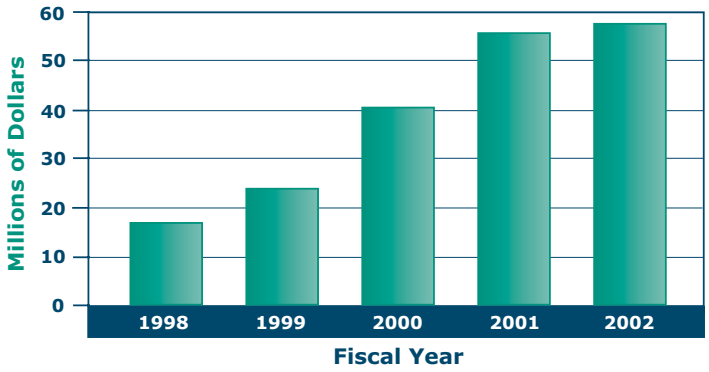
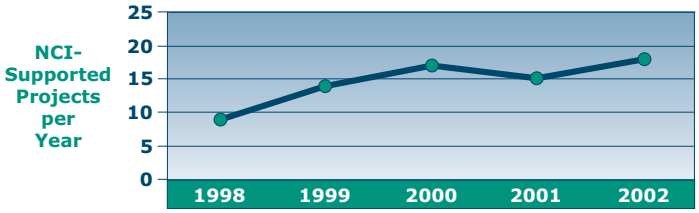


Figure 7-1. NCI's extramural investment in prostate cancer treatment research: 1998–2002 (in millions of dollars).

NCI's responsiveness is summarized in Table 7-1 for the four Prostate Cancer PRG Priority One research questions pertaining to staging and treatment of localized prostate cancer and in Table 7-2 for the seven Priority One research questions pertaining to systemic therapy.

Table 7-1. NCI Efforts Responsive to PRG Priorities in Staging and Treatment of Localized Prostate Cancer[a]

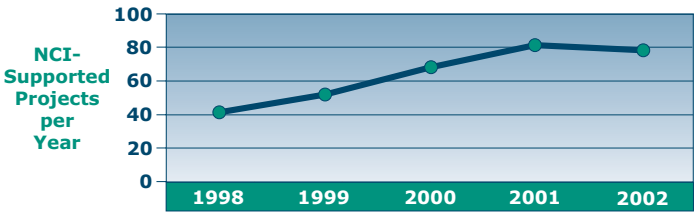
PRG Priority: What new technologies can detect clinically significant metastases prior to treatment? What is the clinical significance of circulating prostate cells detected by molecular techniques and their relationship to treatment failure and metastases?



NCI Efforts:

- In FY 2002, active areas of investigation included iron-containing tracers coupled with magnetic separation technology, microarray analyses to define stage-specific molecular profiles, high-resolution magnetic resonance imaging (MRI), flow cytometry detection of circulating metastatic cells, and reverse transcriptase polymerase chain reaction (RT-PCR)-based detection of prostate specific-antigen (PSA)-positive cells in blood.
- Thirteen projects address the PRG recommendation that assays be developed for detecting circulating cells and that the effects of investigational treatments on circulating cell levels be determined.
- NCI initiatives addressing this priority included Applications of Innovative Technologies for the Molecular Analysis of Cancer and the Cancer Imaging Program (CIP).

PRG Priority: What technologies (e.g., new, irradiation therapy, and localization techniques) can be developed to decrease morbidity and enhance efficacy of therapy for the primary tumor?



NCI Efforts:

- In FY 2002, active areas of investigation included radiosensitization of tumor cells, MRI-guided ultrasound ablation, computer-assisted photodynamic therapy, and imaging techniques for implanting brachytherapy seeds and monitoring brachytherapy response.
- Ten projects addressed the PRG recommendation to develop novel staging tools; five projects and the following two clinical trials addressed the PRG recommendation to further test and refine three-dimensional conformal therapy:
  - *Phase II Study of High-Dose Three-Dimensional Conformal Radiotherapy (3D-CRT) in Patients with Intermediate Prognostic Risk Adenocarcinoma of the Prostate* (NCI-H97-0006)
  - *Phase III Randomized Study of High- versus Standard-Dose Three-Dimensional Conformal Radiotherapy in Patients with Stage I or II Adenocarcinoma of the Prostate* (RTOG-P-0126)
- Additional clinical trials addressing this priority included
  - *Phase I Study of High-Intensity Focused Ultrasound Using the Sonablate System in Patients with Locally Recurrent Prostate Cancer* (NCI-V01-1683)
  - *Phase II Neoadjuvant Study of Androgen Suppression and Transperineal Ultrasound-Guided Brachytherapy after External Beam Radiotherapy in Patients with Locally Recurrent Prostate Adenocarcinoma* (NCCTG-N0052)
  - *Phase II Pilot Study of Magnetic Resonance-Guided High-Dose Rate Brachytherapy before and after External Beam Radiotherapy in Patients with Prostate Cancer* (NCI-02-C-0207)
  - *Phase II Study of Patient Positioning Using Multiple CT Scans in Patients with Prostate Cancer Undergoing External Beam Radiotherapy* (NCI-G01-1968)
  - *Phase I Study of Photodynamic Therapy with Lutetium Texaphyrin in Patients with Locally Recurrent Prostate Adenocarcinoma* (NCI-T99-0042)
  - *Phase II Study of Topical Amifostine for Rectal Protection during Radiotherapy in Patients with Prostate Cancer* (NCI-02-C-0215)

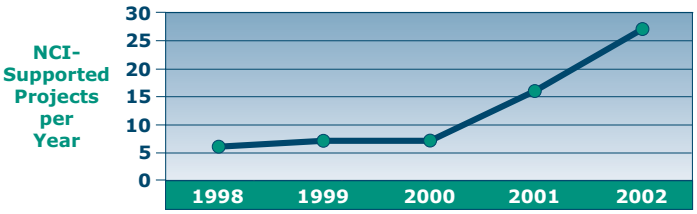
[a] A given project may map to more than one PRG Priority One question and therefore be represented in more than one figure. Projects active in 2002 are listed by Principal Investigator's name for each PRG Priority One question in Appendix B (Tables B-32–B-35).

Table 7-1. (cont.)

- *Phase I Study of Oral Capecitabine as a Radiation Enhancer in Patients with Unresectable, Residual, or Locally Recurrent Cancer Localized in the Pelvis* (NCCTG-984652)

- NCI initiatives addressing this priority included CIP, Development and Applications of Imaging in Therapeutic Studies, Diagnostic Imaging and Guided Therapy in Prostate Cancer, and Exploratory Grants for Correlative Laboratory Studies and Clinical Trials.
- *New Directions in Brachytherapy* was a one and one-half day workshop held in March 2001 to assess the current state of the science in brachytherapy.
- Between 1998 and 2002, NCI co-hosted three National Forums on Biomedical Imaging in Oncology designed to facilitate the development of enhanced imaging devices to address the needs of clinicians and research scientists.

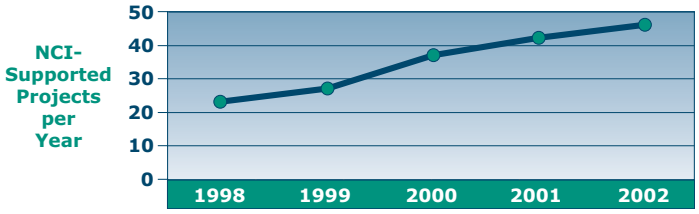
PRG Priority: What critical features of the primary tumor determine treatment success? What clinical, pathological, and molecular determinants can be used as markers of aggressiveness and "indolent" prostate cancer? How can multiple test results be combined using informatics?



NCI Efforts:

- In FY 2002, active areas of investigation included artificial neural networks and Bayesian analyses for outcome prediction, antibody microarray expression analysis, and protein glycosylation electrophoresis to detect metastasis.
- Three projects addressed the PRG recommendation to explore MRI spectroscopy; one project addressed the PRG recommendation to identify markers that correlate with response to therapy.
- NCI initiatives addressing this priority included Prostate Specialized Programs of Research Excellence (SPOREs) and Exploratory Grants for Correlative Laboratory Studies and Clinical Trials.

PRG Priority: Which gene therapies, including immunotherapeutic approaches, appear most suitable for localized and systemic prostate cancer treatment?[b]



NCI Efforts:

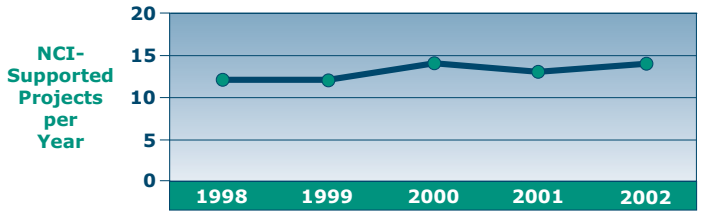
- In FY 2002, active areas of investigation included molecular modeling to engineer immunotoxins, dendritic cells as immunotherapeutics, collagen delivery systems to optimize gene transfer, and optimization of viral vectors for gene therapy.
- Clinical trials addressing this priority included the following:
  - *Phase I/II Study of Leuvectin in Patients with Locally Recurrent Organ-Confined Prostate Cancer after Radiotherapy* (NCI-G00-1721)
  - *Phase I Study of Recombinant Vaccinia Virus Expressing the PSA Antigen for Advanced Adenocarcinoma of the Prostate Progressing after Hormonal Therapy* (NCI-94-C-0118C)
  - *Phase I Study of Recombinant Vaccinia Virus That Expresses Prostate Specific Antigen in Metastatic Adenocarcinoma of the Prostate* (NCI-T95-0086H)
- Other NCI initiatives addressing this priority included Prostate SPORE, Clinical Cancer Therapy Research, Rapid Access to Intervention Development (RAID) Program, and Therapeutic Modulation of Angiogenesis in Disease.

Additional staging and treatment of localized prostate cancer projects that did not address the PRG priority questions in this table. **None.**

[b] See p. 7-5 for related priority "What is the role of gene and cellular therapy for prostate cancer?"

Table 7-2. NCI Efforts Responsive to PRG Priorities in Systemic Therapy[a]

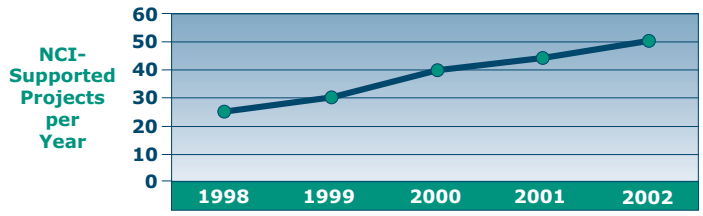
PRG Priority: What are the mechanisms associated with resistance to hormone therapy, immunotherapy, radiation, and chemotherapy?



NCI Efforts:

- In FY 2002, active areas of investigation included androgen receptor mutations associated with resistance to hormonal therapy, genes associated with resistance to chemotherapy, and mechanisms of action and resistance of nucleoside analog drugs.
- Clinical trials addressing this priority include these examples designed to (a) optimize radiotherapy, (b) optimize neoadjuvant or adjuvant hormonal therapy, (c) investigate novel chemotherapeutics in resistant models, and (d) reduce metastases by concurrent hormone and chemotherapies:
  - *Phase I Study of Oral Capecitabine as a Radiation Enhancer in Patients with Unresectable, Residual, or Locally Recurrent Cancer Localized in the Pelvis* (NCCTG-984652)
  - *Phase I Study of High-Intensity Focused Ultrasound Using the Sonablate System in Patients with Locally Recurrent Prostate Cancer* (NCI-V01-1683)
  - *Phase III Randomized Study of Neoadjuvant Total Androgen Suppression and Radiotherapy in Patients with Intermediate-Risk Adenocarcinoma of the Prostate* (RTOG-9910)
  - *Phase II Study of BMS-247550 in Patients with Hormone-Refractory Prostate Cancer* (SWOG-S0111)
  - *Phase III Randomized Study of Adjuvant Androgen Deprivation Therapy with or without Mitoxantrone and Prednisone after Radical Prostatectomy in Patients with High-Risk Adenocarcinoma of the Prostate* (SWOG S9921)
- NCI initiatives addressing this priority included Cooperative Human Tissue Network (CHTN), Cooperative Prostate Cancer Tissue Resource, and Prostate SPOREs.

PRG Priority: What is the role of gene and cellular therapy for prostate cancer?[b]



NCI Efforts:

- In FY 2002, active areas of investigation included dendritic cell vaccines, immunotoxin design, and new vectors for efficient and targeted gene delivery.
- Clinical trials addressing this priority included the following:
  - *Phase II Pilot Randomized Study of Fowlpox-Prostate-Specific Antigen Vaccine with or without Docetaxel in Patients with Metastatic Androgen-Independent Prostate Cancer* (NCI-02-C-0218)
  - *Phase I Study of Activated Autologous T Cells (Xcellerate) in Patients with Hormone-Refractory Prostate Cancer* (NCI-G02-2075)
  - *Phase II Study of Immunization with Prostate-Specific Membrane Antigen-Pulsed Autologous Peripheral Blood Mononuclear Cells and Interleukin-12 in Patients with Metastatic Hormone-Refractory Prostate Cancer* (NCI-1192)
  - *Phase I Study of Autologous Dendritic Cells Transfected with Autologous Total Tumor RNA in Patients with Metastatic Prostate Cancer* (DUMC-000759-00-4R1)
  - *Phase I Study of Recombinant Prostate-Specific Membrane Antigen (rPSMA)-Pulsed Autologous Dendritic Cells (CaPVax) in Patients with Metastatic Hormone-Refractory Prostate Cancer* (NCI-G00-1802)

[a] A given project may map to more than one PRG Priority One question and therefore be represented in more than one figure. Projects active in 2002 are listed by Principal Investigator's name for each PRG Priority One question in Appendix B (Tables B-36–B-43).

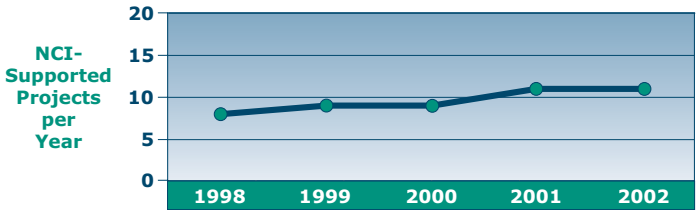
[b] See p. 7-4 for related priority "Which gene therapies, including immunotherapeutic approaches, appear most suitable for localized and systemic prostate cancer treatment?"

Table 7-2. (cont.)

- *Phase I Study of Recombinant Vaccinia Virus Expressing the PSA Antigen for Advanced Adenocarcinoma of the Prostate Progressing after Hormonal Therapy* (NCI-94-C-0118C)
- *Phase I Study of Recombinant Vaccinia Virus That Expresses Prostate Specific Antigen in Metastatic Adenocarcinoma of the Prostate* (NCI-T95-0086H)
- *Phase I/II Study of Active Immunotherapy with Prostate Specific Antigen RNA Pulsed Autologous Dendritic Cells in Patients with Metastatic Prostate Cancer* (NCI-G99-1655)
- *Phase I Study of Autologous Dendritic Cells Transfected with Autologous Total Tumor RNA in Patients with Metastatic Prostate Cancer* (NCI-G00-1910)

◆ NCI initiatives addressing this priority included Prostate SPOREs, Quick-Trials for Prostate Cancer Therapy, National Cooperative Drug Discovery Groups (NCDDGs), and RAID Program.

PRG Priority: What are the relevant endpoints for clinical trials of systemic therapies (e.g., PSA levels, time to progression, quality of life, and survival)? How can endpoints be validated? What is the impact of treatment on survival?



NCI Efforts:

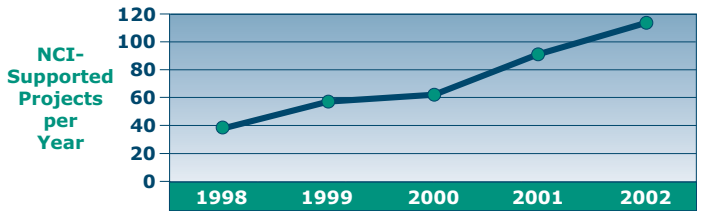
◆ In FY 2002, active areas of investigation included surrogate endpoint validation, PSA endpoint correlation to quality of life and time to progression, and RT-PCR-based detection of PSA-positive cells in blood.

◆ The PRG recommended that the NCI encourage novel trial designs. Intermittent androgen therapy, which may delay the onset of androgen independence and prolong survival (Oliver et al., 2000), is forming the basis of a novel clinical trial design whereby investigational agents are evaluated in a placebo-controlled fashion for their effects on progression-free survival during hormonal rest periods.

◆ The PRG recommended that clinical trials be used to determine whether PSA levels correlate with survival outcomes. The NCI's current strategy is to incorporate PSA-based intermediate endpoints into large, randomized trials in such a way that they can be reported early to support clinical decision making and planning of subsequent studies. Because the trials are large, the eventual outcome data can be used to validate conclusions based on the intermediate PSA endpoint.

◆ The NCI is participating in a working group with the Food and Drug Administration (FDA), American Association for Cancer Research (AACR), and American Society of Clinical Oncology (ASCO) to review and identify appropriate endpoints for clinical trials conducted in prostate cancer patients. Recommendations that address surrogate markers, definitions of clinical benefit, and time-to-event endpoints are expected to be raised at open public FDA Advisory Committee Meetings.

PRG Priority: How can new targets be identified and what is the role of novel therapeutic agents directed at these targets?



NCI Efforts:

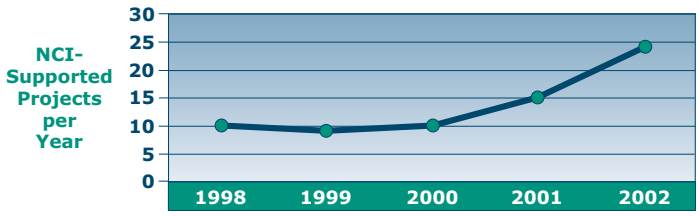
◆ In FY 2002, active areas of investigation included anti-cancer agents that target various biological mechanisms such as angiogenesis, DNA repair, cell-cycle checkpoints, apoptosis, DNA methylation, and cancer cell adhesion; bioinformatics models for rational drug design and evaluation; radioisotopes for therapy and detection; activation mechanisms for prodrugs and probes; high-throughput screens to identify new lead interventions; and immunologic and vaccine development.

Table 7-2. (cont.)

- During the years 1998-2002, NCI's Cancer Therapy Evaluation Program (CTEP) initiated 33 Phase II trials to explore the activity of new agents directed at targets that included all the following:
  - Growth signaling pathways (vascular endothelial growth factor [VEGF] and other angiogenesis targets and farnesyl transferase)
  - Differentiation (retinoids)
  - Arachidonic acid-associated pro-apoptosis signaling (selective cyclooxygenase-2 inhibitors)
  - Steroid sex hormone signaling (Her-2/neu).

  Additional Phase II trials were conducted by the Prostate SPOREs and intramural NCI programs.
- In direct response to the PRG priority, CTEP established a policy that, barring a mechanistic contraindication, all novel therapeutics under development or co-development by the NCI would be tested for activity in prostate cancer.
- The PRG recommended that NCI convene a consensus conference every 3 years, with industry participation, to discuss the newest molecular targets and drug development in prostate cancer. In November 1999, the NCI sponsored the state-of-the-science workshop Prostate Cancer: Molecular Targets. In December 2002, the NCI co-sponsored the Society for Urologic Oncology's SUO2/NCI Urologic Oncology Meeting: Extraordinary Opportunities for Discovery.
- NCI initiatives addressing this priority included Quick-Trials for Prostate Cancer Therapy, Prostate SPOREs, CIP, Cancer Molecular Analysis Project (CMAP), Cancer Therapy-Related Use of Genetically Engineered Mice, Cooperative Human Tissue Network (CHTN), Cooperative Prostate Cancer Tissue Resource, Drug Discovery for Cancer Flexible System to Advance Innovative Research for Cancer Drug Discovery by Small Businesses (FLAIR), Interdisciplinary Research Teams for Molecular Target Assessment, National Cooperative Drug Discovery Groups (NCDDGs), Molecular Target Drug Discovery for Cancer, National Cooperative Drug Discovery Groups (NCDDGs), RAID Program, and Therapeutic Modulation of Angiogenesis in Disease.

PRG Priority: What is the optimal treatment for androgen-independent disease?

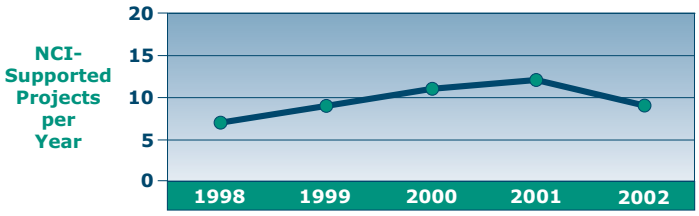


NCI Efforts:

- In FY 2002, active areas of investigation included angiogenesis inhibitors, arsenic compounds, IGF signaling pathway factors that potentiate androgen-independent growth, screening isolates from traditional Chinese herbal medicines, and surrogate markers to measure disease progression.
- Among the 75 active NCI-sponsored prostate cancer treatment trials in early 2003, 19 were being conducted in patients with hormone-refractory disease. Included among these were
  - *Phase II Randomized Study of BMS-275291* [an angiogenesis inhibitor] *in Patients with Hormone-Refractory Prostate Cancer* (NCI-5615)
  - *Phase II Study of Arsenic Trioxide in Patients with Metastatic Hormone-Refractory Prostate Cancer* (NCI-T99-0077)
  - *Phase II Study of Monoclonal Antibody ABX-EGF in Patients with Hormone-Resistant Prostate Cancer with Elevated PSA Levels without Metastasis* (UCLA-0206074)

Table 7-2. (cont.)

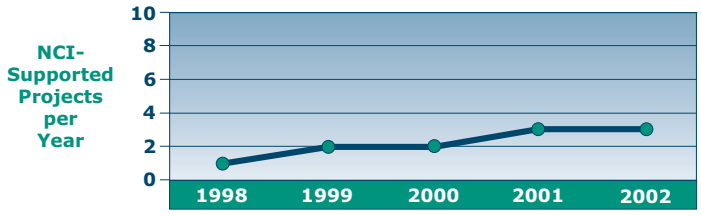
PRG Priority: At what point in the progression of prostate cancer should novel therapeutic agents be initiated (e.g., anti-angiogenic and anti-metastatic agents)?



NCI Efforts:

- In FY 2002, active areas of investigation included microvessel density determinations as a prognostic marker, synergism of anti-angiogenic plus cytostatic agents in advanced prostate cancer, targeted delivery of genes to angiogenic vasculature, tissue factor-mediated angiogenesis, angiogenesis inhibitors and differentiation agents, and compounds that inhibit VEGF production by human cancer cells.
- Clinical trials are being conducted in patients across all stages of prostate cancer. Various trials include proof-of-principle studies administering agents in the neo-adjuvant, Phase I or Phase II setting with correlative science components for future trial designs and populations. In addition, clinical trials of activity are being conducted in men who have a rising PSA and in men with either hormone-sensitive or -insensitive metastatic disease. Examples of clinical trials addressing this priority included the following:
  - *Phase I Study of SU5416* [an angiogenesis inhibitor] *with Standard Androgen Ablation and Radiotherapy in Patients with Intermediate or Advanced-Stage Prostate Cancer* (NCI-4390)
  - *Phase II Study of Trastuzumab (Herceptin) in Patients with Progressive Androgen Dependent and Independent Prostate Cancer* (NCI-G99-1493)
  - *Phase II Study of R115777 in Patients with Progressive, Metastatic, Hormone Refractory Prostate Cancer* (FCCC-99031)
  - *Phase II Randomized Study of Radiotherapy with or without Vaccine Containing Recombinant Vaccinia Prostate Specific Antigen (PSA) and rV-B7.1 Plus Recombinant Fowlpox PSA Vaccine in Patients with Localized Prostate Cancer* (NCI-00-C-0154)
  - *Phase II Study of Paclitaxel and Bryostatin 1 in Patients with Hormone-Refractory, Metastatic Adenocarcinoma of the Prostate* (MSGCC-9948)
  - *Phase II Study of Green Tea Extract in Patients with Androgen-Independent Metastatic Prostate Cancer* (NCCTG-N9951)
  - *Phase II Study of APC8015 (Provenge) and Bevacizumab in Patients with Progressive Prostate Cancer* (UCSF-0155-01)

PRG Priority: When should a patient with a rising PSA be treated?



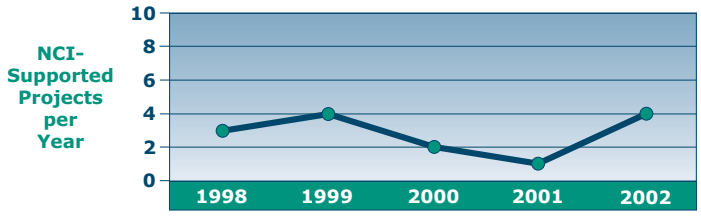
NCI Efforts:

- In FY 2002, active areas of investigation included PSA-screening effectiveness in reducing prostate cancer mortality.
- Ongoing clinical trials addressing all stages of prostate cancer include these trials examining asymptomatic recurrence measured by a rising PSA (i.e., biochemical recurrence):
  - *Phase III Randomized Study of Zoledronate and Standard Therapy vs. Placebo and Standard Therapy in Patients with Asymptomatic Recurrent Prostate Cancer Who Have Castrate Levels of Testosterone and Rising PSA Levels* (NCI-G00-1722)
  - *Phase III Randomized Study of Second-Line Hormonal Therapy (Ketoconazole and Hydrocortisone) versus Combination Chemotherapy (Docetaxel and Estramustine) in Asymptomatic Patients with Prostate Cancer and a Rising PSA after Androgen Suppression* (E-1899)

Table 7-2. (cont.)

- The NCI participated in the panel of experts that developed consensus criteria for use of PSA to monitor patients following radiation therapy (American Society for Therapeutic Radiation and Oncology [ASTRO]) and convened a panel of experts to determine eligibility and response in pilot or Phase II trials of new agents in androgen independent prostate cancer (Bubley et al., 1999). These standards have been generally adopted in both drug and radiation trials expanding the number of patients considered eligible and, therefore, the capacity of the clinical trial infrastructure to accommodate new agents.

Additional treatment projects that did not address the PRG priority questions in this table.



NCI Efforts:

- In FY 2002, active areas of investigation included pharmacology models to improve dose schedules in Phase II and Phase III trials and structure-based therapeutic discovery.

Clinical trials comprised a considerable portion of the NCI's responsiveness to PRG priorities and recommended actions. Over the years 1998–2002, the NCI sponsored[3] 104 new early-phase[4] trials and 18 new Phase III trials in prostate cancer patients. Included among the 83 active treatment trials in 2002 were 67 early-phase trials examining the safety and/or effectiveness of new therapies.

The initiatives that impacted research on prostate cancer treatment between FY 1998 and FY 2002 include the following list of general initiatives that are described in Table 2-1[5] (Chapter 2) and the category-specific initiatives that are listed and described in Table 7-3:[6]

- Applications of Innovative Technologies for the Molecular Analysis of Cancer
- Cancer Centers Program
- Cancer Imaging Program (CIP)
- Cancer Molecular Analysis Project (CMAP)
- Cancer Prognosis and Prediction
- Cancer Research Training, Career Development, and Education Opportunities
- Cancer Therapy-Related Use of Genetically Engineered Mice
- Clinical Trials Cooperative Group Program
- Common Data Elements (CDE) Initiative
- Community Clinical Oncology Program (CCOP)

[3] An NCI-sponsored clinical trial in the Physician Data Query (PDQ) database meets one or more of the following criteria: the protocol (1) has been reviewed and approved by NCI's CTEP Protocol Review Committee or by an approved NCI-designated Cancer Center Protocol Review and Monitoring System and/or (2) receives support through an NCI Grant or cooperative agreement. Information on ongoing treatment trials for the different stages of prostate cancer can be obtained via the NCI's Search for Clinical Trials webpage. To limit one's search to only those trials that are sponsored by the NCI, it is necessary to use the advanced search function.

[4] Early-phase trials include those that are in Phase I, II, or I/II.

[5] Initiatives that impact multiple categories of prostate cancer research.

[6] Initiatives that are unique to the treatment research category.

- Cooperative Human Tissue Network (CHTN)
- Cooperative Prostate Cancer Tissue Resource (CPCTR)
- Diagnostic Imaging and Guided Therapy in Prostate Cancer
- Exploratory Grants for Correlative Laboratory Studies and Clinical Trials
- Flexible System to Advance Innovative Research for Cancer Drug Discovery by Small Businesses (FLAIR)
- Improving DNA, RNA, and Protein Availability in Fixed Tissue
- Interdisciplinary Research Teams for Molecular Target Assessment
- In Vivo Cellular and Molecular Imaging Centers (ICMICs)
- Minority Institution/Cancer Center Partnership (MI/CCP) Program
- Minority-Based Community Clinical Oncology Program (MBCCOP)
- Molecular Profiling Initiative (MPI)
- Molecular Target Drug Discovery for Cancer
- NCI Center for Bioinformatics (NCICB)
- Program for the Assessment of Clinical Cancer Tests (PACCT)
- Prostate Cancer Intervention Versus Observation Trial (PIVOT)
- Prostate, Lung, Colorectal & Ovarian Cancer Screening Trial (PLCO)
- Prostate Specialized Programs of Research Excellence (SPOREs)
- Shared Resources for Scientists outside NCI Cancer Centers
- Small Animal Imaging Resource Program (SAIRP)
- Special Populations Networks (SPNs)
- Specimen Resource Locator

Table 7-3. NCI Initiatives Relevant to Prostate Cancer Research: Treatment

INITIATIVES FOCUSED ON PROSTATE CANCER

Quick-Trials for Prostate Cancer Therapy (PA-00-047)

Objective: Established in 1999 as a rapid grant review process to facilitate pilot studies of innovative, mechanism-based therapeutics not yet tested in humans. First made available for prostate cancer trials and subsequently open to other cancers, this is a pilot program to provide investigators with rapid access to support for pilot, Phase I, and Phase II cancer clinical trials along with patient monitoring and laboratory studies to ensure the timely development of new therapeutic approaches. In 2002, the program was expanded into *Quick-Trials for Novel Cancer Therapies,* which pertains to all cancer sites.

Relevant Research Projects Resulting from This Program Announcement (PA):

- Ad-OC-TK/Val Gene Therapy Clinical Correlates
- Arsenic Trioxide in Advanced Prostate Cancer
- Biologic Effects of 17AA Geldanamycin
- Calcitriol in Recurrent Prostate Cancer
- Combinatorial Approaches for Novel Anticancer Agents
- Dendritic Cell Vaccine in Metastatic Prostate Cancer
- A Feasibility Study of L-Selenomethionine and Alpha-Tocopherol
- Molecular Correlates of Soy in Humans

Table 7-3. (cont.)

- Phase I Study of Combined Viral and Suicide Gene Therapies
- Phase I Trial of PDT in Patients with Prostate Carcinoma
- Phase II Trial of Tetrathiomolybdate in Prostate Cancer
- A Pilot Phase IB Trial of a PSA Peptide Vaccine
- Radionuclide Therapy of Skeletal Metastases from Cancer

INITIATIVES WITH PROSTATE CANCER-RELEVANT COMPONENTS

Cancer Drug Discovery: Diversity Generation and Smart Assays (RFA-CA-98-009)

Objective: Innovative approaches to the generation of structural diversity, such as (a) combinatorial synthesis, parallel synthesis, or genetic manipulation of biosynthetic pathways in producer organisms and (b) Smart assay development for cancer drug discovery.

Relevant Research Project Resulting from This Request for Applications (RFA): Combinatorial Creation of New Anticancer Agents

Cancer Trials Support Unit (CTSU) (http://www.ctsu.org)

Objective: A national network of physicians to participate in NCI-sponsored Phase III treatment trials that include randomized trials for all clinical states as well as protocols offering a variety of treatment modalities.

Relevant Program Resulting from This Initiative: A pilot program initiated in 2000, prostate cancer trials were the first for which this mechanism was activated. In early 2003, there were eight CTSU-listed trials for prostate cancer:

- *Phase III Randomized Study of Second-Line Hormonal Therapy (Ketoconazole and Hydrocortisone) versus Combination Chemotherapy (Docetaxel and Estramustine) in Asymptomatic Patients with Prostate Cancer and a Rising PSA after Androgen Suppression* (E-1899)
- *Phase III Randomized Trial Comparing Intermittent versus Continuous Androgen Suppression for Patients with Prostate-Specific-Antigen Progression in the Clinical Absence of Distant Metastases Following Radiotherapy for Prostate Cancer* (CAN-NCIC-PR7)
- *Prospective Randomized Phase III Trial Comparing Consolidation Therapy with or without Strontium-89 Following Induction Chemotherapy in Androgen-Independent Prostate Cancer* (NCI-3410)
- *Phase III Protocol of Androgen Suppression (AS) and Radiation Therapy (RT) vs. AS and RT Followed by Chemotherapy with Paclitaxel, Estramustine, and Etoposide (TEE) for Localized, High-Risk Prostate Cancer* (RTOG-99-02)
- *Phase III Trial to Evaluate the Duration of Neoadjuvant Total Androgen Suppression (TAS) and Radiation Therapy (RT) in Intermediate-Risk Prostate Cancer* (RTOG-99-10)
- *Phase III Randomized Study of Adjuvant Therapy for High Risk pT2-3N0 Prostate Cancer* (CAN-NCIC-PR9)
- *Phase III Randomized Study of Patients with High Risk, Hormone-Naive Prostate Cancer: Androgen Blockade with 4 Cycles of Immediate Chemotherapy versus Androgen Blockade with Delayed Chemotherapy* (RTOG-P-0014)
- *Adjuvant Androgen Deprivation versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy: Phase III* (S9921)

Clinical Cancer Therapy Research (PA-02-002)

Objective: Translate insights in cancer biology and the development of new agents into innovative cancer therapeutic studies.

Relevant Research Project Resulting from This PA: Telomerase RNA Transfected Dendritic Cell Vaccines

Development and Applications of Imaging in Therapeutic Studies (RFA-CA-98-024)

Objective: Apply imaging technologies in the assessment of investigational cancer therapeutic agents.

Relevant Research Project Resulting from This RFA: TNT Imaging to Monitor the Efficacy of Cancer Therapy

Table 7-3. (cont.)

Expanded Participation Project (EPP) (http://spitfire.emmes.com/study/epp)

Objective: Demonstration project for providing broader access to Cooperative Group Phase III trials for prostate and three other cancer types.

Relevant Program Resulting from This Initiative: Twenty-eight participating institutions were recruited to pilot centralized access to clinical trials, which included two prostate cancer trials. After the goals of the EPP were reached, most of these institutions elected to continue with centralized access by joining the CTSU.

National Cooperative Drug Discovery Groups (NCDDGs) (http://dtp.nci.nih.gov/branches/gcob/gcob_web3.html)

Objective: Discovery of new and more effective anticancer treatments.

Relevant Research Project Resulting from This Initiative: A Vaccine for Prostate Cancer (Provenge)

Rapid Access to Intervention Development (RAID) Program (http://dtp.nci.nih.gov/docs/raid/raid_index.html)

Objective: Assist translation to the clinic of novel anticancer therapies deriving from academia.

Relevant Research Projects Resulting from This Initiative:

- Enzymatic Activation of a Thapsigargin Prodrug by Prostate-Specific Antigen (PSA) as Treatment for Metastatic Prostate Cancer
- A Novel Gene Therapy Approach for the Treatment of Prostate Cancer: A Preclinical to Clinical Transition
- A Prolactin Growth Antagonist as a Potential Therapeutic for Androgen-Independent Prostate Cancer
- Tumor-Specific Targeting of WT p53 by Anti-Transferrin Receptor Single-Chain Antibody: New Therapeutic Strategy for Prostate Cancer Treatment

Therapeutic Modulation of Angiogenesis in Disease (PAR-98-096)

Objective: Translate basic knowledge of the angiogenic process into therapeutic applications.

Relevant Research Projects Resulting from This PA:

- Novel Angiogenesis Inhibitor from Cartilage
- Targeted Delivery of Genes to Angiogenic Vasculature

Translational Research Initiative (http://ctep.cancer.gov/resources/trf-overview.html)

Objective: Conduct correlative studies with material from or examinations of patients participating in NCI-sponsored early-phase clinical trials with CTEP Investigational New Drug (IND) agents.

Relevant Clinical Trial Supported by This Initiative: Phase II Study of Zoledronate and BMS-275291 in Patients with Hormone-Refractory Prostate Cancer (NCI-5361)

Ongoing NCI Research: Recent Progress in Prostate Cancer Treatment

Progress in Preclinical Models

Recent advances in the development of complementary transgenic and xenograft mouse models displaying aspects of prostate cancer disease progression, including bone metastasis, have led to changes in the way promising therapeutic agents are tested. (See Chapter 6 for more details.) Agents recently studied in transgenic mouse models include the vitamin D analog EB 1089 (Perez-Stable et al., 2002) and the nonsteroidal anti-inflammatory drug E-7869 (R-flurbiprofen) (Wechter et al., 2000). NCI-funded researchers are also using transgenic models to assess the effectiveness of novel agents for the treatment of prostate cancer. In recent years, immunodeficient mice xenografted with prostate cancer cell lines have been used for testing all types of agents, including stimulators of apoptosis, angiogenesis inhibitors, gene therapies, and prodrugs.

Early-Stage Disease

The incidence of prostate cancer in the United States increased noticeably following the introduction of the PSA screening assay. (See Chapter 1, Figure 1-1.) Cause-specific mortality initially increased as well, peaking in 1992; however, the rate has since fallen to levels observed in the early 1970s. (See Chapter 1, Figure 1-2.) The following explanations have been proposed to address this decline in mortality: (1) Diagnosis occurs at an earlier stage of cancer due to PSA screening (see Chapter 5 for progress related to early detection and diagnosis) and/or (2) the impact of treatment on localized disease has changed with the greatly enhanced use of hormonal therapy. Several recent developments provide support for the hypothesis that treatment has a major impact on survival:

- Results of an NCI-sponsored trial support the hypothesis that early initiation of hormonal therapy can prolong survival in men at high risk for recurrence (Messing et al., 1999). Patients who were found to have microscopic metastases in their lymph nodes at the time of prostatectomy were assigned to either receive immediate hormonal therapy or to undergo observation until the time of disease progression. Prostate cancer-related mortality and disease recurrence were significantly lower in men receiving the hormonal therapy than in the observational group after a median of 7.1 years following treatment. This finding has led to a change in the standard of care for node-positive prostate cancer patients.
- Follow-up data from multiple randomized trials conducted by the RTOG have matured (Horwitz et al., 2001 and Pilepich et al., 2001) and together with results from the EORTC (Bolla et al., 1997 and 2002) provide strong evidence that the addition of androgen-deprivation therapy to external beam radiotherapy can improve cause-specific and overall survival in subsets of patients with poorly differentiated or locally advanced disease.
- The Prostate Cancer Intervention Versus Observation Trial (PIVOT) was conducted in the United States in 44 VA Medical Centers and 8 NCI sites, completing accrual in 2002. Data are not yet mature, but the results from PIVOT are expected to clarify whether surgery can improve outcomes in individuals diagnosed in the early stages of disease due to PSA screening.

Since prostate cancer is a heterogeneous disease, an important area of research is the development and validation of prognostic nomograms, not only to provide information for an individual patient but also to facilitate data interpretation and the appropriate design of subsequent trials. Recent relevant publications address the utility of considering the percentage of positive prostate biopsies (D'Amico et al., 2000), the prognostic significance of Gleason score (Chan et al., 2000), the importance of pretreatment blood biomarker levels as determined by RT-PCR (Shariat et al., 2002), the development of a continuous probability model (Kattan et al., 1998), and nomograms following surgery or radiotherapy (D'Amico et al., 1999).

Biochemical Recurrence

The practice of monitoring PSA levels after treatment of patients with curative intent has created a new asymptomatic patient population whose only evidence of disease is a rising PSA. Since these patients have minimal disease, are asymptomatic, and may live a long time after a rising PSA, clinical trial methodology specific to this population needs to be considered. In 2001 and 2002, NCI (CTEP) joined investigators from Memorial Sloan-Kettering Cancer Center and Prostate Cancer Foundation to organize and participate in a working group to address drug development paradigms, clinical trial methodology, and reporting standards for this population. Proceedings are to be published in the *Journal of Clinical Oncology*.

A variety of Phase II and Phase III NCI-sponsored protocols are open to this population, including the following:

- *Phase III Randomized Crossover Study of Oral Thalidomide versus Placebo in Patients with Androgen Dependent Prostate Cancer Following Limited Hormonal Ablation* (T99-0053)
- *Phase III Randomized Study of Intermittent versus Continuous Androgen Suppression in Patients with PSA Progression after Prior Radiotherapy* (SWOG JPR7)
- *Phase III Randomized Study of Second-Line Hormonal Therapy (Ketoconazole and Hydrocortisone) versus Docetaxel/Estramustine in Asymptomatic Patients and a Rising PSA after Androgen Suppression* (ECOG 1899)
- Phase II trials of anti-angiogenesis agents, immunotherapy, an alkylphospholipid, and differentiating agents

In general, large randomized trials in the adjuvant setting or in patients with biochemical recurrence (i.e., those trials in which the endpoint of survival will require long-term follow-up) are prospectively designed for analysis and reporting of biochemical outcomes prior to their survival data. This approach is intended to expedite clinical research, as well as to eventually provide information on the correlation of PSA levels with outcome.

Advanced Disease

The identification of active treatments for androgen-independent disease is a major challenge, in part due to the prior lack of standardization of PSA response definitions (Dawson, 1998). In 1999, NCI convened a PSA working group composed of expert clinical investigators in an effort to standardize eligibility and response criteria for Phase II clinical trials in androgen-independent disease. The resulting consensus guidelines have become the standard for the conduct of clinical trials in this patient population (Bubley et al., 1999). A majority of Phase II treatment trials sponsored by the NCI now utilize PSA-based endpoints when evaluating and prioritizing new therapies for use in larger-scale and/or definitive clinical tests.

A hallmark of prostate cancer is its propensity to metastasize to bone, with evidence of bone metastases at autopsy in up to 85 percent of men with prostate cancer (Galasko, 1981). Research into the biology of bone metastases and tumor cell–stromal interactions is being conducted in multiple disciplines using in vitro and in vivo model systems (Chapters 3 and 6). To facilitate crossdisciplinary communication and translation to the clinic, NCI sponsored a workshop entitled “Mechanisms of Tumor Metastasis to the Bone: Challenges and Opportunities” in November 2000 and co-sponsored the Third International Conference on Cancer-Induced Bone Diseases with the Paget Foundation in 2001.

NCI-supported clinical researchers are exploring a variety of approaches for targeting bone metastases, and are studying the use of bisphosphonates, matrix metalloproteinase inhibitors, integrin antagonists, growth factor receptor inhibitors and antiangiogenesis agents alone and in combination for treatment of metastases.

- Zoledronic acid (Zometa®), which targets cancers that metastasize to bone by inhibiting osteoclast function and skeletal calcium release, was the first bisphosphonate to be approved by the FDA for use in prostate cancer. A new national trial sponsored by NCI will evaluate men with hormone-sensitive prostate cancer metastatic to bone to determine whether early use of zoledronic acid (i.e., before androgen independence) can delay the progression of bone disease as well as skeletal complications and androgen-associated osteoporosis.
- NCI-supported investigators also tested whether the use of radioisotopes in addition to standard treatment could improve the outcome of bone-targeted therapy in patients with clinically symptomatic bone metastases (Tu et al., 2001). Patients responding to chemotherapy were selected at random to receive either additional chemotherapy alone or in combination with radiostrontium (Sr-89). Sr-89 is a radioactive calcium analogue that is targeted to the site of osteoblastic metastases.

Although the study was small, the median survival of patients who received Sr-89 was approximately 65 percent longer than that of patients who received chemotherapy alone. These results suggest that targeting the growth of bone metastases and/or altering their capacity to develop resistance to chemotherapy could prolong survival in addition to providing symptomatic relief. This finding is currently being followed up in a larger, national, randomized Phase III study (*Phase III Randomized Study of Consolidation Therapy with or without Strontium Chloride Sr-89 after Induction Chemotherapy in Patients with Androgen-Independent Prostate Cancer* - NCI-3410) to definitively determine whether the approach works and, if so, whether markers can be identified that predict development and progression of bone metastases.

After many years in which the value of chemotherapy in prostate cancer treatment was questionable, the FDA approved the use of the combination regimen mitoxantrone and prednisone for the palliation of symptomatic bone metastases in 1996. Subsequently, microtubulin inhibitors such as estramustine and the taxane drugs, particularly when used in combination, were found to produce significant responses as measured by both the soft-tissue disease and surrogate endpoint of reduced PSA levels (Hudes et al., 1995; Pienta and Smith,1997; Petrylak et al., 1999). Various chemotherapy-based approaches are now being tested in large, randomized trials that include patients in each of the clinical states, such as those with localized disease at high risk for recurrence following prostatectomy or radiotherapy, those with biochemical recurrence, and patients with metastatic disease. Some examples are as follows:

- *Phase III Protocol of Androgen Suppression (AS) and Radiation Therapy (RT) versus AS and RT Followed by Chemotherapy with Paclitaxel, Estramustine, and Etoposide (TEE) in Localized, High-Risk Prostate Cancer* (RTOG-9902)
- *Phase III Randomized Study of Adjuvant Androgen Deprivation Therapy with or without Mitoxantrone and Prednisone after Radical Prostatectomy in Patients with High-Risk Adenocarcinoma of the Prostate* (SWOG S9921)
- *Phase III Randomized Study of Second-line Hormonal Therapy (Ketoconazole and Hydrocortisone) versus Docetaxel/Estramustine in Asymptomatic Patients and a Rising PSA after Androgen Suppression* (ECOG 1899)
- *Phase III Randomized Study of Docetaxel and Estramustine versus Mitoxantrone and Prednisone in Patients with Hormone-Refractory, Metastatic Adenocarcinoma of the Prostate* (SWOG 9916)

The National Cancer Institute's goal for prostate cancer treatment over the next five years is to "accelerate development and validation of optimal treatments that target the molecular and cellular characteristics of prostate cancer."

– National Institutes of Health, Prostate Cancer Research Plan for FY 2003–2008.

Continuing Needs and Evolution

Although genuine options are available for curing prostate cancer when it is localized, tools to more accurately assess both risk for recurrence and response to treatment in an individual patient are needed. As the genetic machinery that governs the behavior of prostate cancer cells evolves, novel agents can be rationally designed to target critical pathways in each clinical state. To ensure that novel therapeutics can be adequately explored, there remains a need for translational research and early-phase clinical trials. Larger scale, randomized trials will be needed to validate biomarkers and surrogate endpoints, as well as to confirm and extend promising findings. Adequate infrastructure is needed to allow for the acquisition, storage, and use of clinically annotated tissue banks in all stages of trials in order to support translational research. Although in its infancy, functional imaging holds promise for oncology clinical trials in areas such as diagnosis, initial staging, risk classification, and detection of biochemical recurrence, as well as for the prediction of response to therapy based on function before structural changes are detectable and even in sites traditionally difficult to assess (e.g., bone).

NCI's Future Investment in Prostate Cancer Treatment

The NIH Prostate Cancer Research Plan for FY 2003–2008 describes the NCI's planned objectives for research on treatment of prostate cancer. The plans are based on the priorities that were identified by the PRG and the advances that have taken place since completion of the PRG's work. The four FY 2003–2008 objectives and their alignment to the 12 PRG priorities are summarized in Figure 7-2.

These objectives encompass all 12 PRG treatment priorities, with one objective consolidating the issues addressed by seven of the PRG priorities and another objective addressing a PRG priority in the area of resources needed. Over the next few years, the NCI will continue to invest in research and support new initiatives that address the objectives listed in Figure 7-2. Emphasis will be placed on research addressing reliable means to predict the behavior of individual cancers and optimal treatments for all stages of prostate cancer.

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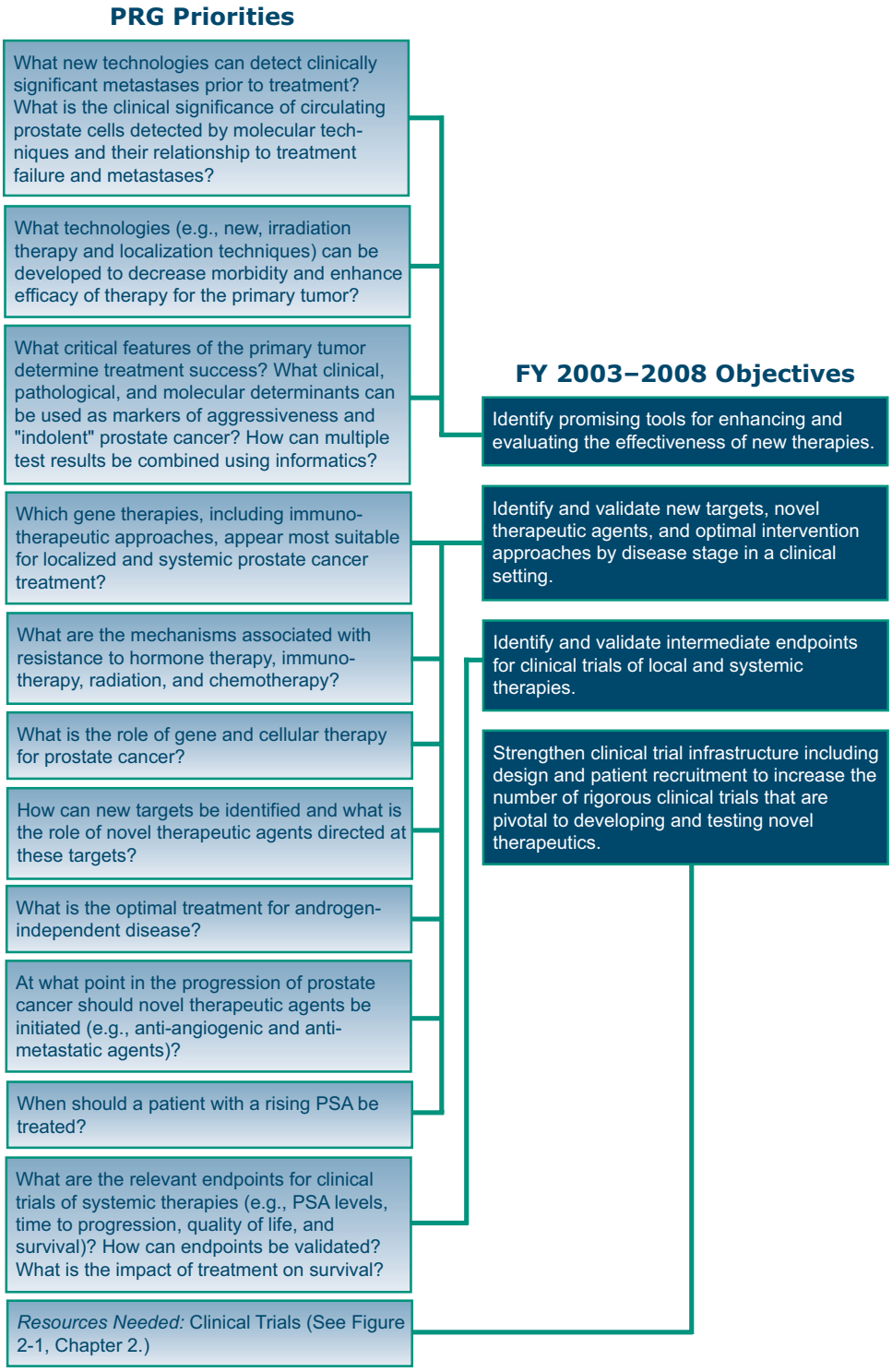

Figure 7-2. NIH's FY 2003–2008 prostate cancer treatment research objectives build upon the 1998 PRG priorities.

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CHAPTER 8

Prostate Cancer Control, Survivorship, and Outcomes: NCI's Investment and Recent Progress

Most men diagnosed with prostate cancer die with the disease rather than from the disease. As shown in Figure 8-1, after adjusting for other causes of death, over 80 percent of men who were diagnosed with prostate cancer in 1990[1] were still alive in 2000.

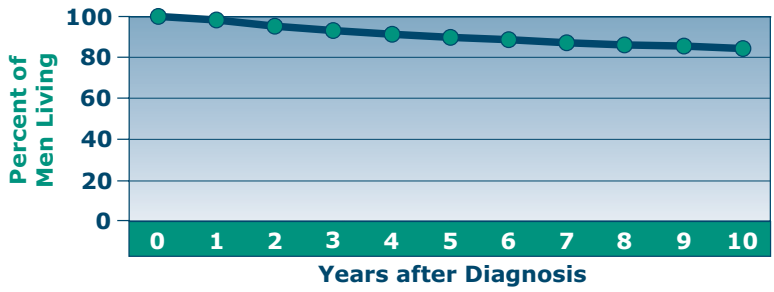


Figure 8-1. Survival of U.S. men who were diagnosed with prostate cancer in 1990.

Rates have been adjusted to exclude causes of death other than prostate cancer.
This figure uses data derived from Table XXII-5 in *SEER Cancer Statistics Review, 1975-2001*, SEER Program, National Cancer Institute.

Although curing prostate cancer is one criterion of successful cancer therapy, understanding the long-term impact on quality of life will ultimately determine the effectiveness of new and existing treatments.

– Defeating Prostate Cancer: Crucial Directions for Research - Report of the Prostate Cancer Progress Review Group, August 1998.

In order to improve the lives of men who are at risk or who have already been diagnosed with prostate cancer, the NCI supports the following relatively new areas of research:

- **Cancer Control Research:** Basic and applied research in the behavioral, social, and population sciences to create or enhance interventions that, independently or in combination with biomedical approaches, reduce cancer risk, incidence, morbidity, and mortality.[2]

- **Survivorship Research:** Research that encompasses the physical, psychosocial, and economic sequelae of cancer diagnosis and its treatment among survivors of cancer.[3]
- **Outcomes Research:** Research that describes, interprets, and predicts the impact of various influences, especially (but not exclusively) interventions on endpoints that matter to decision makers: patients, providers, private payers, government agencies, accrediting organizations, or society at large.[4]

[1] The most recent year for which SEER 10-year survival data are available.

[2] Definition derived from the NCI Division of Extramural Activities (DEA) Cancer Control Review Group.

[3] Definition derived from the NCI Division of Cancer Control and Population Sciences (DCCPS).

[4] Definition derived from the NCI DEA Cancer Control Review Group.

In their 1998 report, the Prostate Cancer PRG described promising directions and unmet needs in the area of outcomes research. The report indicated that methodologies have recently become available to quantitatively evaluate both clinical outcomes, such as overall and disease-free survival, and patient-focused outcomes, such as quality of life, treatment-related morbidity, economic outcomes, and access to care, in a systematic way. Although assessments of patient-focused outcomes had already been incorporated into most large clinical trials, the absence of standardized methodology hindered comparison of results between trials. Furthermore, few NCI-sponsored projects had been focused on long-term morbidity, late complications, or supportive care—issues that had increased in importance following the dissemination of screening and treatment approaches that were believed to, but had not yet been proven to, extend the lives of men with prostate cancer.

The Prostate Cancer PRG identified three Priority One questions affecting the area of cancer control, survivorship, and outcomes. The questions and their accompanying recommendations addressed the need for refining, standardizing, and applying the new methodologies and for determining the impact of prostate cancer screening and treatment on the population as a whole, and on racial/ethnic minorities and medically underserved populations.

The NCI has responded to the three PRG Priority One questions and recommendations. In fiscal years (FYs) 1998 through 2002, NCI increased its dollar investment in cancer control, survivorship, and outcomes research more than threefold. Recent results from NCI-sponsored research have reshaped our knowledge of the long-term effects of prostate cancer therapy and PSA screening.

NCI's Investment and Response

From FY 1998 to FY 2002, NCI's extramural investment in cancer control, survivorship, and outcomes research grew from $6.5 million (M) to $20.3M (Figure 8-2). Much of this investment was made in the form of increases in the number of projects that respond to PRG Priority One questions. Table 8-1 summarizes NCI's response to the three Prostate Cancer PRG Priority One research questions in this area.

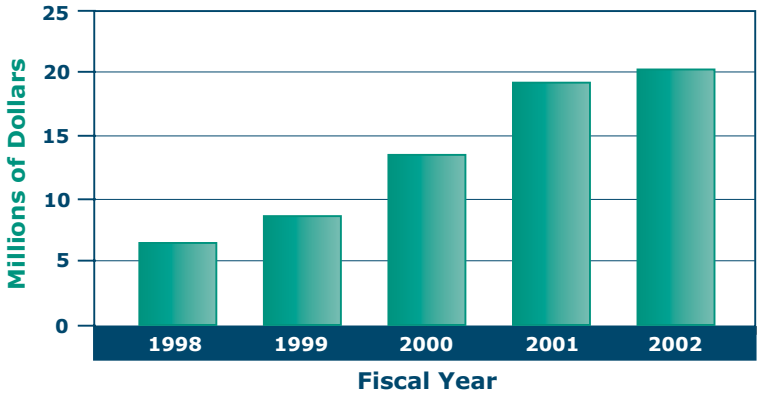
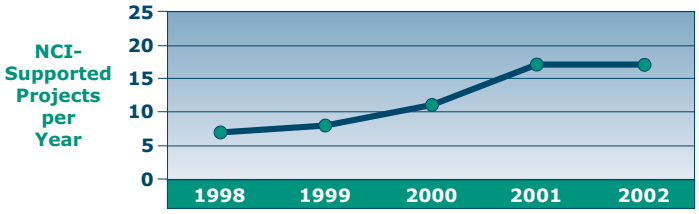


Figure 8-2. NCI's extramural investment in cancer control, survivorship, and outcomes research: 1998–2002 (in millions of dollars).

Table 8-1. NCI Efforts Responsive to PRG Priorities in Prostate Cancer Control, Survivorship, and Outcomes[a]

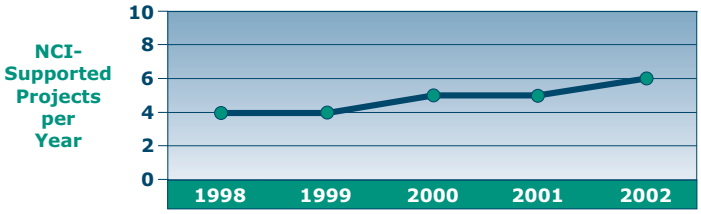
PRG Priority: What is the impact on outcomes of treatment, community settings versus clinical trials/centers of excellence, and provider characteristics (e.g., volume and expertise)? How do benefits differ among patient subsets (e.g., age and race)? How do patients value tradeoffs between length of survival and quality of life?



NCI Efforts:

- In FY 2002, active areas of investigation included quality-of-life determinations in prostate cancer patients and long-term survivors, with emphasis on elderly men and African American men; underlying causes for the observed racial/ethnic disparities in prostate cancer incidence and mortality; and new tools for disseminating information on treatments and their outcomes to patients and family members.
- NCI initiatives addressing this priority included the Prostate Cancer Intervention Versus Observation Trial (PIVOT) and the Prostate Cancer Outcomes Study (PCOS).

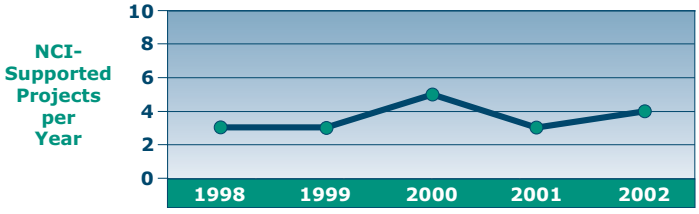
PRG Priority: How are different types of outcomes defined and standardized (e.g., quality of life, morbidity, and patient satisfaction)?



NCI Efforts:

- In FY 2002, active areas of investigation included development, validation, and introduction of quality-of-life survey instruments and effectiveness, costs, and cost effectiveness of screening and treatment.
- The NCI Cancer Outcomes Measurement Working Group (COMWG) was established in 2001 to assess and improve measurement of key patient outcomes in prostate and three other cancer sites. This working group addresses the PRG recommendations to identify key patient-focused variables and to encourage common mechanisms for reporting patient outcomes.

PRG Priority: What is the impact of early detection and screening on outcomes?[b]



NCI Efforts:

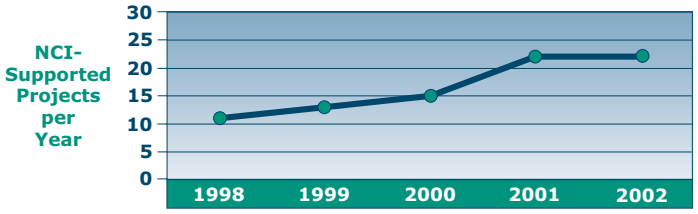
- In FY 2002, active areas of investigation included prospective clinical trials, retrospective analysis, modeling and characteristics of health insurance, and managed care plans that influence the practice of cancer screening.
- The ongoing Prostate, Lung, Colorectal & Ovarian Cancer Screening Trial (PLCO) is determining whether PSA screening reduces mortality from prostate cancer.
- Other NCI initiatives addressing this priority included the Cancer Intervention and Surveillance Modeling Network (CISNET) and the Cancer Surveillance Using Health Claims-Based Data System.

[a] A given project may map to more than one PRG Priority One question and therefore be represented in more than one figure. Projects active in 2002 are listed by Principal Investigator's name for each PRG Priority One question in Appendix B (Tables B-44–B-47).

[b] See p. 5-4 for related priorities "Does early detection change mortality from prostate cancer?" and "What are the effects of early detection on morbidity and quality of life?"

Table 8-1. (cont.)

Additional cancer control, surveillance, and outcomes projects



NCI Efforts:

- In FY 2002, active areas of investigation included characteristics of successful social support systems for men, influence of market forces on cancer care, cancer information and education programs tailored to specific communities, and clinical trials of behavioral and pharmacological interventions to counteract fatigue, improve quality of life, and improve physical health in patients.

Initiatives comprised a considerable portion of NCI's response to the PRG's priorities and recommended actions. The initiatives relevant to research on prostate cancer control, survivorship, and outcomes between FYs 1998 and 2002 include the following list of general initiatives that are described in Table 2-1[5] (Chapter 2) and the category-specific initiatives that are listed and described in Table 8-2:[6]

- Cancer Research Training, Career Development, and Education Opportunities
  - Cancer Prevention, Control, Behavioral, and Population Sciences Career Development Award
  - Established Investigator Award in Cancer Prevention, Control, Behavioral, and Population Research
- Clinical Trials Cooperative Group Program
- Community Clinical Oncology Program (CCOP)
- Minority Institution/Cancer Center Partnership (MI/CCP) Program
- Minority-Based Community Clinical Oncology Program (MBCCOP)
- Prostate Cancer Intervention Versus Observation Trial (PIVOT)
- Prostate, Lung, Colorectal & Ovarian Cancer Screening Trial (PLCO)
- Prostate Specialized Programs of Research Excellence (SPOREs)
- Special Populations Networks (SPNs)

[5] Initiatives relevant to multiple categories of prostate cancer research.

[6] Initiatives unique to the research category of cancer control, survivorship, and outcomes.

Table 8-2. NCI Initiatives Relevant to Prostate Cancer Research: Cancer Control, Survivorship, and Outcomes

INITIATIVES FOCUSED ON PROSTATE CANCER

Prostate Cancer Outcomes Study (PCOS) (http://healthservices.cancer.gov/pcos)

Objective: Determine the impact of primary prostate cancer treatments on quality of life.

Relevant Program Resulting from This Initiative: Program was begun in 1994. Six cancer registries that are part of NCI's Surveillance, Epidemiology, and End Results (SEER) program collect supplemental data from patients diagnosed with prostate cancer to support study of the extent of treatment-induced urinary, bowel, and sexual complications. PCOS data sets and data collection instruments are available to outside investigators.

INITIATIVES WITH PROSTATE CANCER-RELEVANT COMPONENTS

Cancer Intervention and Surveillance Modeling Network (CISNET) (http://cisnet.cancer.gov/about)

Objective: Collaborative research using simulation and other modeling techniques to describe the impact of prevention, screening, and/or treatment interventions in population-based settings.

Relevant Resource Resulting from This Initiative: Begun in 1999, CISNET was expanded in 2002 to include its fourth cancer site and additional prostate cancer projects. To disseminate results and facilitate comparisons of the models developed by different CISNET investigators, the web-based Model Profiler tool was developed for capturing details that are generally not included in journal articles.

Relevant Research Projects Resulting from This Initiative:

- PSA Screening and U.S. Prostate Cancer Trends
- Survival Effects of Prostate Cancer Surveillance

Cancer Outcomes Measurement Working Group (COMWG) (http://outcomes.cancer.gov/methods/measures/comwg)

Objective: Evaluate existing endpoint measures and instruments and formulate alternative strategies for identifying valid, reliable, sensitive, and feasible clinical and patient-centered endpoint measures for use in quality of cancer care studies.

Relevant Resource Resulting from This Initiative: Established in 2001, the COMWG focuses on prostate and three other cancer types. The Working Group's findings have been reported to the NCI and will be published as the book *Outcomes Assessment in Cancer*.

Cancer Research Network (CRN) (http://cancercontrol.cancer.gov/bb/can_research.html)

Objective: Stimulate research on cancer prevention, early detection, long-term care, and post-diagnosis monitoring.

Relevant Resource Resulting from This Initiative: Initiated in 1999, the CRN is comprised of 10 managed care research organizations. The CRN is developing integrated data systems to support studies that will include the use of hormonal therapies in prostate cancer patients.

Cancer Surveillance Using Health Claims-Based Data System (http://dccps.nci.nih.gov/ARP/research/health.asp)

Objective: Investigate health claims information as a reporting source for assessing cancer burden.

Relevant Research Project Resulting from This Initiative: Managed Care Penetration and Cancer Care

Economic Studies in Cancer Prevention, Screening, and Care (http://cancercontrol.cancer.gov/ARP/research/economic.asp)

Objective: Increase knowledge of the economic aspects of cancer prevention, screening, and care.

Relevant Research Project Resulting from This Initiative: Use of Cancer Screening in a Managed Care Environment

Exploratory Grants for Behavioral Research in Cancer Control (PA-99-163)

Objective: Test novel or creative ideas to advance behavioral research in cancer prevention and control.

Relevant Research Project Resulting from This Initiative: A Multimedia Prostate Cancer Intelligent Expert System

Table 8-2. (cont.)

Minority and Underserved Cancer Survivors (http://dccps.nci.nih.gov/ocs/underserved)

Objective: Promote survivorship research among minority and underserved populations, and enhance communication between these communities and cancer centers.

Relevant Research Project Resulting from This Initiative: Partner-Assisted Coping Skills Training for Prostate Cancer Survivors

SEER–Medicare Linked Database (http://healthservices.cancer.gov/seermedicare)

Objective: Linkage of two large population-based data sources that provide detailed information about elderly persons with cancer.

Relevant Resource Resulting from This Initiative: The current SEER–Medicare linkage, completed in December 2001, includes all Medicare-eligible persons appearing in the SEER data through 1999 and their Medicare claims through 2001. Because the database is large and complex, the initiative's website includes a section on analytic support to assist researchers who use the database.

SEER Patterns of Care/Quality of Care (POC/QOC) Initiative (http://cancercontrol.cancer.gov/bb/seer_pattern.html)

Objective: Evaluate the dissemination of state-of-the-art therapy into community practice, disseminate research findings into scientific journals and professional meetings, and work with professional organizations to develop relevant educational or training opportunities.

Relevant Program Resulting from This Initiative: Program began in 1987. In 2001, a mechanism was established whereby POC/QOC studies would be performed by the SEER registries every 3–5 years for the major cancer sites (including prostate). Cancer sites with emerging new treatments or concerns regarding provision of state-of-the-art therapy would be conducted in the alternate years.

Small Grants Program for Behavioral Research in Cancer Control (http://dccps.nci.nih.gov/smallgrants/index.html)

Objective: Facilitate the growth of a nationwide cohort of scientists with expertise in behavioral research addressing cancer prevention and control.

Relevant Research Projects Resulting from This Initiative:

- Disparities in Prostate Cancer Decision-Making and Quality of Life
- Dyadic Social Support for Men with Prostate Cancer
- Family Members and the Survivorship Phase of Cancer
- Prostate Cancer Survivor Narratives and Doctors' Responses
- A Training Curriculum Guide for Prostate Cancer Control

Surveillance, Epidemiology, and End Results (SEER) (http://seer.cancer.gov/)

Objective: Collect, analyze, and publish information on cancer incidence and survival.

Relevant Resource Resulting from This Initiative: Begun in 1973, its most recent expansion was in 2001. SEER currently collects and publishes data from 11 population-based cancer registries and three supplemental registries; approximately 26 percent of the U.S. population, including a substantial portion of racial/ethnic minorities and other medically underserved populations, is covered. In 1999, SEER published the monograph *Prostate Cancer Trends, 1973–1995*.

Ongoing NCI Research: Recent Progress in Prostate Cancer Control, Survivorship, and Outcomes

Survivorship and Outcomes

The lingering uncertainty about the superiority of any single treatment modality for clinically localized prostate cancer and the relatively long survivorship of men diagnosed with this disease have stimulated progress in the area of cancer control, survivorship, and outcomes. Much of the literature on this topic in the past 3 years has emphasized patient-focused outcomes such as quality of life and patient satisfaction, rather than clinical outcomes such as recurrence and survival. The primary focus has been on the long-term complications of prostate cancer treatment, particularly urinary, sexual, and bowel dysfunction. Although most studies have used patient surveys to examine these outcomes (Stanford et al., 2000; Bacon et al., 2001; Hamilton et al., 2001; Potosky et al., 2001b; Bacon et al., 2002; Potosky et al., 2002; Penson et al., 2003), claims data have also been used (Begg et al., 2002).

During the late 1980s and early 1990s, the complication rates for the most common initial prostate cancer treatment modalities—watchful waiting, external beam radiation, and prostatectomy—were derived mainly from studies involving small numbers of patients in large, academic medical centers. In these studies, the complication rates were relatively low (e.g., 10–20 percent impotence rates following radical prostatectomy). More recent results, from the large PCOS (Stanford et al., 2000; Potosky et al., 2001b) and other studies (Bacon et al., 2001; Bacon et al., 2002) involving patients who better represent general clinical practice, have shown complication rates that are much higher (e.g., impotence rates in excess of 60 percent following radical prostatectomy). Starting in October 1999, analyses of PCOS data were published on topics that included the following:

- Quality of life following androgen deprivation (AD) therapy or no therapy for localized prostate cancer
- Urinary, bowel, and sexual function after prostatectomy or radiotherapy for localized prostate cancer
- Factors associated with selection of various initial therapy approaches for localized prostate cancer
- Factors associated with initial presentation of advanced prostate cancer in different minority populations
- Impact of decrements in urinary and sexual function on quality of life
- Effects of treatments on patient satisfaction with care

Due to the rapid adoption of injectable AD during the past decade, a particularly important area of progress has been determining the effects of AD therapy on sexual function and other quality-of-life measures (Potosky et al., 2001b; Potosky et al., 2002). There has also been research examining the complications associated with newer forms of radiotherapy, particularly conformal-beam radiotherapy (Hanlon et al., 2001) and brachytherapy (Lee et al., 2000; Bacon et al., 2001; Eton et al., 2001; Hollenbeck et al., 2002). A recent review article (Eton et al., 2001) has addressed the many factors that affect quality of life in men with prostate cancer.

An important advance in the study of patient-focused outcomes has been the development of a new questionnaire, the Expanded Prostate Cancer Index Composite (EPIC). This 50-item survey instrument, which is an expansion of an older 20-item instrument, may be adopted as a standard approach for measuring urinary, sexual, bowel, and hormonal symptoms following prostate cancer therapy (Wei et al., 2000). EPIC is currently being used in a number of multi-institutional trials funded by the NCI and other organizations.

Statistical Trends and Surveillance of Practice Patterns

In addition to the emphasis on patient-focused outcomes, there has been effort devoted to assessment and analysis of the trends in prostate cancer incidence (Etzioni et al., 1999; Hankey et al., 1999; Schwartz et al., 1999; Etzioni et al., 2002) and mortality (Feuer et al., 1999; Cronin and Feuer, 2000) rates.[7] One current perspective is that PSA screening might be an important contributory factor to the mortality decline that began in the mid-1990s. Pending results from ongoing screening trials, it is possible to speculate that other potential reasons for the mortality decline include changes in treatment patterns (such as increasing use of hormonal therapy) and cause of death misclassification. These issues were addressed in a recent review (Potosky et al., 2001a), and in more detail in a three-part series of articles analyzing SEER Program data published in the *Journal of the National Cancer Institute* (Etzioni et al., 1999; Feuer et al., 1999; Hankey et al., 1999).

Another important area of focus has been racial disparities. Recent studies have explored differences among whites, African Americans, and other racial/ethnic groups in screening (Etzioni et al., 2002a), stage at diagnosis (Hoffman et al., 2001), treatment (Harlan et al., 2001; Polednak, 2001; Zietman et al., 2001; Shavers and Brown, 2002), treatment complications (Eton et al., 2001), and survival (Polednak, 2001; Thompson et al., 2001; Clegg et al., 2002; Lin et al., 2002). It is clear that African American men are diagnosed at more advanced stages of disease, have poorer survival[8] and survival duration, and are sometimes treated less aggressively than men who are white or of other racial/ethnic groups. However, it is not clear why differences in treatment translate to increased mortality, since randomized trials have not established the superiority of any single treatment strategy. Several investigators have explored the reasons underlying increased prostate cancer incidence and mortality in African American men (Montie and Pienta, 1999; Polednak, 2001).

The National Cancer Institute's goal for prostate cancer control, survivorship, and outcomes over the next five years is to "achieve a continuously improved understanding of the impact of prostate cancer and its care on individuals, families and populations with special emphasis on enhancing survivorship, improving quality of care, and steadily reducing disparities in both care and outcomes."

- National Institutes of Health, Prostate Cancer Research Plan for FY 2003–2008.

Continuing Needs and Evolution

Prostate cancer mortality rates displayed a long-term gradual increase up until the early 1990s that was followed by a decline (see Chapter 1, Figure 1-2). There have also been dramatic improvements in the survival of men after diagnosis. There continues to be scientific debate over whether the improvement in mortality and survival is due primarily to changes in the nature of the prostate cancers being detected (see Chapter 5, Figure 5-1 for prostate cancer incidence rates by grade during the years 1975–2000) or to the increased use of interventions that are used to screen for and treat prostate

[7] Overall and racial/ethnic group-specific rates for prostate cancer incidence and mortality can be viewed in Figure 1-1 and Figure 1-2 of Chapter 1.

[8] Ibid.

cancer. It is still not known whether PSA screening, as currently practiced, is of ultimate benefit to the many U.S. men who opt for the test.

Until definitive information is reported from randomized controlled trials of screening and treatment, interpretations of the reasons for these population trends in mortality and survival will remain uncertain. Additional results concerning these issues will come to light following the completion of data collection for the NCI-sponsored PLCO trial in 2007 and the European Randomized Study of Screening for Prostate Cancer (ERSPC), which will complete a third round of screening in 2007. With knowledge that PSA screening leads to likely prostate cancer overdiagnosis (Etzioni et al., 2002b), there is a need to know to what extent the overdiagnosed are being overtreated. As initial PIVOT findings and ultimately final results are published, we will know more about the long-term (up to 15-year) clinical and patient-focused outcomes of expectant observation.[9]

Research on cancer control, survivorship, and outcomes is made more challenging by the long length of time that is often required for data collection and the changes that are adopted in treatment, supportive care, and cancer control practices during the course of data collection. With new knowledge that the long-term side effects of prostate cancer therapy are more prevalent than originally thought, many patients and physicians want to know whether recently adopted practice changes and supportive care measures (e.g., nerve-sparing prostatectomy, increasing use of LHRH agonists for primary therapy for early-stage disease, conformal-beam radiotherapy, brachytherapy, and Viagra®) are efficacious at preventing or alleviating these effects.

NCI's Future Investment in Prostate Cancer Control, Survivorship, and Outcomes

The NIH Prostate Cancer Research Plan for FY 2003–2008 describes NCI's planned objectives for cancer control, survivorship, and outcomes research pertaining to prostate cancer. The objectives are based on the priorities that were identified by the PRG and the advances that have taken place since completion of the PRG's work. The five FY 2003–2008 objectives and their alignment to the three prostate cancer control, survivorship, and outcomes PRG priorities are summarized in Figure 8-3.

The objectives developed for the 2003–2008 plan emphasized the need for research on quality of life, quality of care, and the impact of screening and treatment—areas that were emphasized by the Prostate Cancer PRG in both outcomes and early detection, diagnosis, and prognosis. However, compared to the PRG's plan, the 2003–2008 plan placed greater emphasis on the dissemination of research findings (addressed in a specific PRG recommendation but not a PRG research priority) and surveillance research (not specifically addressed by the PRG).

Greater emphasis on dissemination of research findings is warranted because of the results that are now emerging from outcomes analyses and the widespread adoption of new multimedia and interactive technologies. Greater emphasis on surveillance research is needed because of the stabilization in prostate cancer incidence and the decline in prostate cancer mortality that have taken place since 1995—the last year for which retrospective SEER data were available to the Prostate Cancer PRG.

[9] With expectant observation, interventions are reserved for symptomatic or confirmed metastatic disease.

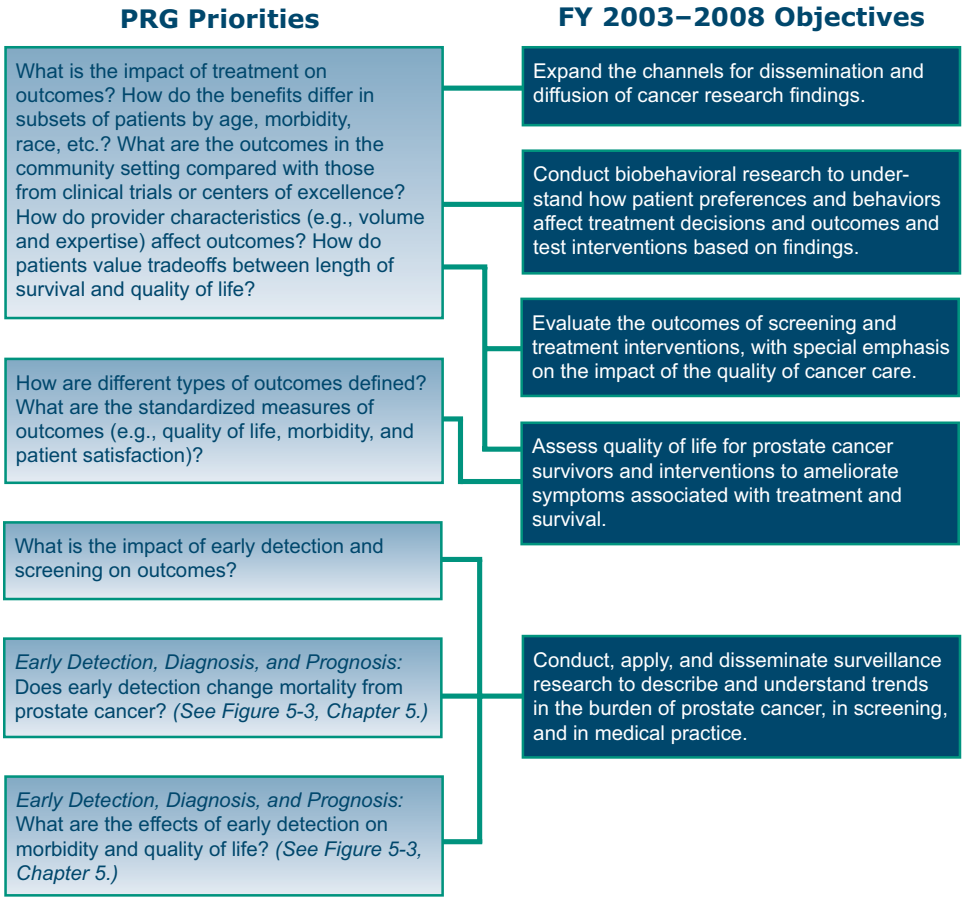


Figure 8-3. NIH's FY 2003–2008 prostate cancer control, survivorship, and outcomes research objectives build upon the 1998 PRG priorities.

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APPENDIX A

Prostate Cancer Working Group Membership Roster

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APPENDIX
B

NCI-Supported Research Projects Relevant to Prostate Cancer That Were Active in 2002

These tables list all of the prostate cancer-relevant projects that were active in 2002. The projects that are listed directly relate to the specific priority questions addressed in the body of this report and are grouped according to their appearance in each chapter. Within each table, projects are sorted alphabetically according to the Principal Investigator's name. Projects that were supported through a Request for Applications (RFA) or a Program Announcement (PA) list an RFA or a PA number next to the project's title. Investigator-initiated projects do not list an RFA or a PA number. Project IDs (grant numbers) are indicated in the last column.

FY 2002 Biology Projects

Table B-1

NCI Projects Supported in 2002 Addressing the PRG Priority: What are the potential roles of nuclear receptors, their interactive proteins, and ligand-metabolizing enzymes on prostate growth, tissue interactions, and development?

Principal Investigator	Title	RFA or PA	Project ID
Bai, Wenlong	AR-PTEN Antagonism in Prostate Cell Growth and Apoptosis		CA93666
Balk, Steven	The Androgen Receptor in Hormone Refractory Disease	PAR-99-167	CA90381-Sub-05
Barrack, Evelyn R	Project 3: Androgen Receptor Gene Structure and Function in Human Prostate Cancer	CA-94-031	CA58236-Sub-03
Chang, Chawnshang	AR-Associated Proteins in Prostate Carcinogenesis		CA77532
Chang, Chawnshang	T- vs. DHT-Specific Antiandrogens in Prostate Cancer		CA55639
Cohen, Pinchas	Interactions between IGFBPs and Nuclear Receptors in Prostate Cancer	PAR-99-167	CA92131-Sub-03
Dalton, James	Nonsteroidal Affinity Ligands for the Androgen Receptor		CA68096
De Vere White, Ralph	hAR Alterations and Androgen Independent Prostate Cancer		CA92069
Emmert-Buck, Michael R	Genetic Progression of Cancer		SC10437
Everson, Richard	Receptor Gene Polymorphisms in Prostate Cancer		CA81240
Farrar, William L	Molecular Mechanisms of Growth Factor Modulated Proliferation		BC10253
Feldman, David	Androgen-Independent Prostate Cancer: Mechanisms and Treatment	PA-99-081	CA92238
Fletterick, Robert J	Inhibition of Androgen Receptor Activation	PAR-01-045	CA95324
Gao, Allen	STAT3 in Androgen Receptor Signaling in Prostate Cancer		CA90271
Gelmann, Edward	Beta Catenin in Prostate Cancer	PA-99-081	CA87855
Gelmann, Edward P	Beta Catenin in Prostate Cancer		CA96854
Hager, Gordon L	Function of Steroid Receptors in Subcellular Compartments		BC10027
Hamburger, Anne	EBP1 Control of Prostate Cancer Cell Growth	PA-99-081	CA88882
Hayward, Simon	Hormonal Carcinogenesis in Rb-Knockout Mouse Prostate		CA96403
Imperato-McGinley, Julianne	Androgens Regulate IGF Pathway and Prostate Diseases	PAR-98-023	CA85435
Johnson, Candace	Glucocorticoids and Vitamin D: Role in Anti-Tumor Effects		CA85142
Kakar, Sham	Molecular Characterization of GnRH Receptors		CA60871
Knudsen, Karen E	Bis-Phenol A: Signaling and Mitogenesis in the Prostate		CA93404
Lange, Paul H	Mechanisms and Markers of Prostate Cancer Metastases		CA85859
Liao, Shutsung	Molecular Mechanisms of Growth Control—Prostate Cancer		CA58073

Table B-1 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Libermann, Towia	Role of a New Ets Factor, PDEF, in Prostate Cancer	PA-99-081	CA85467
Lu, Michael L	Molecular Regulation of Androgen Receptor Activation	PA-99-081	CA87997
Mohler, James	Prostate Cancer: Transition to Androgen-Independence		CA77739
Mueller, Elisabetta	PPAR as a Target of Therapy for Prostate Cancer	PAR-99-167	CA90381-Sub-02
Navone, Nora	Growth Regulation of Prostatic Cells by Androgen		CA75499
Penning, Trevor	Human Aldo-Keto Reductases and Steroid Hormone Action		CA90744
Pestell, Richard	Cyclin D1 Function in Prostate Cancer	PA-99-081	CA86072
Rosenfeld, Michael G	Repressors in Prostate Cancer	PA-99-081	CA97134
Stearns, Mark	IL-10 and IGF1 Receptor Axis in Prostate Cancer		CA90397
Sun, Zijie	Androgen Receptor Associated Proteins in Prostate Cancer		CA70297
Sun, Zijie	TGF-Beta/Smads and Androgen Signaling in Prostate Cancer	PA-99-081	CA87767
Tsai, Ming-Jer	Project 7: Endocrinology and the Role of Stroma Genes in Prostate Cancer	PAR-00-087	CA58204-Sub-07
Yamamoto, Keith	Gene Regulation by Steroid Receptor Proteins		CA20535
Yamamoto, Keith	Project 1: Mechanisms of Hormone Resistance in Prostate Cancer	PAR-99-167	CA89520-Sub-01
Young, Charles Y	Growth Control of Prostate Cancer Cells by Plant Phenols	PA-99-081	CA88900
Zhang, Xiao-Kun	TR3/Nur77 in Survival and Death of Cancer Cells		CA87000

Table B-2

NCI Projects Supported in 2002 Addressing the PRG Priority: What are the molecular determinants that govern cancer invasion, migration, and metastasis?

Principal Investigator	Title	RFA or PA	Project ID
Abato, Paul	Validation of Prostate Cancer Oncogenes		CA96276
Aebersold, Ruedi	Novel Quantitative, Comprehensive Proteomic Technology	CA-01-011	CA93302
Agus, David	The Role of the Her-Kinase Axis in Emergence of Androgen Independence in Human Prostate Cancer	PAR-99-167	CA92131-Sub-04
Arap, Wadih	Project 4: Exploring the Molecular Diversity of Blood Vessels for Diagnostic and Therapeutic Targeting in Prostate Cancer	PAR-99-167	CA90270-Sub-04
Barrett, J Carl	A Metastasis Suppressor Gene for Prostatic Cancer		BC10431
Beitz, Alvin J	In Vivo Analysis of Tumor Peptide Secretion	PAR-01-106	CA86330
Beranova-Giorgianni, Sarka	Cancer Relevant Proteins in the Human Prostate Proteome	PAR-00-025	CA91254
Boss, Gerry R	Analysis of Ras and Rho Activation in Prostate Cancer	PA-00-080	CA90932
Bova, G	Modes of Prostate Cancer Progression—Role of p53 Pathway	PA-99-081	CA92234
Brothman, Arthur	Molecular and Cytogenetic Analysis of Prostate Carcinoma		CA46269
Cavalieri, Ercole	Molecular Origin Cancer—Catechol Estrogen-3,4-Quinones		CA49210
Chakrabarti, Ratna	Molecular Markers for Prostate Cancer		CA81329
Chang, Chawnshang	AR-Associated Proteins in Prostate Carcinogenesis		CA77532
Chang, David D	Expression and Function of Eplin		CA90498
Cheng, Leo	Characterization of Prostate Cancer with HRMAS 1HMRS	PA-98-022	CA80901
Cher, Michael	Prostate Cancer, Bone Metastasis, and Metalloproteinases	PA-99-081	CA88028
Chinnadurai, Govindaswamy	Oncogenic and Chemoresistance by BCL-2		CA73803
Chinnaiyan, Arul M	The Role of Polycomb Group Proteins in Prostate Cancer		CA97063
Chung, Leland	Extracellular Matrix Integrin Signaling in Prostate Cancer		CA76620
Coffey, Donald	Models of Prostate Cancer—Cell Structure and Dynamics		CA15416
Coffey, Donald	Project 4: Human Prostate Cancer Nuclei: Abnormalities in Structure and the Development of New Molecular Markers	CA-94-031	CA58236-Sub-04
Cohen, Michael B	Trail Mediated Apoptosis in Prostate Cancer		CA93870
Cohen, Pinchas	Interactions between IGFBPs and Nuclear Receptors in Prostate Cancer	PAR-99-167	CA92131-Sub-03
Couch, Fergus	p21 Induction by BRCA2		CA78878
Demarzo, Angelo	Inflammation and Atrophy in Prostate Carcinogenesis	PA-99-005	CA84997
Ellis, William	Genomic and Gene Expression Profiling of Disseminated Prostate Cancer	PAR-00-087	CA97186-Sub-02
Emmert-Buck, Michael R	Genetic Progression of Cancer		SC10437
Epner, Daniel	GAPDH—Novel Regulator of Cell Structure and Migration		CA78355

Table B-2 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Falzon, Miriam	PTH-Related Peptide and Vitamin D in Prostate Cancer Growth		CA83940
Farrar, William L	Molecular Mechanisms of Growth Factor Modulated Proliferation		BC10253
Feldman, David	Androgen-Independent Prostate Cancer: Mechanisms and Treatment	PA-99-081	CA92238
Fidler, Isiah	Project 1: The Biology of Human Prostate Cancer Metastasis	PAR-99-167	CA90270-Sub-01
Figg, William D	Development of Angiogenesis Inhibitors Using Prostate Cancer as a Tumor Model		SC06538
Fisher, Paul	Novel Prostate Cancer Gene and Monoclonal Antibody		CA74468
Freeman, Michael	Prostate Cancer-Bone Interaction—Secretion of EGFR	PA-97-019	CA77386
Gelman, Irwin H	PKC/PKA Regulation in Prostate Cancer by SSeCKS/Gravin		CA94108
Gelmann, Edward P	Beta Catenin in Prostate Cancer		CA96854
Gerald, William	Molecular Classification of Prostate Cancer	CA-98-027	CA84999
Giovannucci, Edward	Genetic and Serologic Determinants of Prostate Cancer Risk and Progression	PAR-99-167	CA90381-Sub-01
Gleave, Martin	Characterization of Anti-Apoptotic Genes Induced during Androgen Independent Progression and Chemotherapy	PAR-00-087	CA97186-Sub-03
Glinsky, Gennadi	Transcriptome of Metastatic Prostate Cancer		CA89827
Golub, Todd	Genomic Expression Analysis of Tumors after Radical Prostatectomy	PAR-99-167	CA90381-Sub-04
Green, Jeffrey E	Transgenic Models for Prostate and Breast Cancer		BC05740
Gupta, Smiti	NF-kB: A Marker for Cellular Oxidative Stress		CA91658
Hixson, Douglas	Molecular Determinants of Multicellular Organization		CA42714
Holt, Jeffrey	Mechanisms of Carcinogenesis in BRCA2 Mutant Cells		CA85269
Hood, Leroy	Transcriptome and Proteome Stratification of Prostate Adenocarcinoma Phenotypes	PAR-00-087	CA97186-Sub-04
Hoosein, Naseema	Neuroendocrine Factors in Prostate Cancer		CA63225
Jenkins, Robert	Biologic and Clinical Studies of Overrepresented 8q24 Region Associated with Prostate Cancer Progression	PAR-99-167	CA91956-Sub-03
Kelly, Kathleen	ERK-Dependent Growth and Differentiation Pathways		SC09358
Koff, Andrew	p27Kip1 Expression, a Prognostic Indicator—But Why?		CA89563
Kung, Hsing-Jien	ErbB Kinase Activation and Transformation		CA39207
Lange, Paul H	Mechanisms and Markers of Prostate Cancer Metastases		CA85859
Languino, Lucia	Integrin Signaling Pathways in Prostate Cancer	PA-99-081	CA89720
Lauffenburger, Douglas	Cell Motility in Prostate Tumor Invasion	PAR-02-052	CA88865
Lee, Chung	Project 1: Clusterin as a Negative Prognostic Indicator in Prostate Cancer	PAR-99-167	CA90386-Sub-01
Lin, Sue-Hwa	Regulation of Angiogenesis by C-CAM1		CA86342

Table B-2 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Livingston, David	Gene Expression Analysis of Prostate and Lung Cancer	CA-98-027	CA84995
Lu, Michael L	Molecular Regulation of Androgen Receptor Activation	PA-99-081	CA87997
Lynch, Kevin	Lysophosphatidic Acid and the Progression of Prostate Cancer		CA88994
Malins, Donald	FT-IR/GC-MS Models for Predicting Prostate Cancer		CA79690
Mason, Ralph	MR Measurement of Tumor pH, pO2, and Vascularity In Vivo		CA79515
Moore, Bethany	CXC Chemokine Regulation of Prostate Cancer Angiogenesis		CA79046
Morton, Ronald	E-Cadherin—Marker of Prostate Cancer Progression		CA74290
Moscatelli, David A	Angiopoietins in Prostate Biology and Disease	PA-99-081	CA90593
Muschel, Ruth	Molecular Mechanisms of Metastasis		CA46830
Nagle, Raymond	Prostate Carcinoma—Invasion and Metastasis Factors		CA56666
Nelson, Peter	Serine Proteases in Prostate Cancer Metastasis	PA-99-081	CA85286
Ornstein, David K	Proteomic Study of Androgen Independent Prostate Cancer	PA-01-010	CA93759
Pandolfi, Pier Paolo	Molecular Analysis of Carcinogenesis in the Mouse and Human Prostate	PAR-99-167	CA92629-Sub-02
Parkos, Charles	Phage Display and Prostate Neoplasia Progression	PAR-99-102	CA91435
Pasqualini, Renata	Project 2: Targeting Prostate Cancer Bone Metastasis	PAR-99-167	CA90270-Sub-02
Petros, John A	Mitochondrial DNA in Mutations in Prostate Cancer		CA96994
Pienta, Kenneth	Project 5: Inhibition of Human Prostate Cancer Metastasis	CA-94-031	CA69568-Sub-05
Pretlow, Thomas	Cytogenetics and Biochemistry of Prostate Cancer		CA57179
Qiu, Yun	IL-6 and Neuroendocrine Differentiation of Prostate Cancer		CA85380
Reiter, Robert	Prostate Stem Cell Antigen (PSCA) in the Biology and Therapy of Prostate Cancer	PAR-99-167	CA92131-Sub-01
Rinker-Schaeffer, Carrie	Prostate Cancer Metastatic Colonization—Role of MKK4	PA-99-081	CA89569
Rosenfeld, Michael G	Repressors in Prostate Cancer	PA-99-081	CA97134
Roy-Burman, Pradip	Pathogenesis of Human Prostate Carcinomas		CA59705
Sehgal, Inder	Neuropeptide Regulation of Prostate Cancer Metastasis	PA-98-022	CA82139
Sheng, Shijie	A Role of Maspin in Prostate Cancer		CA84176
Shuman, Marc	Proteases in Cancer—Biology and Drug Development		CA72006
Simons, Jonathon	Project 5: Cellular and Molecular Basis of Prostate Metastasis to Bone	CA-94-031	CA58236-Sub-05
Skelton, Timothy	Decoding Cancer Signature Glycoforms of Serum Tumor Mark	PAR-00-025	CA89730
Slamon, Dennis J	Signal Transduction in Oncogenesis		CA32737
Soff, Gerald	Project 3: Generation of, and Angiostatin Levels in, Prostate Cancer	PAR-99-167	CA90386-Sub-03
Stampfer, Meir J	Growth Factors and Prostate Cancer Risk		CA90598

Table B-2 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Stanford, Jean	Molecular Predictors of Prostate Cancer Progression and Mortality	PAR-00-087	CA97186-Sub-01
Stearns, Mark	IL-10 and IGF1 Receptor Axis in Prostate Cancer		CA90397
Stearns, Mark	TIMP-1 Regulatory Factors in Human Prostate Cancer		CA76639
Strom, Sara	Project 5: Clinical, Epidemiological, and Molecular Markers of Prostate Cancer Progression	PAR-99-167	CA90270-Sub-05
Sun, Zijie	Androgen Receptor Associated Proteins in Prostate Cancer		CA70297
Sytkowski, Arthur J	Chemopreventive Action of Human Selenium Binding Protein	PAR-00-025	CA96047
Theodorescu, Dan	Endothelial Growth Factor in Prostate Cancer Metastasis	PA-99-081	CA85329
Thompson, Timothy	Mechanisms of Metastasis in Experimental Prostate Cancer	PA-99-081	CA68814
Thompson, Timothy	Progression Mechanisms—Oncogene Induced Prostate Cancer	PA-99-081	CA50588
Wang, Bing-Cheng	Eph Kinase Signaling in Prostate Cancer	DK-01-008	CA96533
Wang, Bing-Cheng	EphA2 Agonists as Novel Inhibitors of Tumor Progression	PA-99-081	CA92259
Wang, Zhou	Project 2: Suppressive Role of Androgen-Response Gene Calreticulin in Prostate Cancer	PAR-99-167	CA90386-Sub-02
Wheeler, Thomas	Project 1: Markers of Progression and Metastasis	PAR-00-087	CA58204-Sub-01
Wu, Guan	Neuroendocrine Differentiation in Prostate Cancer		CA72872
Yamamoto, Keith	Project 1: Mechanisms of Hormone Resistance in Prostate Cancer	PAR-99-167	CA89520-Sub-01
Yang, Catherine	Proteolyic Activity of Prostate Specific Antigen		CA89162
Young, Charles	Human Kallikreins as Novel Markers of Prostate Cancer	PAR-99-167	CA91956-Sub-02
Zetter, Bruce	Cell Motility in Tumor Metastasis		CA37393
Zhau, Haiyen	Characterization of an Invasive Human Prostate Cancer		CA82739

Table B-3

NCI Projects Supported in 2002 Addressing the PRG Priority: What are the biochemical and molecular events that govern the continuation of prostate development from early embryogenesis to the onset of adulthood, through maturation, aging, and death?

Principal Investigator	Title	RFA or PA	Project ID
Abate-Shen, Cory	Nkx3.1 and Prostate Development and Cancer		CA76501
Chang, David D	Expression and Function of Eplin		CA90498
Couch, Fergus	p21 Induction by BRCA2		CA78878
Hixson, Douglas	Molecular Determinants of Multicellular Organization		CA42714
Jarrard, David F	Modulation of IGF-II Imprinting in the Aging Prostate		CA97131
Kakar, Sham	Molecular Characterization of GnRH Receptors		CA60871
Milbrandt, Jeffrey	Nkx3.1 and Prostate Development and Cancer		CA81564
Miller, Gary	Role of Homeodomain Genes in Human Prostate Cancer		CA84269
Mueller, Elisabetta	PPAR as a Target of Therapy for Prostate Cancer	PAR-99-167	CA90381-Sub-02
Slamon, Dennis J	Signal Transduction in Oncogenesis		CA32737

Table B-4

NCI Projects Supported in 2002 Addressing the PRG Priority: What are the specific cell–cell interactions between and among developing epithelial cells, stromal cells, endothelial cells, neuroepithelial cells, and inflammatory cells?

Principal Investigator	Title	RFA or PA	Project ID
Celis, Esteban	Immune-Based Therapeutic Approach for Prostate Cancer		CA82677
Celis, Esteban	An Immune-Based Therapeutic Approach for Prostate Cancer	PAR-99-167	CA91956-Sub-04
Chung, Leland	Extracellular Matrix Integrin Signaling in Prostate Cancer		CA76620
Couch, Fergus	p21 Induction by BRCA2		CA78878
Cunha, Gerald	Cell–Cell Interactions in Prostate Cancer		CA59831
Demarzo, Angelo	Inflammation and Atrophy in Prostate Carcinogenesis	PA-99-005	CA84997
Emmert-Buck, Michael R	Genetic Progression of Cancer		SC10437
Fisher, Paul	Novel Prostate Cancer Gene and Monoclonal Antibody		CA74468
Frelinger, John	Targeted CTL Mediated Immunity for Prostate Cancer		CA70218
Kwon, Eugene	CTLA-4 Blockade Immunotherapy for Prostate Cancer		CA82185
Languino, Lucia	Molecular Analysis of B1 Integrins		CA71870
Lin, Sue-Hwa	Function of C-CAM in Prostate Cancer		CA64856
Morton, Ronald	E-Cadherin—Marker of Prostate Cancer Progression		CA74290
Parsons, Sarah	Neuroendocrine Cell Signaling in Prostate Cancer		CA76649
Pasqualini, Renata	Project 2: Targeting Prostate Cancer Bone Metastasis	PAR-99-167	CA90270-Sub-02
Ratliff, Timothy	Host/Tumor Interactions in Immunotherapy of Prostate Cancer	PA-99-081	CA89062
Sherman, Simon	Immunogenic Tumor Associated Mucin Peptides		CA84106
Tlsty, Thea	Fibroblast Regulation of Human Prostatic Carcinogenesis		CA83812
Tsai, Ming-Jer	Project 7: Endocrinology and the Role of Stroma Genes in Prostate Cancer	PAR-00-087	CA58204-Sub-07
Wang, Zhou	Project 2: Suppressive Role of Androgen-Response Gene Calreticulin in Prostate Cancer	PAR-99-167	CA90386-Sub-02
Wu, Guan	Neuroendocrine Differentiation in Prostate Cancer		CA72872

Table B-5

NCI Projects Supported in 2002 Addressing the PRG Priority: What are the regulatory effector molecules that control reciprocal interactions between epithelial and stromal cells, among clonal cancer epithelial cells, and between cancer cells and most immune-reactive cells?

Principal Investigator	Title	RFA or PA	Project ID
Boynton, Alton	Mediators of Platelet Derived Growth Factor Action		CA57064
Bushman, Wade A	Shh Signaling as a Therapeutic Target in Prostate Cancer	PAR-01-045	CA95386
Chang, David D	Expression and Function of Eplin		CA90498
Cunha, Gerald	Smooth Muscle–Epithelial Interactions in Prostate Cancer		CA64872
Cuttitta, Frank	Identification of Peptide Growth Factors That Regulate Human Tumor Proliferation		SC00173
Cuttitta, Frank	Growth of Human Tumor Cell Lines in Protein-Free/Hormone-Free Media		SC00192
Day, Mark	Project 4: Rb as a Regulator of Prostate Tumorigenesis	CA-94-031	CA69568-Sub-04
Fidler, Isiah	Project 1: The Biology of Human Prostate Cancer Metastasis	PAR-99-167	CA90270-Sub-01
Greenberg, Norman	KGF in Prostate Cancer—A Transgenic Animal Model		CA64851
Hixson, Douglas	Molecular Determinants of Multicellular Organization		CA42714
Lange, Paul H	Mechanisms and Markers of Prostate Cancer Metastases		CA85859
Lin, Ming-Fong	Steroid Regulation of Human Prostate Cancer Cells		CA72274
Lin, Sue-Hwa	Function of C-CAM in Prostate Cancer		CA64856
Lin, Sue-Hwa	Regulation of Angiogenesis by C-CAM1		CA86342
Lokeshwar, Balakrishna	Control of Metastatic Progression of Prostate Cancer		CA61038
Lynch, Kevin	Lysophosphatidic Acid and the Progression of Prostate Cancer		CA88994
Moscatelli, David A	Angiopoietins in Prostate Biology and Disease	PA-99-081	CA90593
Mulder, Kathleen	Mechanisms of TGF-Beta Production in Human Cancer Cells		CA90765
Muschel, Ruth	Molecular Mechanisms of Metastasis		CA46830
Parsons, Sarah	Neuroendocrine Cell Signaling in Prostate Cancer		CA76649
Rowley, David	Mesenchymal Derived Growth Factors in Prostatic Cancer		CA58093
Shah, Girish	Calcitonin in Prostate Growth and Neoplasia	DK-01-008	CA96534
Simons, Jonathon	Project 5: Cellular and Molecular Basis of Prostate Metastasis to Bone	CA-94-031	CA58236-Sub-05
Smith, Gary	Age and Microenvironment Effect on Prostate Cancer		CA64865
Sun, Luzhe Z	Targeting Transforming Growth Factor Beta for Cancer Treatment		CA75253
Theodorescu, Dan	Endothelial Growth Factor in Prostate Cancer Metastasis	PA-99-081	CA85329
Wang, Zhou	Project 2: Suppressive Role of Androgen-Response Gene Calreticulin in Prostate Cancer	PAR-99-167	CA90386-Sub-02
Weber, Michael	Cell Signaling in Prostate Cancer Progression		CA76465

Table B-6

NCI Projects Supported in 2002 Addressing the PRG Priority: Are there features of DNA damage, DNA repair, or cell-cycle progression that are novel in prostate cancer cells?

Principal Investigator	Title	RFA or PA	Project ID
Cavalieri, Ercole	Molecular Origin Cancer—Catechol Estrogen-3,4-Quinones		CA49210
Dent, Paul	Carcinoma Cell Radiosensitization by MAPK Inhibition		CA88906
DeWeese, Theodore	Project 14: Determinants of Radiosensitivity in Prostate Cancer	CA-94-031	CA58236-Sub-14
El-Zein, Randa	Molecular Biomarkers for Prostate Cancer Susceptibility		CA88301
Gelmann, Edward	Apoptosis in Prostate Cancer		CA79912
Green, Jeffrey E	Transgenic Models for Prostate and Breast Cancer		BC05740
Griffith, Jeffrey	Prognostic Value of Telomere DNA in Prostate Biopsy	PAR-99-102	CA86136
Harper, J Wade	Project 2: The Role of CDK Inhibitors in Prostate Cancer	PAR-00-087	CA58204-Sub-02
Hay, Nissim	PI3K/PTEN/Akt (PKB), Signaling, and Genesis of Cancer		CA90764
Holt, Jeffrey	Mechanisms of Carcinogenesis in BRCA2 Mutant Cells		CA85269
Jenkins, Robert	Biologic and Clinical Studies of Overrepresented 8q24 Region Associated with Prostate Cancer Progression	PAR-99-167	CA91956-Sub-03
Kim, Seong Jin	Molecular Mechanisms of Resistance to TGF-Beta-Mediated Apoptosis		BC10050
Loda, Massimo	Isopeptidases, Ubiquitin-Degradation, and Prostate Cancer		CA81755
Malins, Donald	DNA Damage in Mouse Tumors Evaluated by IR Spectroscopy		CA79479
Malins, Donald	FT-IR/GC-MS Models for Predicting Prostate Cancer		CA79690
McDonnell, Timothy	Project 3: Therapeutic Modulation of Apoptosis in Prostate Cancer Patients	PAR-99-167	CA90270-Sub-03
Nelson, William	Project 12: Rational Prostate Cancer Prevention Studies	CA-94-031	CA58236-Sub-12
Rauscher, Frank	Role of the BRCA1 Associated Protein BAP1 in DNA Repair		CA92088
Rosen, Eliot	Role of BRCA1 as a Human Prostate Suppressor Gene		CA80000
Sellers, William	Single Nucleotide Repeat Polymorphism Analysis of Recurrent Prostate Cancer after Radiation Therapy	PAR-99-167	CA90381-Sub-03
Uhr, Jonathan	Early Detection/Characterization of Tumor Cells in Blood		CA78303
Wahl, Geoffrey	Anticancer Agent Sensitivity and Cell Cycle Control		CA61449
Yeh, Grace Chao	Dietary Regulation of Biochemical/Molecular Changes in Carcinogen Resistant Cells		BC00189
Zimbrick, John	Radiation Biochemistry of Clustered Damage Sites in DNA		CA80211

Table B-7

NCI Projects Supported in 2002 Addressing the PRG Priority: What are the genetic and epigenetic determinants that affect progression of prostate cancer from the localized to disseminated state? What molecular markers are associated with such progression?

Principal Investigator	Title	RFA or PA	Project ID
Abate-Shen, Cory	Nkx3.1 and Prostate Development and Cancer		CA76501
Abato, Paul	Validation of Prostate Cancer Oncogenes		CA96276
Aebersold, Ruedi	Novel Quantitative, Comprehensive Proteomic Technology	CA-01-011	CA93302
Altieri, Dario	Control of Apoptosis in Cancer by Survivin		CA78810
Arap, Wadih	Project 4: Exploring the Molecular Diversity of Blood Vessels for Diagnostic and Therapeutic Targeting in Prostate Cancer	PAR-99-167	CA90270-Sub-04
Balk, Steven	The Androgen Receptor in Hormone Refractory Disease	PAR-99-167	CA90381-Sub-05
Barrett, J Carl	A Metastasis Suppressor Gene for Prostatic Cancer		BC10431
Baserga, Renato L	Biology of the p53 Protein		CA89640
Bova, G	Modes of Prostate Cancer Progression—Role of p53 Pathway	PA-99-081	CA92234
Brothman, Arthur	Molecular and Cytogenetic Analysis of Prostate Carcinoma		CA46269
Chakrabarti, Ratna	Molecular Markers for Prostate Cancer	PA-98-022	CA81329
Cho-Chung, Yoon S	Mechanism of cAMP-Growth Regulatory Function		BC08281
Coffey, Donald	Project 4: Human Prostate Cancer Nuclei: Abnormalities in Structure and the Development of New Molecular Markers	CA-94-031	CA58236-Sub-04
Cohen, Pinchas	Interactions between IGFBPs and Nuclear Receptors in Prostate Cancer	PAR-99-167	CA92131-Sub-03
Collins, Colin	Project 2: Genomics of Prostate Cancer	PAR-99-167	CA89520-Sub-02
Couch, Fergus	p21 Induction by BRCA2		CA78878
Danielpour, David	Function and Regulation of Trespin, a Novel Serpin		CA83069
Dong, Jin-Tang	Molecular Dissection of 13q14 in Prostate Cancer	PA-99-081	CA85560
Dong, Jin-Tang	Tumor Suppressor Gene at 13q21 in Prostate Cancer	PA-99-081	CA87921
Ellis, William	Genomic and Gene Expression Profiling of Disseminated Prostate Cancer	PAR-00-087	CA97186-Sub-02
Emmert-Buck, Michael R	Genetic Progression of Cancer		SC10437
Everson, Richard	Receptor Gene Polymorphisms in Prostate Cancer		CA81240
Felton, James S	Carcinogenic Significance of Heterocyclic Amines		CA55861
Figg, William D	Development of Angiogenesis Inhibitors Using Prostate Cancer as a Tumor Model		SC06538
Garcia-Blanco, Mariano A	Imaging Alternative Splicing during Tumor Progression	PAR-01-106	CA97502
Gerald, William	Molecular Classification of Prostate Cancer	CA-98-027	CA84999
Giovannucci, Edward	Genetic and Serologic Determinants of Prostate Cancer Risk and Progression	PAR-99-167	CA90381-Sub-01

Table B-7 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Gleave, Martin	Characterization of Anti-Apoptotic Genes Induced during Androgen Independent Progression and Chemotherapy	PAR-00-087	CA97186-Sub-03
Glinsky, Gennadi	Transcriptome of Metastatic Prostate Cancer		CA89827
Golub, Todd	Genomic Expression Analysis of Tumors after Radical Prostatectomy	PAR-99-167	CA90381-Sub-04
Green, Jeffrey E	Transgenic Models for Prostate and Breast Cancer		BC05740
Hendrix, Mary	Prostatic Vasculogenic Mimicry: A New Metastatic Pathway	PA-99-081	CA88043
Isaacs, John T	Project 8: Down Regulation of Metastasis Suppressor Genes as Diagnostic Methods for Predicting the Biologic Behavior of Histologically Detectable Prostate Cancer	CA-94-031	CA58236-Sub-08
Issa, Jean-Pierre J	Neoplasia and Methylated CpG Islands Amplification	PAR-99-100	CA89837
Jarrard, David F	Modulation of IGF-II Imprinting in the Aging Prostate		CA97131
Jenkins, Robert	Biologic and Clinical Studies of Overrepresented 8q24 Region Associated with Prostate Cancer Progression	PAR-99-167	CA91956-Sub-03
Kelly, Kathleen	ERK-Dependent Growth and Differentiation Pathways		SC09358
Languino, Lucia	Integrin Signaling Pathways in Prostate Cancer	PA-99-081	CA89720
Lee, Byungkook	Molecular Modeling and Bioinformatics		BC08759
Liao, Shutsung	Molecular Mechanisms of Growth Control—Prostate Cancer		CA58073
Lin, Ming-Fong	Signaling in Androgen Refractory Prostate Cancer	PA-99-055	CA88184
Linehan, W Marston	Molecular Genetics of Prostate Cancer		SC10095
Liotta, Lance	Laser Capture Microdissection Applied to Human Pathophysiology		SC09185
Malins, Donald	FT-IR/GC-MS Models for Predicting Prostate Cancer		CA79690
Mc Keehan, Wallace	Growth Factors in Prostate Cancer		CA59971
Mikovits, Judy A	Development of DNA Methyltransferase Inhibitors as Anti*	PA-01-091	CA92828
Milbrandt, Jeffrey	Nkx3.1 and Prostate Development and Cancer		CA81564
Mueller, Elisabetta	PPAR as a Target of Therapy for Prostate Cancer	PAR-99-167	CA90381-Sub-02
Nelson, Peter	Serine Proteases in Prostate Cancer Metastasis	PA-99-081	CA85286
Nelson, William	Project 12: Rational Prostate Cancer Prevention Studies	CA-94-031	CA58236-Sub-12
Ornstein, David K	Proteomic Study of Androgen Independent Prostate Cancer	PA-01-010	CA93759
Pandolfi, Pier Paolo	Molecular Analysis of Carcinogenesis in the Mouse and Human Prostate	PAR-99-167	CA92629-Sub-02
Parkos, Charles	Phage Display and Prostate Neoplasia Progression	PAR-99-102	CA91435
Pasqualini, Renata	Project 2: Targeting Prostate Cancer Bone Metastasis	PAR-99-167	CA90270-Sub-02
Petros, John A	Mitochondrial DNA in Mutations in Prostate Cancer		CA96994
Pretlow, Thomas	Cytogenetics and Biochemistry of Prostate Cancer		CA57179
Rangnekar, Vivek	Mechanism of Apoptosis by Par4		CA60872

Table B-7 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Reiter, Robert	Prostate Stem Cell Antigen (PSCA) in the Biology and Therapy of Prostate Cancer	PAR-99-167	CA92131-Sub-01
Sawyers, Charles	Targeted Therapy of PTEN Null Prostate Cancer	PAR-99-167	CA92131-Sub-02
Scher, Howard	Mechanism Based Therapy for Prostate Cancer	PAR-99-167	CA92629-Sub-04
Sellers, William	Functional Analysis of the PTEN Tumor Suppressor Protein	PA-99-081	CA85912
Sellers, William	Single Nucleotide Repeat Polymorphism Analysis of Recurrent Prostate Cancer after Radiation Therapy	PAR-99-167	CA90381-Sub-03
Sheikh, M	Death Receptors in Prostate Cancer Biology and Apoptosis	PA-99-081	CA89043
Singal, Rakesh	GSTP1 Gene Repression in Prostate Cancer	PA-99-081	CA89348
Skelton, Timothy	Decoding Cancer Signature Glycoforms of Serum Tumor Mark	PAR-00-025	CA89730
Spencer, David	FGFR Signaling in Prostate Development and Cancer	PA-99-081	CA87569
Stanford, Janet	Molecular Predictors of Prostate Cancer Progression and Mortality	PAR-00-087	CA97186-Sub-01
Strom, Sara	Project 5: Clinical, Epidemiological, and Molecular Markers of Prostate Cancer Progression	PAR-99-167	CA90270-Sub-05
Veltri, Robert	Methylation Specific PCR for Cancer Diagnosis/Prognosis		CA90007
Waalkes, Michael P	Mechanisms of Inorganic Carcinogenesis		BC05488
Wang, Zhou	Project 2: Suppressive Role of Androgen-Response Gene Calreticulin in Prostate Cancer	PAR-99-167	CA90386-Sub-02
Weber, Michael	Cell Signaling in Prostate Cancer Progression		CA76465
Wheeler, Thomas	Project 1: Markers of Progression and Metastasis	PAR-00-087	CA58204-Sub-01
Wu, Guan	Neuroendocrine Differentiation in Prostate Cancer		CA72872
Yamamoto, Fumiichiro	Technology to Detect Genome Wide DNA Methylation Changes	PAR-99-100	CA84704
Yamamoto, Keith	Project 1: Mechanisms of Hormone Resistance in Prostate Cancer	PAR-99-167	CA89520-Sub-01
Ying, Shao-Yao	Novel Molecular Profiling of Prostate Cancer Signatures		CA85722
Zhao, Yingming	Identification of Prostate and Ovarian Cancer Markers	CA-98-028	CA85146

Table B-8

NCI Projects Supported in 2002 Addressing the PRG Priority: Are there hereditary markers, angiogenesis switches, and / or biochemical and molecular determinants that predict progression?

Principal Investigator	Title	RFA or PA	Project ID
Abdulkadir, Sarki A	Modeling Prostate Cancer by Conditional Gene Targeting		CA94858
Aebersold, Ruedi	Novel Quantitative, Comprehensive Proteomic Technology	CA-01-011	CA93302
Agus, David	The Role of the Her-Kinase Axis in Emergence of Androgen Independence in Human Prostate Cancer	PAR-99-167	CA92131-Sub-04
Ahmed, Mansoor	EGR-1 and Apoptosis in Prostate Cancer		CA78471
Ambs, Stefan	Identification of Allele Variant Genes That Are Risk Factors for Human Breast and Prostate Cancer		BC10439
Arap, Wadih	Project 4: Exploring the Molecular Diversity of Blood Vessels for Diagnostic and Therapeutic Targeting in Prostate Cancer	PAR-99-167	CA90270-Sub-4
Barrack, Evelyn R	Project 3: Androgen Receptor Gene Structure and Function in Human Prostate Cancer	CA-94-031	CA58236-Sub-3
Bova, G	Modes of Prostate Cancer Progression—Role of p53 Pathway	PA-99-081	CA92234
Cheng, Jin	AKT1 Oncogene in Carcinogenesis		CA89242
Chinnaiyan, Arul M	The Role of Polycomb Group Proteins in Prostate Cancer		CA97063
Coffey, Donald	Project 4: Human Prostate Cancer Nuclei: Abnormalities in Structure and the Development of New Molecular Markers	CA-94-031	CA58236-Sub-04
Cohen, Pinchas	Interactions between IGFBPs and Nuclear Receptors in Prostate Cancer	PAR-99-167	CA92131-Sub-3
Day, Mark	Project 4: Rb as a Regulator of Prostate Tumorigenesis	CA-94-031	CA69568-Sub-04
De Vere White, Ralph	hAR Alterations and Androgen Independent Prostate Cancer		CA92069
Ellis, William	Genomic and Gene Expression Profiling of Disseminated Prostate Cancer	PAR-00-087	CA97186-Sub-2
Everson, Richard	Receptor Gene Polymorphisms in Prostate Cancer		CA81240
Fidler, Isiah	Project 1: The Biology of Human Prostate Cancer Metastasis	PAR-99-167	CA90270-Sub-01
Figg, William D	Development of Angiogenesis Inhibitors Using Prostate Cancer as a Tumor Model		SC06538
Gelmann, Edward	Apoptosis in Prostate Cancer		CA79912
Gerald, William	Molecular Classification of Prostate Cancer	CA-98-027	CA84999
Giovannucci, Edward	Genetic and Serologic Determinants of Prostate Cancer Risk and Progression	PAR-99-167	CA90381-Sub-01
Gleave, Martin	Characterization of Anti-Apoptotic Genes Induced during Androgen Independent Progression and Chemotherapy	PAR-00-087	CA97186-Sub-03
Golub, Todd	Genomic Expression Analysis of Tumors after Radical Prostatectomy	PAR-99-167	CA90381-Sub-4
Hay, Nissim	PI3K/PTEN/Akt (PKB), Signaling, and Genesis of Cancer		CA90764
Heeb, Mary	Forms of Prostate Specific Antigen and hK2 in Cancer		CA59979
Hixson, Douglas	Molecular Determinants of Multicellular Organization		CA42714
Holt, Jeffrey	Mechanisms of Carcinogenesis in BRCA2 Mutant Cells		CA85269

Table B-8 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Hood, Leroy	Transcriptome and Proteome Stratification of Prostate Adenocarcinoma Phenotypes	PAR-00-087	CA97186-Sub-4
Isaacs, John T	Project 8: Down Regulation of Metastasis Suppressor Genes as Diagnostic Methods for Predicting the Biologic Behavior of Histologically Detectable Prostate Cancer	CA-94-031	CA58236-Sub-8
Isaacs, William B	Project 2: Search for Hereditary Prostate Cancer Genes Using Linkage Analysis and Positional Cloning Approaches	CA-94-031	CA58236-Sub-2
Languino, Lucia	Integrin Signaling Pathways in Prostate Cancer	PA-99-081	CA89720
Lawrence, Daniel	Regulation of Angiogenesis by PAI1		CA83090
Lee, Chung	Project 1: Clusterin as a Negative Prognostic Indicator in Prostate Cancer	PAR-99-167	CA90386-Sub-01
Livingston, David	Gene Expression Analysis of Prostate and Lung Cancer	CA-98-027	CA84995
Loda, Massimo	Isopeptidases, Ubiquitin-Degradation, and Prostate Cancer		CA81755
Lynch, Kevin	Lysophosphatidic Acid and the Progression of Prostate Cancer		CA88994
McDonnell, Timothy	Project 3: Therapeutic Modulation of Apoptosis in Prostate Cancer Patients	PAR-99-167	CA90270-Sub-03
Pandolfi, Pier Paolo	Molecular Analysis of Carcinogenesis in the Mouse and Human Prostate	PAR-99-167	CA92629
Parkos, Charles	Phage Display and Prostate Neoplasia Progression	PAR-99-102	CA91435
Parsons, Ramon	PTEN Tumor Suppressor and Signal Transduction		CA82783
Rauscher, Frank	Role of the BRCA1 Associated Protein BAP1 in DNA Repair		CA92088
Ross, Jeffrey	Human RNA Binding Protein as a Cancer Marker	PA-01-010	CA94082
Sellers, William	Single Nucleotide Repeat Polymorphism Analysis of Recurrent Prostate Cancer after Radiation Therapy	PAR-99-167	CA90381-Sub-3
Shreve, Paul	C11 Acetate PET Imaging of Prostate and Renal Cancer		CA89448
Simons, Jonathon	Project 5: Cellular and Molecular Basis of Prostate Metastasis to Bone	CA-94-031	CA58236-Sub-05
Skelton, Timothy	Decoding Cancer Signature Glycoforms of Serum Tumor Mark	PAR-00-025	CA89730
Smith, Steven	DNA Methylation in Early Detection of Prostate Cancer	PAR-00-025	CA91234
Soff, Gerald	Project 3: Generation of, and Angiostatin Levels in, Prostate Cancer	PAR-99-167	CA90386-Sub-03
Stampfer, Meir J	Growth Factors and Prostate Cancer Risk		CA90598
Stanford, Janet	Molecular Predictors of Prostate Cancer Progression and Mortality	PAR-00-087	CA97186-Sub-01
Wang, Bing-Cheng	EphA2 Agonists as Novel Inhibitors of Tumor Progression	PA-99-081	CA92259
Wang, Zhou	Project 2: Suppressive Role of Androgen-Response Gene Calreticulin in Prostate Cancer	PAR-99-167	CA90386-Sub-02
Wheeler, Thomas	Project 1: Markers of Progression and Metastasis	PAR-00-087	CA58204-Sub-01
Yamamoto, Keith	Project 1: Mechanisms of Hormone Resistance in Prostate Cancer	PAR-99-167	CA89520-Sub-01
Yang, Catherine	Proteolytic Activity of Prostate Specific Antigen		CA89162

Table B-9

NCI Projects Supported in 2002 Addressing the PRG Priority: What are the critical housekeeping and regulatory genes that may be associated with human prostate cancer development and progression?

Principal Investigator	Title	RFA or PA	Project ID
Agus, David	The Role of the Her-Kinase Axis in Emergence of Androgen Independence in Human Prostate Cancer	PAR-99-167	CA92131-Sub-04
Ahmed, Khalil	Normal and Neoplastic Prostate		CA15062
Aoki, Masahiro	Nuclear Targets of AKT Oncoproteins		CA93837
Bai, Wenlong	AR-PTEN Antagonism in Prostate Cell Growth and Apoptosis		CA93666
Baldwin, Albert	Antiapoptotic Mechanisms in Prostate Cancer		CA75080
Baldwin, Albert	Regulation of BCL2 by Ras and Tumor Suppressors		CA72771
Balmain, Allan	Project 5: Identification of Prostate Tumor Susceptibility Genes Using Mouse Models for Prostate Cancer	PAR-99-167	CA89520-Sub-05
Barrett, J Carl	A Metastasis Suppressor Gene for Prostatic Cancer		BC10431
Baserga, Renato L	Biology of the p53 Protein		CA89640
Boss, Gerry R	Analysis of Ras and Rho Activation in Prostate Cancer	PA-00-080	CA90932
Bova, G	Modes of Prostate Cancer Progression—Role of p53 Pathway	PA-99-081	CA92234
Bova, Steven G	Project 1: Molecular Genetics of Human Prostate Cancer	CA-94-031	CA58236-Sub-01
Boynton, Alton	Mediators of Platelet Derived Growth Factor Action		CA57064
Cantley, Lewis	The Role of PTEN and the PI3K Pathway in Prostate Cancer		CA89021
Caprioli, Richard M	Molecular Analysis of Cancer—Imaging Mass Spectrometry	PAR-99-102	CA86243
Chakrabarti, Ratna	Molecular Markers for Prostate Cancer	PA-98-022	CA81329
Chen, Ching-Shih	Apoptosis Regulation by Lipid Signals in Prostate Cancer	PA-99-081	CA94829
Cheng, Jin	AKT1 Oncogene in Carcinogenesis		CA89242
Chinault, Craig	Project 3: Physical and Functional Analysis of Prostate Cancer Genes	PAR-00-087	CA58204-Sub-03
Cho-Chung, Yoon S	Mechanism of cAMP-Growth Regulatory Function		BC08281
Cho-Chung, Yoon S	The Role of cAMP-Dependent Protein Kinase in Growth Control		BC05216
Cohen, Michael	Fas-Mediated Apoptosis in Prostate Cancer		CA76673
Cohen, Michael	TNF Alpha Mediated Apoptosis in Prostate Cancer	PA-99-081	CA87617
Cohen, Michael B	Trail Mediated Apoptosis in Prostate Cancer		CA93870
Collins, Colin	Project 2: Genomics of Prostate Cancer	PAR-99-167	CA89520-Sub-02
Couch, Fergus	p21 Induction by BRCA2		CA78878
Croce, Carlo	8p22 Alterations, in Prostate, Breast, and Esophageal Cancer		CA83698
Cuttitta, Frank	Identification of Peptide Growth Factors the Regulate Human Tumor Proliferation		SC00173
Dang, Chi	c-Myc Targets in the Pathogenesis of Human Cancers		CA57341
Day, Mark	Project 4: Rb as a Regulator of Prostate Tumorigenesis	CA-94-031	CA69568-Sub-04
De Vere White, Ralph	hAR Alterations and Androgen Independent Prostate Cancer		CA92069

Table B-9 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Deluca, L	Retinoids in Differentiation and Neoplasia		BC04798
Fisher, Paul	Novel Prostate Cancer Gene and Monoclonal Antibody		CA74468
Franklin, Renty	Zinc Transport Relationships in Prostate Cancer Cells		CA79903
Gao, Allen	STAT3 in Androgen Receptor Signaling in Prostate Cancer		CA90271
Garcia-Blanco, Mariano A	Imaging Alternative Splicing during Tumor Progression	PAR-01-106	CA97502
Gelman, Irwin H	PKC/PKA Regulation in Prostate Cancer by SSeCKS/Gravin		CA94108
Gelmann, Edward	Apoptosis in Prostate Cancer		CA79912
Gelmann, Edward	Beta Catenin in Prostate Cancer	PA-99-081	CA87855
Gerald, William	Molecular Classification of Prostate Cancer	CA-98-027	CA84999
Giovannucci, Edward	Genetic and Serologic Determinants of Prostate Cancer Risk and Progression	PAR-99-167	CA90381-Sub-01
Gleave, Martin	Characterization of Anti-Apoptotic Genes Induced during Androgen Independent Progression and Chemotherapy	PAR-00-087	CA97186-Sub-03
Golub, Todd	Genomic Expression Analysis of Tumors after Radical Prostatectomy	PAR-99-167	CA90381-Sub-04
Green, Jeffrey E	Transgenic Models for Prostate and Breast Cancer		BC05740
Greenberg, Norman	IGF Axis in Prostate Cancer—Transgenic Study		CA82807
Greenberg, Norman	Project 6: Prostate-Specific Gene Expression in Transgenic Animals	PAR-00-087	CA58204-Sub-06
Hann, Stephen	B-Myc Regulation and Function		CA78888
Hayward, Simon	Hormonal Carcinogenesis in Rb-Knockout Mouse Prostate		CA96403
Ho, Shuk-Mei	Metallothionein and Cadmium Carcinogenesis in Rat Prostate		CA62269
Holt, Jeffrey	Mechanisms of Carcinogenesis in BRCA2 Mutant Cells		CA85269
Hood, Leroy	Transcriptome and Proteome Stratification of Prostate Adenocarcinoma Phenotypes	PAR-00-087	CA97186-Sub-04
Hoosein, Naseema	Neuroendocrine Factors in Prostate Cancer		CA63225
Isaacs, John T	Project 8: Down Regulation of Metastasis Suppressor Genes as Diagnostic Methods for Predicting the Biologic Behavior of Histologically Detectable Prostate Cancer	CA-94-031	CA58236-Sub-08
Jarrard, David F	Modulation of IGF-II Imprinting in the Aging Prostate		CA97131
Jay, Gilbert	Large Scale Gene Discovery—Human Prostate Cancer		CA81900
Jenkins, Robert	Biologic and Clinical Studies of Overrepresented 8q24 Region Associated with Prostate Cancer Progression	PAR-99-167	CA91956-Sub-03
Kazanietz, Marcelo	Prostate Carcinogenesis and PKC Signaling	PA-99-081	CA89202
Kelly, Kathleen	ERK-Dependent Growth and Differentiation Pathways		SC09358
Kim, Seong Jin	Molecular Mechanisms of Resistance to TGF-Beta-Mediated Apoptosis		BC10050
Koff, Andrew	p27Kip1 Expression, a Prognostic Indicator—But Why?		CA89563

Table B-9 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Kraft, Andrew	Regulation of Prostate Cancer Programmed Cell Death		CA78631
Kung, Hsing-Jien	ErbB Kinase Activation and Transformation		CA39207
Lange, Paul H	Mechanisms and Markers of Prostate Cancer Metastases		CA85859
Lee, Byungkook	Molecular Modeling and Bioinformatics		BC08759
Lee, Chung	Clusterin—An Anti-Apoptotic Mediator in Prostate Cancer		CA80953
Lee, Chung	Project 1: Clusterin as a Negative Prognostic Indicator in Prostate Cancer	PAR-99-167	CA90386-Sub-01
Libermann, Towia	Role of a New Ets Factor, PDEF, in Prostate Cancer	PA-99-081	CA85467
Lin, Ming-Fong	Steroid Regulation of Human Prostate Cancer Cells		CA72274
Linehan, W Marston	Molecular Genetics of Prostate Cancer		SC10095
Loda, Massimo	Isopeptidases, Ubiquitin-Degradation, and Prostate Cancer		CA81755
Lynch, Kevin	Lysophosphatidic Acid and the Progression of Prostate Cancer		CA88994
McKeon, Frank	Murine p73 in Tumorigenesis		CA75340
Mercola, Dan	Oncogenic Role of Jun Kinase in Human Prostate Cancer		CA84107
Mercola, Daniel	Jun Kinase and Human Tumors		CA63783
Morton, Ronald	E-Cadherin—Marker of Prostate Cancer Progression		CA74290
Mulder, Kathleen	Mechanisms of TGF-Beta Production in Human Cancer Cells		CA90765
Nanus, David	Neutral Endopeptidase Inactivation in Advanced Prostate	PA-99-081	CA80240
Nelson, William	GSTPI Promoter Hypermethylation in Human Prostate Cancer		CA70196
Nelson, William	Project 12: Rational Prostate Cancer Prevention Studies	CA-94-031	CA58236-Sub-12
Pandolfi, Pier Paolo	Molecular Analysis of Carcinogenesis in the Mouse and Human Prostate	PAR-99-167	CA92629-Sub-02
Parsons, Ramon	PTEN Tumor Suppressor and Signal Transduction		CA82783
Parsons, Ramon E	PI-3 Kinase Therapy in Mouse Tumor Models	PAR-02-051	CA99523
Pasqualini, Renata	A Receptor for Tumor Homing Peptides in Vasculature		CA78512
Pestell, Richard	Cyclin D1 Function in Prostate Cancer	PA-99-081	CA86072
Pincus, Matthew	Protein Structure and Oncogenesis		CA42500
Pretlow, Thomas	Cytogenetics and Biochemistry of Prostate Cancer		CA57179
Qiu, Yun	IL-6 and Neuroendocrine Differentiation of Prostate Cancer		CA85380
Rangnekar, Vivek	Mechanism of Apoptosis by Par4	PA-99-081	CA60872
Rauscher, Frank	Role of the BRCA1 Associated Protein BAP1 in DNA Repair		CA92088
Rosenfeld, Ron	Insulin-Like Growth Factors and Prostate Carcinogenesis		CA58110
Ross, Jeffrey	Human RNA Binding Protein as a Cancer Marker	PA-01-010	CA94082
Roy-Burman, Pradip	Pathogenesis of Human Prostate Carcinomas		CA59705

Table B-9 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Rui, Hallgeir	Targeting of Tyrosine Kinase Pathways in Prostate Cancer		CA83813
Sawyers, Charles	Regulation of the PTEN Gene in Prostate Cancer		CA87079
Sellers, William	Single Nucleotide Repeat Polymorphism Analysis of Recurrent Prostate Cancer after Radiation Therapy	PAR-99-167	CA90381-Sub-03
Shah, Girish	Calcitonin in Prostate Growth and Neoplasia	DK-01-008	CA96534
Singal, Rakesh	GSTP1 Gene Repression in Prostate Cancer	PA-99-081	CA89348
Slamon, Dennis J	Signal Transduction in Oncogenesis		CA32737
Smith, Steven	DNA Methylation in Early Detection of Prostate Cancer	PAR-00-025	CA91234
Soff, Gerald	Project 3: Generation of, and Angiostatin Levels in, Prostate Cancer	PAR-99-167	CA90386-Sub-03
Srivastava, Shiv	Characterization of Novel Prostate Specific Gene, PCGEM1		CA85596
Stampfer, Meir J	Growth Factors and Prostate Cancer Risk		CA90598
Stearns, Mark	IL-10 and IGF1 Receptor Axis in Prostate Cancer		CA90397
Stein, Cy A	Orthogonal Strategies for Specific Knockout Production		CA91058
Sun, Zijie	TGF-Beta/Smads and Androgen Signaling in Prostate Cancer	PA-99-081	CA87767
Sytkowski, Arthur J	Chemopreventive Action of Human Selenium Binding Protein	PAR-00-025	CA96047
Tang, Dean	Mitochondria Signaled Apoptosis in Prostate Cancer Cells		CA90297
Thibodeau, Stephen	Genetic Susceptibility in Prostate Cancer	PAR-99-167	CA91956-Sub-01
Tsai, Ming-Jer	Project 7: Endocrinology and the Role of Stroma Genes in Prostate Cancer	PAR-00-087	CA58204-Sub-07
Veltri, Robert	Methylation Specific PCR for Cancer Diagnosis/Prognosis		CA90007
Wakefield, Lalage M	Epithelial Homeostasis and Tumorigenesis in TGF-Compromised Mouse Models		BC05785
Walden, Paul	BTG2 Antiproliferative Gene and Prostate Cancer		CA84441
Wang, Bing-Cheng	EphA2 Agonists as Novel Inhibitors of Tumor Progression	PA-99-081	CA92259
Wang, Jean	Nuclear Function of the cABL Protooncoprotein		CA43054
Wang, Zhou	Project 2: Suppressive Role of Androgen-Response Gene Calreticulin in Prostate Cancer	PAR-99-167	CA90386-Sub-02
Watabe, Kounosuke	Tumor Metastasis Suppressor Gene on Human Chromosome 16		CA79473
Waterman, Marian	Activities of Beta Catenin and LEF/TCF Complexes		CA83982
Weber, Michael	Cell Signaling in Prostate Cancer Progression		CA76465
Wheeler, Thomas	Project 1: Markers of Progression and Metastasis	PAR-00-087	CA58204-Sub-01
Yamamoto, Fumiichiro	Technology to Detect Genome Wide DNA Methylation Changes	PAR-99-100	CA84704
Yamamoto, Keith	Project 1: Mechanisms of Hormone Resistance in Prostate Cancer	PAR-99-167	CA89520-Sub-01
Yung, Wai-Kwan	10q Tumor Suppressor Gene		CA56041
Zhou, Ming-Ming	Structure/Function of the MAPK Phosphatase—PAC1		CA80938

Table B-10

NCI Projects Supported in 2002 Addressing the PRG Priority: How do we define genetic susceptibility of individuals to prostate cancer, and how is such susceptibility associated with other forms of malignancies or diseases?

Principal Investigator	Title	RFA or PA	Project ID
Ambs, Stefan	Identification of Allele Variant Genes That Are Risk Factors for Human Breast and Prostate Cancer		BC10439
Barany, Francis	Identifying Genome Changes in Cancer Development		CA81467
Cooney, Kathleen	Project 3: Hereditary Prostate Cancer in African American Families	CA-94-031	CA69568-Sub-03
Couch, Fergus	p21 Induction by BRCA2		CA78878
Everson, Richard	Receptor Gene Polymorphisms in Prostate Cancer		CA81240
Giusti, Ruthann	Israeli Prostate Cancer		CP10144-Sub-08185
Green, Jeffrey E	Transgenic Models for Prostate and Breast Cancer		BC05740
Isaacs, William B	Project 2: Search for Hereditary Prostate Cancer Genes Using Linkage Analysis and Positional Cloning Approaches	CA-94-031	CA58236-Sub-02
Isaacs, William B	Prostate Cancer Susceptibility: The ICPCQ Study		CA89600
Linehan, W Marston	Molecular Genetics of Prostate Cancer		SC10095
Mandal, Diptasri M	Genetics of Prostate Cancer in an African American Population	PA-01-021	CA97778
O'Brien, Stephen J	Approaches to Gene Mapping Development and Applications		BC05681
Smith, Michael W	Prostate and Breast Cancer Susceptibility Genes in African Americans and Hispanics		BC05800
Stanford, Janet	Molecular Predictors of Prostate Cancer Progression and Mortality	PAR-00-087	CA97186-Sub-01
Thibodeau, Stephen	Genetic Susceptibility in Prostate Cancer	PAR-99-167	CA91956-Sub-01
Weber, Barbara	University of Pennsylvania Cancer Genetics Network	CA-97-004	CA78156

Table B-11
Additional Prostate Cancer Biology Projects

Principal Investigator	Title	RFA or PA	Project ID
Gann, Peter	Project 5: Clinical Trial on Lycopene	PAR-99-167	CA90386-Sub-05
Glazer, Robert I	Structure Based Discovery of Akt Inhibitors	PAR-01-045	CA95378
Gupta, Smiti	NF-kB: A Marker for Cellular Oxidative Stress		CA91658
Hu, Ming	Absorption and Metabolism of Isoflavones		CA87779
Ma, Jianjie	Calcium Signaling and Cytochrome C Release in Apoptosis		CA95739
McVary, Kevin	Project 4: Molecular Mechanisms of Neuropathic Erectile Dysfunction	PAR-99-167	CA90386-Sub-04
Piwnica-Worms, David R	Washington University Molecular Imaging Center	CA-01-014	CA94056
Woods, Catherine	Novel Prostate Homing Peptides as Potential Diagnostics		CA92933

FY 2002 Etiology and Prevention Projects

Table B-12

NCI Projects Supported in 2002 Addressing the PRG Priority: What genes are important in the etiology of prostate cancer? What fraction of familial prostate cancer is monogenic with Mendelian inheritance of susceptibility alleles? What is the function of such genes?

Principal Investigator	Title	RFA or PA	Project ID
	Validation of Family History of Cancer Questionnaire		PC95039
Ambs, Stefan	Identification of Allele Variant Genes That Are Risk Factors for Human Breast and Prostate Cancer		BC10439
Balmain, Allan	Project 5: Identification of Prostate Tumor Susceptibility Genes Using Mouse Models for Prostate Cancer	PAR-99-167	CA89520-Sub-05
Barany, Francis	Identifying Genome Changes in Cancer Development		CA81467
Barrack, Evelyn	Androgen Receptor Variants and Prostate Cancer Etiology	CA-94-028	CA68645
Bova, Steven G	Project 1: Molecular Genetics of Human Prostate Cancer	CA-94-031	CA58236-Sub-01
Buetow, Kenneth	Molecular Genetic Epidemiology of Leading U.S. Cancers		CP10140
Bunker, Clareann	Molecular Epidemiology of Prostate Cancer In Tobagonians	PA-99-055	CA84950
Cannon-Albright, Lisa	Mapping and Cloning Prostate Cancer Predisposition Loci	PA-00-080	CA90752
Chen, Chu	Endogenous Sex Hormones, Genetics, and Prostate Cancer	PA-95-084	CA78812
Chinault, Craig	Project 3: Physical and Functional Analysis of Prostate Cancer Genes	PAR-00-087	CA58204-Sub-03
Church, Timothy	Molecular Epidemiology of Prostate Carcinogenesis	PA-95-084	CA74103
Coetzee, Gerhard	Androgen Receptor and Prostate Cancer Risk in Chinese	PA-99-055	CA84890
Cooney, Kathleen	Genetic Analysis of Hereditary Prostate Cancer Families		CA79596
Cooney, Kathleen	Project 3: Hereditary Prostate Cancer in African American Families	CA-94-031	CA69568-Sub-03
Demarzo, Angelo	Inflammation and Atrophy in Prostate Carcinogenesis	PA-99-055	CA84997
Everson, Richard	Polymorphisms in Prostate Cancer Carcinogenesis	PA-99-055	CA84989
Figg, William D	Development of Angiogenesis Inhibitors Using Prostate Cancer as a Tumor Model		SC06538
Figg, William D	Identify SNPs and Polymorphisms That Are Important in the Development of Prostate Cancer		BC10453
Geliebter, Jan	Gene Expression in Diet Induced Prostate Cancer	PA-99-081	CA88982
Giovannucci, Edward	Diet and Genetic Interactions in Prostate Cancer		CA76622
Giovannucci, Edward	Nutritional and Hormonal Biomarkers in Prostate Cancer		CA72036
Giusti, Ruthann	BRCA Prostate Cancer Intervention Study		CP10144-Sub-07035
Giusti, Ruthann	Israeli Prostate Cancer		CP10144-Sub-08185
Golub, Todd	Genomic Expression Analysis of Tumors after Radical Prostatectomy	PAR-99-167	CA90381-Sub-04
Greene, Mark H	Clinical and Genetic Studies of Familial and Hereditary Cancer Syndromes		CP10144

Table B-12 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Harris, C	Molecular Epidemiology of Human Cancer		BC05480
Hayes, Richard	Prostate Cancer in the PLCO Trial		CP10152-Sub-10003
Hein, David	Pharmacogenetics of Drug and Carcinogen Metabolism	PA-95-084	CA34627
Helzlsouer, Kathy	Epidemiology of Prostate Cancer—ODC and AR Genotypes		CA88180
Ho, Shuk-Mei	Metallothionein and Cadmium Carcinogenesis in Rat Prostate		CA62269
Isaacs, John T	Project 8: Down Regulation of Metastasis Suppressor Genes as Diagnostic Methods for Predicting the Biologic Behavior of Histologically Detectable Prostate Cancer	CA-94-031	CA58236-Sub-08
Isaacs, William B	Project 2: Search for Hereditary Prostate Cancer Genes Using Linkage Analysis and Positional Cloning Approaches	CA-94-031	CA58236-Sub-02
Isaacs, William B	Prostate Cancer Susceptibility: The ICPCQ Study		CA89600
Jay, Gilbert	Large Scale Gene Discovery—Human Prostate Cancer		CA81900
Koff, Andrew	p27Kip1 Expression, a Prognostic Indicator—But Why?		CA89563
Lee, Byungkook	Molecular Modeling and Bioinformatics		BC08759
Mandal, Diptasri M	Genetics of Prostate Cancer in an African American Population	PA-01-021	CA97778
McDonnell, Timothy	Project 3: Therapeutic Modulation of Apoptosis in Prostate Cancer Patients	PAR-99-167	CA90270-Sub-03
Meyskens, Frank	Chemoprevention of Familial Prostate Cancer	CA-98-012	CA81886
Montie, James	Project 2: Epidemiology of Prostate Cancer in African Americans	CA-94-031	CA69568-Sub-02
Nelson, William	Project 12: Rational Prostate Cancer Prevention Studies	CA-94-031	CA58236-Sub-12
O'Brien, Stephen J	Approaches to Gene Mapping Development and Applications		BC05681
Ostrander, Elaine	Genetics of Prostate Cancer Susceptibility		CA78836
Pandolfi, Pier Paolo	Molecular Analysis of Carcinogenesis in the Mouse and Human Prostate	PAR-99-167	CA92629-Sub-02
Rangnekar, Vivek	Mechanism of Apoptosis by Par4	PA-99-081	CA60872
Rebbeck, Timothy	Molecular Epidemiology of Prostate Cancer	PA-99-055	CA85074
Reichardt, Juergen	5 Alpha Reductase Genotype, Race Prostate Cancer Risk	PA-95-084	CA68581
Rosen, Eliot	Role of BRCA1 as a Human Prostate Suppressor Gene		CA80000
Sellers, William	Single Nucleotide Repeat Polymorphism Analysis of Recurrent Prostate Cancer after Radiation Therapy	PAR-99-167	CA90381-Sub-03
Smith, Michael W	High-Throughput Genotyping for Genetic Analysis		BC10270
Stampfer, Meir	Dietary and Biochemical Markers of Prostate Cancer Risk		CA58684
Stanford, Janet	Genetic Epidemiology of Prostate Cancer		CA80122
Stanford, Janet	Genetic Polymorphisms and Prostate Cancer Risk		CA82664
Stanford, Janet	Molecular Predictors of Prostate Cancer Progression and Mortality	PAR-00-087	CA97186-Sub-01

Table B-12 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Strom, Sara	Project 5: Clinical, Epidemiological, and Molecular Markers of Prostate Cancer Progression	PAR-99-167	CA90270-Sub-05
Strom, Sara	Prostate Cancer in Mexican Americans and African American	PA-99-055	CA84964
Thibodeau, Stephen	Genetic Susceptibility in Prostate Cancer	PAR-99-167	CA91956-Sub-01
Thibodeau, Stephen	Localization of Susceptibility Loci in Prostate Cancer		CA72818
Thompson, Patricia	Beta 2 Adrenergic Receptors and Prostate Cancer Risk	PAR-98-023	CA88299
Ware, Joy	Mechanisms of Prostate Epithelial Cell Transformation		CA58126
Weber, Barbara	University of Pennsylvania Cancer Genetics Network	CA-97-004	CA78156
Weiss, Noel	Androgen Pathway and Genetic Risk of Prostate Cancer	PAR-98-023	CA92706
Weiss, Noel	IGF-I Levels, IGF-I Genotype, and Prostate Cancer	PA-99-055	CA85064
White, Raymond	Rocky Mountain Cancer Genetics Coalition	CA-97-004	CA78174
Whittemore, Alice	Genetic Epidemiology of Prostate Cancer		CA67044
Willett, Walter	Prospective Studies of Diet and Cancer in Men and Women		CA55075
Witte, John	Genetic Epidemiology of Prostate Cancer Aggressiveness	PA-99-055	CA88164
Witte, John S	Androgen Pathway Factors and Prostate Cancer	PA-00-080	CA94211
Zhao, Yingming	Identification of Prostate and Ovarian Cancer Markers	CA-98-028	CA85146

Table B-13

NCI Projects Supported in 2002 Addressing the PRG Priority: Which dietary nutrients affect risk of prostate cancer (e.g., fat, phytoestrogens, and micronutrients)? What are the mechanisms by which these nutrients alter risk?

Principal Investigator	Title	RFA or PA	Project ID
Albanes, D	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study and Cohort Follow-Up		SC00100
Albanes, Demetrius	ATBC Study		CP10127-Sub-03031
Aronson, William	The Role of Quantity and Composition of Dietary Fat in the Prevention of Prostate Cancer	PAR-99-167	CA92131-Sub-05
Bergan, Raymond C	Molecular Correlates of Soy in Humans	PA-00-047	CA99263
Bosland, Maarten	Preclinical Prostate Cancer Chemoprevention Studies		CA76426
Brown, Linda Morris	PHS Black/White Study		CP10113-Sub-00430
Church, Timothy	Molecular Epidemiology of Prostate Carcinogenesis	PA-95-084	CA74103
Coltman, Charles	Selenium Based Chemoprevention	CA-98-001	CA77178
Deluca, L	Retinoids in Differentiation and Neoplasia		BC04798
Demark-Wahnefried, Wendy	Prostate Cancer: Impact of Fat and Flaxseed Modified Diet		CA85740
Felton, James S	Carcinogenic Significance of Heterocyclic Amines		CA55861
Fraser, Gary	Cancer Epidemiology in Adventists—A Low Risk Group		CA94594
Gann, Peter	Project 5: Clinical Trial on Lycopene	PAR-99-167	CA90386-Sub-05
Gann, Peter H	Effects of Lycopene on High-Risk Prostatic Tissue	PA-00-080	CA90759
Gapstur, Susan	Determinants of Steroid Hormones in Black and White Men		CA77704
Gaziano, Michael J	Physicians Health Study II: Prevention Trial of Vitamins		CA97193
Geliebter, Jan	Gene Expression in Diet Induced Prostate Cancer	PA-99-081	CA88982
Giovannucci, Edward	Diet and Genetic Interactions in Prostate Cancer		CA76622
Giovannucci, Edward	Nutritional and Hormonal Biomarkers in Prostate Cancer		CA72036
Gladyshev, Vadim	Selenoprotein as a Target for Cancer Prevention		CA80946
Gupta, Sanjay	Inhibition of Prostate Carcinogenesis by Apigenin	PAR-00-025	CA99049
Gupta, Sanjay	Prostate Cancer Chemoprevention by Apigenin	PAR-00-025	CA94248
Guttenplan, Joseph	Antimutagenesis by Lycopene and Selenium in Lac Rodents		CA76281
Hatfield, Dolph L	Role of Selenium in Cancer and Human Health		BC05317
Ho, Shuk-Mei	Metallothionein and Cadmium Carcinogenesis in Rat Prostate		CA62269
Hsing, Ann	Pilot Study of Prostate Cancer in Africa		CP10180-Sub-01130
Hsing, Ann	Shanghai Prostate Cancer Study		CP10180-Sub-01140
Hu, Ming	Absorption and Metabolism of Isoflavones		CA87779
Ingles, Sue	Risk Factors for Advanced Prostate Cancer	PA-99-055	CA84979

Table B-13 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Kim, Jeri	A Feasibility Study of L-Selenomethionine and Alpha-Tocopherol	PA-99-070	CA88761
Kolonel, Laurence	Multiethnic/Minority Cohort Study of Diet and Cancer		CA54281
Lewis, Kevin C	Systems-Based Modeling of Retinoid—Drug Interactions		BC00162
Liao, Shutsung	Molecular Mechanisms of Growth Control—Prostate Cancer		CA58073
Lin, Young C	Chemopreventive Effects of Dietary Cottonseed Oil	PAR-00-025	CA95915
Marshall, James	Nutritional Prevention of Cancer		CA49764
Marshall, James	Phase II Chemoprevention Trial of SE and Prostate Cancer		CA79080
Marshall, James	Phase III Trial of Selenium for Prostate Cancer Prevention		CA77789
Mukhtar, Hasan	Cancer Chemopreventive Mechanisms of Green Tea		CA78809
Nomura, Abraham	Cancer Sero Epidemiology among the Japanese in Hawaii		CA33644
Pinto, John T	Allium Compounds in Control of Human Prostate Cancer		CA89815
Rice, Lori	Dietary Isoflavone Regulated Genes in Prostate Cancer	PAR-00-025	CA91231
Sinha, Rashmi	Genetic, Dietary, and Hormonal Risk Factors in Breast and Prostate Cancer (GEM)		CP10127-Sub-03060
Sporn, Michael	New Triterpenoids for Chemoprevention of Cancer	PAR-01-046	CA78814
Stampfer, Meir	Dietary and Biochemical Markers of Prostate Cancer Risk		CA58684
Stampfer, Meir	Nutritional and Biochemical/Genetic Markers of Cancer		CA42182
Sytkowski, Arthur J	Chemopreventive Action of Human Selenium Binding Protein	PAR-00-025	CA96047
Van Breemen, Richard	Prevention of DNA Oxidation by Tocopherol and Carotenoids		CA70771
Weigel, Nancy	Inhibition of Prostate Cancer Cell Growth by Vitamin D		CA75337
White, Emily	Cohort Study of Dietary Supplements and Cancer Risk		CA74846
Whittemore, Alice	Cancer Epidemiology and Biostatistics		CA47448
Willett, Walter	Prospective Studies of Diet and Cancer in Men and Women		CA55075
Witte, John S	Androgen Pathway Factors and Prostate Cancer	PA-00-080	CA94211
Young, Charles Y	Growth Control of Prostate Cancer Cells by Plant Phenols	PA-99-081	CA88900
Zhou, Jin-Rong	Dietary Soybean Components' Effect on Prostate Cancer Progression		CA78521
Ziegler, Regina G	Blood Micronutrients, Fatty Acids, and Prostate Cancer (U.S. Black/White Study)		CP10169-Sub-03033
Ziegler, Regina G	Nutritional and Metabolic Determinants of Cancer		CP10169
Ziegler, Regina G	NHANES Follow-Up Study		CP10169-Sub-03210

Table B-14

NCI Projects Supported in 2002 Addressing the PRG Priority: What other exogenous risk factors are involved in prostate cancer (e.g., viral, exercise, vasectomy, and sexual factors)?

Principal Investigator	Title	RFA or PA	Project ID
Ahmad, Nihal	Chemoprevention of Prostate Cancer by Sanguinarine	PAR-00-025	CA89723
Alavanja, Michael	Prospective Study of Farmers and Their Families (Agricultural Health Study)		CP10119-Sub-02020
Blair, Aaron	Selected Cancers, Serum Organochlorines in the Norwegian JANUS Cohort		CP10120-Sub-02135
Blair, Aaron	Occupation and Cancer Risk in Sweden: The Cancer Environment Registry		CP10120-Sub-44-95-03
Chen, Chu	Endogenous Sex Hormones, Genetics, and Prostate Cancer	PA-95-084	CA78812
Church, Timothy	Molecular Epidemiology of Prostate Carcinogenesis	PA-95-084	CA74103
Deluca, L	Retinoids in Differentiation and Neoplasia		BC04798
DeWeese, Theodore	Project 14: Determinants of Radiosensitivity in Prostate Cancer	CA-94-031	CA58236-Sub-14
Dosemeci, Mustafa	Occupational Exposures and Cancer Risk in Turkey		CP10120-Sub-02366
Eisen, Ellen A	Prostate Cancer Morbidity and Metal Working Fluids	PA-01-021	CA99514
Gail, Mitchell	Record-Linkage Studies of Cancer		CP10105
Gapstur, Susan	Determinants of Steroid Hormones in Black and White Men		CA77704
Goedert, James	Epidemiology and Natural History of Cancer-Associated Viruses		CP10176
Goedert, James	PCA—Prostate Cancer Study		CP10176-Sub-05624
Haase, Ashley	Trans and Pathog of KS-Associated Herpesvirus Infection		CA75172
Hayes, Richard	Prostate Cancer in the PLCO Trial		CP10152-Sub-10003
Hoover, Robert	Early Life Exposures and Subsequent Cancer Risk		CP10168
Hsing, Ann	Pilot Study of Prostate Cancer in Africa		CP10180-Sub-01130
Hsing, Ann	Shanghai Prostate Cancer Study		CP10180-Sub-01140
Kash, Kathryn	Behavioral Aspects of Familial Risk for Prostate Cancer	PA-97-055	CA86826
Land, Charles	Cancer Risk among Japanese A-Bomb Survivors		CP10134-Sub-04016
Lubin, Jay H	Studies of Environmental and Occupational Exposures		CP10113
Mukhtar, Hasan	Prostate Cancer Chemoprevention by Cox 2 Inhibition	PAR-00-025	CA89739
Ron, Elaine	Studies of Medical Radiation and Other Therapeutic Agents		CP10131
Ron, Elaine	Studies of Populations Exposed to Occupational Sources of Radiation		CP10133
Sinha, Rashmi	Genetic, Dietary, and Hormonal Risk Factors in Breast and Prostate Cancer (GEM)		CP10127-Sub-03060
Skelton, Timothy	Decoding Cancer Signature Glycoforms of Serum Tumor Mark	PAR-00-025	CA89730
Stanford, Janet	NSAIDs and Other Medications in Prostate Cancer Etiology	PA-00-080	CA92579
Stanford, Janet L	Oncogenic Human Papillomaviruses and Prostate Cancer Risk	PAR-98-023	CA92777
Tarone, Robert	Consulting and Collaboration on Epidemiologic Studies		CP10118
Waalkes, Michael P	Mechanisms of Inorganic Carcinogenesis		BC05488
Whittemore, Alice	Cancer Epidemiology and Biostatistics		CA47448
Yeh, Grace Chao	Dietary Regulation of Biochemical/Molecular Changes in Carcinogen Resistant Cells		BC00189

Table B-15

NCI Projects Supported in 2002 Addressing the PRG Priority: Which genetic and exogenous risk factors account for differences in incidence and mortality among African American, Caucasian, Hispanic, and Asian American populations?

Principal Investigator	Title	RFA or PA	Project ID
Barrack, Evelyn R	Project 3: Androgen Receptor Gene Structure and Function in Human Prostate Cancer	CA-94-031	CA58236-Sub-03
Bova, G	Modes of Prostate Cancer Progression—Role of p53 Pathway	PA-99-081	CA92234
Brown, Linda Morris	PHS Black/White Study		CP10113-Sub-00430
Chen, Chu	Endogenous Sex Hormones, Genetics, and Prostate Cancer	PA-95-084	CA78812
Cooney, Kathleen	Project 3: Hereditary Prostate Cancer in African American Families	CA-94-031	CA69568-Sub-03
Demarzo, Angelo	Inflammation and Atrophy in Prostate Carcinogenesis	PA-99-055	CA84997
Eisen, Ellen A	Prostate Cancer Morbidity and Metal Working Fluids	PA-01-021	CA99514
Erwin, Deborah	Arkansas Special Populations Access Network (A-Span)	CA-99-003	CA86081
Etzioni, Ruth	PSA Screening and U.S. Prostate Cancer Trends	CA-99-013	CA88160
Everson, Richard	Polymorphisms in Prostate Cancer Carcinogenesis	PA-99-055	CA84989
Everson, Richard	Receptor Gene Polymorphisms in Prostate Cancer		CA81240
Figg, William D	Development of Angiogenesis Inhibitors Using Prostate Cancer as a Tumor Model		SC06538
Fraser, Gary	Cancer Epidemiology in Adventists—A Low Risk Group		CA94594
Gany, Francesca	Cancer Awareness Network for Immigrant Minority Populations		CA86286
Giovannucci, Edward	Genetic and Serologic Determinants of Prostate Cancer Risk and Progression	PAR-99-167	CA90381-Sub-01
Hayes, Richard	South Carolina Older Men's Health Project		CP10136-Sub-02317
Hsing, Ann	Pilot Study of Prostate Cancer in Africa		CP10180-Sub-01130
Hsing, Ann	Shanghai Prostate Cancer Study		CP10180-Sub-01140
Jensen, Ronald	Feasibility of New Prostate Cancer Molecular Genetic Techniques		CA81625
Kash, Kathryn	Behavioral Aspects of Familial Risk for Prostate Cancer	PA-97-055	CA86826
Kolonel, Laurence	Multiethnic/Minority Cohort Study of Diet and Cancer		CA54281
Mandal, Diptasri M	Genetics of Prostate Cancer in an African American Population	PA-01-021	CA97778
Mohler, James	Prostate Cancer: Transition to Androgen-Independence		CA77739
Montie, James	Project 2: Epidemiology of Prostate Cancer in African Americans	CA-94-031	CA69568-Sub-02
Myers, Ronald	Increasing Access to Clinical and Educational Studies	CA-99-003	CA86084
Ramirez, Amelie	Redes En Accion—Cancer Awareness, Training, and Research	CA-99-003	CA86117
Rebbeck, Timothy	Molecular Epidemiology of Prostate Cancer	PA-99-055	CA85074
Reichardt, Juergen	5 Alpha Reductase Genotype, Race Prostate Cancer Risk	PA-95-084	CA68581
Rice, Lori	Dietary Isoflavone Regulated Genes in Prostate Cancer	PAR-00-025	CA91231
Smith, Michael W	High-Throughput Genotyping for Genetic Analysis		BC10270

Table B-15 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Smith, Michael W	Prostate and Breast Cancer Susceptibility Genes in African Americans and Hispanics		BC05800
Strom, Sara	Project 5: Clinical, Epidemiological, and Molecular Markers of Prostate Cancer Progression	PAR-99-167	CA90270-Sub-05
Strom, Sara	Prostate Cancer in Mexican Americans and African Americans	PA-99-055	CA84964
Sullivan, Louis	National Black Leadership Cancer Control Research and Training Network	CA-99-003	CA86274
Thompson, Ian	San Antonio Center of Biomarkers of Risk for Prostate Cancer	CA-99-007	CA86402
Whittemore, Alice	Genetic Epidemiology of Prostate Cancer		CA67044
Young, Charles	Human Kallikreins as Novel Markers of Prostate Cancer	PAR-99-167	CA91956-Sub-02

Table B-16

NCI Projects Supported in 2002 Addressing the PRG Priority: Are there genetic or exogenous factors associated with prostate cancer progression, as opposed to its incidence?

Principal Investigator	Title	RFA or PA	Project ID
Ambs, Stefan	Identification of Allele Variant Genes That Are Risk Factors for Human Breast and Prostate Cancer		BC10439
Balk, Steven	The Androgen Receptor in Hormone Refractory Disease	PAR-99-167	CA90381-Sub-05
Bova, Steven G	Project 1: Molecular Genetics of Human Prostate Cancer	CA-94-031	CA58236-Sub-01
Bunker, Clareann	Molecular Epidemiology of Prostate Cancer in Tobagonians	PA-99-055	CA84950
Chen, Chu	Endogenous Sex Hormones, Genetics, and Prostate Cancer	PA-95-084	CA78812
Day, Mark	Project 4: Rb as a Regulator of Prostate Tumorigenesis	CA-94-031	CA69568-Sub-04
Demark-Wahnefried, Wendy	Prostate Cancer: Impact of Fat and Flaxseed Modified Diet		CA85740
Ellis, William	Genomic and Gene Expression Profiling of Disseminated Prostate Cancer	PAR-00-087	CA97186-Sub-02
Emmert-Buck, Michael R	Genetic Progression of Cancer		SC10437
Etzioni, Ruth	PSA Screening and U.S. Prostate Cancer Trends	CA-99-013	CA88160
Figg, William D	Development of Angiogenesis Inhibitors Using Prostate Cancer as a Tumor Model		SC06538
Figg, William D	Identify SNPs and Polymorphisms That Are Important in the Development of Prostate Cancer		BC10453
Gann, Peter	Project 5: Clinical Trial on Lycopene	PAR-99-167	CA90386-Sub-05
Giovannucci, Edward	Genetic and Serologic Determinants of Prostate Cancer Risk and Progression	PAR-99-167	CA90381-Sub-01
Gleave, Martin	Characterization of Anti-Apoptotic Genes Induced during Androgen Independent Progression and Chemotherapy	PAR-00-087	CA97186-Sub-03
Golub, Todd	Genomic Expression Analysis of Tumors after Radical Prostatectomy	PAR-99-167	CA90381-Sub-04
Hood, Leroy	Transcriptome and Proteome Stratification of Prostate Adenocarcinoma Phenotypes	PAR-00-087	CA97186-Sub-04
Hsing, Ann	GW Prostate Tissue Study		CP10180-Sub-01072
Ingles, Sue	Risk Factors for Advanced Prostate Cancer	PA-99-055	CA84979
Jenkins, Robert	Biologic and Clinical Studies of Overrepresented 8q24 Region Associated with Prostate Cancer Progression	PAR-99-167	CA91956-Sub-03
Jensen, Ronald	Feasibility of New Prostate Cancer Molecular Genetic Techniques		CA81625
Katten, Michael	Natural History of Prostate Cancer, Prognostic Models, and Decision Making	PAR-99-167	CA92629-Sub-01
Loeb, Lawrence	Oxygen Induced DNA Damage, Mutations, and Cancer		CA80993
Marshall, James	Phase II Chemoprevention Trial of SE and Prostate Cancer		CA79080
Marshall, James	Phase III Trial of Selenium for Prostate Cancer Prevention		CA77789
McDonnell, Timothy	Project 3: Therapeutic Modulation of Apoptosis in Prostate Cancer Patients	PAR-99-167	CA90270-Sub-03

Table B-16 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Reichardt, Juergen	5 Alpha Reductase Genotype, Race Prostate Cancer Risk	PA-95-084	CA68581
Reiter, Robert	Prostate Stem Cell Antigen (PSCA) in the Biology and Therapy of Prostate Cancer	PAR-99-167	CA92131-Sub-01
Sellers, William	Single Nucleotide Repeat Polymorphism Analysis of Recurrent Prostate Cancer after Radiation Therapy	PAR-99-167	CA90381-Sub-03
Skelton, Timothy	Decoding Cancer Signature Glycoforms of Serum Tumor Mark	PAR-00-025	CA89730
Stanford, Jean	Molecular Predictors of Prostate Cancer Progression and Mortality	PAR-00-087	CA97186-Sub-01
Strom, Sara	Project 5: Clinical, Epidemiological, and Molecular Markers of Prostate Cancer Progression	PAR-99-167	CA90270-Sub-05
Thibodeau, Stephen	Localization of Susceptibility Loci in Prostate Cancer		CA72818
Witte, John	Genetic Epidemiology of Prostate Cancer Aggressiveness	PA-99-055	CA88164
Woodson, Karen	Gene Methylation in Prostate Cancer		BC10459
Ying, Shao-Yao	Novel Molecular Profiling of Prostate Cancer Signatures		CA85722
Young, Charles	Human Kallikreins as Novel Markers of Prostate Cancer	PAR-99-167	CA91956-Sub-02

Table B-17

NCI Projects Supported in 2002 Addressing the PRG Priority: Are there interactions between genetic predisposition and exogenous exposures?

Principal Investigator	Title	RFA or PA	Project ID
Alavanja, Michael	Prospective Study of Farmers and Their Families (Agricultural Health Study)		CP10119-Sub-02020
Albanes, D	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study and Cohort Follow-Up		SC00100
Balmain, Allan	Project 5: Identification of Prostate Tumor Susceptibility Genes Using Mouse Models for Prostate Cancer	PAR-99-167	CA89520-Sub-05
Buetow, Kenneth	Molecular Genetic Epidemiology of Leading U.S. Cancers		CP10140
Bunker, Clareann	Molecular Epidemiology of Prostate Cancer in Tobagonians	PA-99-055	CA84950
Church, Timothy	Molecular Epidemiology of Prostate Carcinogenesis	PA-95-084	CA74103
Gapstur, Susan	Determinants of Steroid Hormones in Black and White Men		CA77704
Geliebter, Jan	Gene Expression in Diet Induced Prostate Cancer	PA-99-081	CA88982
Giovannucci, Edward	Diet and Genetic Interactions in Prostate Cancer		CA76622
Giovannucci, Edward	Nutritional and Hormonal Biomarkers in Prostate Cancer		CA72036
Hayes, Richard	Prostate Cancer in the PLCO Trial		CP10152-Sub-10003
Hein, David	Pharmacogenetics of Drug and Carcinogen Metabolism	PA-95-084	CA34627
Hsing, Ann	Shanghai Prostate Cancer Study		CP10180-Sub-01140
Meyskens, Frank	Chemoprevention of Familial Prostate Cancer	CA-98-012	CA81886
Sinha, Rashmi	Genetic, Dietary, and Hormonal Risk Factors in Breast and Prostate Cancer (GEM)		CP10127-Sub-03060
Stampfer, Meir	Nutritional and Biochemical/Genetic Markers of Cancer		CA42182
Stanford, Janet	Molecular Predictors of Prostate Cancer Progression and Mortality	PAR-00-087	CA97186-Sub-01
Strom, Sara	Prostate Cancer in Mexican Americans and African Americans	PA-99-055	CA84964
Whittemore, Alice	Cancer Epidemiology and Biostatistics		CA47448
Willett, Walter	Prospective Studies of Diet and Cancer in Men and Women		CA55075
Witte, John S	Androgen Pathway Factors and Prostate Cancer	PA-00-080	CA94211

Table B-18

NCI Projects Supported in 2002 Addressing the PRG Priority: What interventions can alter the underlying etiology of prostate cancer? What are the most promising potential preventive agents and activities?

Principal Investigator	Title	RFA or PA	Project ID
Agarwal, Rajesh	Receptor Signaling, Phytic Acid, and Prostate Cancer		CA83741
Ahmad, Nihal	Chemoprevention of Prostate Cancer by Sanguinarine	PAR-00-025	CA89723
Albanes, D	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study and Cohort Follow-Up		SC00100
Aronson, William	The Role of Quantity and Composition of Dietary Fat in the Prevention of Prostate Cancer	PAR-99-167	CA92131-Sub-05
Bergan, Raymond C	Molecular Correlates of Soy in Humans	PA-00-047	CA99263
Bosland, Maarten	Preclinical Prostate Cancer Chemoprevention Studies		CA76426
Bosland, Maarten	Prostate Cancer Chemoprevention Clinical Trials	CA-96-001	CA72290
Coltman, Charles	Selenium Based Chemoprevention	CA-98-001	CA77178
Cunha, Gerald	Preclinical Evaluations of Intermediate Endpoints and Their Modulation of Chemoprevention		CN15114
Demark-Wahnefried, Wendy	Prostate Cancer: Impact of Fat and Flaxseed Modified Diet		CA85740
Demarzo, Angelo	Inflammation and Atrophy in Prostate Carcinogenesis	PA-99-055	CA84997
Ensley, Burt	Selenium Enriched Plant Material for Chemoprevention		CA80444
Foster, Barbara A	Vitamin D Analogs for Chemoprevention of Prostate Cancer		CA95367
Gann, Peter	Project 5: Clinical Trial on Lycopene	PAR-99-167	CA90386-Sub-05
Gann, Peter H	Effects of Lycopene on High-Risk Prostatic Tissue	PA-00-080	CA90759
Gaziano, Michael J	Physicians Health Study II: Prevention Trial of Vitamins		CA97193
Gupta, Sanjay	Inhibition of Prostate Carcinogenesis by Apigenin	PAR-00-025	CA99049
Gupta, Sanjay	Prostate Cancer Chemoprevention by Apigenin	PAR-00-025	CA94248
Gupta, Smiti	NF-kB: A Marker for Cellular Oxidative Stress		CA91658
Henning, Susanne	Bioavailability of Tea Polyphenols in Prostate Cancer	PAR-00-025	CA91163
Kennedy, Ann	Screening of Chemopreventive Agents by Molecular Profiling Using Stable Clones of		CN15134
Kim, Jeri	A Feasibility Study of L-Selenomethionine and Alpha-Tocopherol	PA-99-070	CA88761
Lee, Chung	Project 1: Clusterin as a Negative Prognostic Indicator in Prostate Cancer	PAR-99-167	CA90386-Sub-01
Lewis, Kevin C	Systems-Based Modeling of Retinoid-Drug Interactions		BC00162
Lin, Young C	Chemopreventive Effects of Dietary Cottonseed Oil	PAR-00-025	CA95915
Marshall, James	Phase II Chemoprevention Trial of SE and Prostate Cancer		CA79080
Marshall, James	Phase III Trial of Selenium for Prostate Cancer Prevention		CA77789
McCormick, David	Efficacy Studies of Chemopreventive Agents in Animal Models, WS 90		CN15110
McCormick, David	Efficacy Studies of Chemopreventive Agents in Animal Models, WS 97		CN25113

Table B-18 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Meyskens, Frank	Chemoprevention of Familial Prostate Cancer	CA-98-012	CA81886
Mueller, Elisabetta	PPAR as a Target of Therapy for Prostate Cancer	PAR-99-167	CA90381-Sub-02
Mukhtar, Hasan	Prostate Cancer Chemoprevention by Cox 2 Inhibition	PAR-00-025	CA89739
Nelson, William	Project 12: Rational Prostate Cancer Prevention Studies	CA-94-031	CA58236-Sub-12
Sarkar, Fazlul	Molecular Mechanism of Genistein in Prostate Cancer		CA83695
Sheikh, M	Death Receptors in Prostate Cancer Biology and Apoptosis	PA-99-081	CA89043
Weigel, Nancy	Inhibition of Prostate Cancer Cell Growth by Vitamin D		CA75337

Table B-19

NCI Projects Supported in 2002 Addressing the PRG Priority: What is the potential of new animal models for testing of potential chemopreventive agents?

Principal Investigator	Title	RFA or PA	Project ID
Bosland, Maarten	Preclinical Prostate Cancer Chemoprevention Studies		CA76426
Cunha, Gerald	Preclinical Evaluations of Intermediate Endpoints and Their Modulation of Chemoprevention		CN15114
Gupta, Sanjay	Inhibition of Prostate Carcinogenesis by Apigenin	PAR-00-025	CA99049
Guttenplan, Joseph	Antimutagenesis by Lycopene and Selenium in Lac Rodents		CA76281
Lee, Eva	Mouse Cancer Models by Regulated Inactivation of Tumor Suppressor Genes	CA-98-013	CA84241
McCormick, David	Efficacy Studies of Chemopreventive Agents in Animal Models, WS 90		CN15110
McCormick, David	Efficacy Studies of Chemopreventive Agents in Animal Models, WS 94		CN25017
McCormick, David	Efficacy Studies of Chemopreventive Agents in Animal Models, WS 97		CN25113
Mukhtar, Hasan	Efficacy Testing of Selected Chemopreventive Agents in the TRAMP		CN15147
Mukhtar, Hasan	Prostate Cancer Chemoprevention by Cox 2 Inhibition	PAR-00-025	CA89739
Nelson, William	Project 12: Rational Prostate Cancer Prevention Studies	CA-94-031	CA58236-Sub-12
Schwartz, Gary	Calcidiol Therapy for Prostate Cancer	PAR-98-023	CA85750
Young, Charles Y	Growth Control of Prostate Cancer Cells by Plant Phenols	PA-99-081	CA88900

Table B-20
Additional NCI Etiology and Prevention Projects Supported in 2002

Principal Investigator	Title	RFA or PA	Project ID
Devesa, Susan	General Descriptive Studies		CP10108
Ross, Richardus	Isoflavone-Rich Pasta—Clinical and Commercial Potential		CA69878

FY 2002 Early Detection, Diagnosis, and Prognosis Projects

Table B-21

NCI Projects Supported in 2002 Addressing the PRG Priority: What biologic determinants, independent of stage, can provide a better definition of the malignant phenotype, natural history, and prognosis with various therapeutic interventions?

Principal Investigator	Title	RFA or PA	Project ID
Abato, Paul	Validation of Prostate Cancer Oncogenes		CA96276
Aebersold, Ruedi	Novel Quantitative, Comprehensive Proteomic Technology	CA-01-011	CA93302
Agus, David	The Role of the Her-Kinase Axis in Emergence of Androgen Independence in Human Prostate Cancer	PAR-99-167	CA92131-Sub-04
Arap, Wadih	Project 4: Exploring the Molecular Diversity of Blood Vessels for Diagnostic and Therapeutic Targeting in Prostate Cancer	PAR-99-167	CA90270-Sub-04
Balk, Steven	The Androgen Receptor in Hormone Refractory Disease	PAR-99-167	CA90381-Sub-05
Balmain, Allan	Project 5: Identification of Prostate Tumor Susceptibility Genes Using Mouse Models for Prostate Cancer	PAR-99-167	CA89520-Sub-05
Beach, Kirk	Tissue Pulsatility Imaging for Cancer Detection		CO07118
Beranova-Giorgianni, Sarka	Cancer Relevant Proteins in the Human Prostate Proteome	PAR-00-025	CA91254
Bernardi, Richard	Real-Time Ultrasonic Tissue Imaging for Prostate Cancer		CA78097
Bhujwalla, Zaver	Functional Imaging of the Metastatic Phenotype		CA73850
Blasberg, Ronald	MSKCC Center for In Vivo Molecular Imaging in Cancer	CA-99-004	CA86438
Bova, Steven G	Project 1: Molecular Genetics of Human Prostate Cancer	CA-94-031	CA58236-Sub-01
Brothman, Arthur	Molecular and Cytogenetic Analysis of Prostate Carcinoma		CA46269
Brown, Patrick	A Cancer Taxonomy Based on Gene Expression Patterns	CA-98-027	CA85129
Carter, H Ballentine	Project 6: Longitudinal Studies of Men with and without Prostate Cancer	CA-94-031	CA58236-Sub-06
Chakrabarti, Ratna	Molecular Markers for Prostate Cancer	PA-98-022	CA81329
Cheng, Leo	Characterization of Prostate Cancer with HRMAS 1HMRS	PA-98-022	CA80901
Christens-Barry, William	Project 13: New Methods to Determine Tissue Architecture and Chromatin Structure	CA-94-031	CA58236-Sub-13
Clinthorne, Neal	Compton Imaging Probe for the Prostate	CA-99-015	CA88179
Coffey, Donald	Project 4: Human Prostate Cancer Nuclei: Abnormalities in Structure and the Development of New Molecular Markers	CA-94-031	CA58236-Sub-04
Cohen, Pinchas	Interactions between IGFBPs and Nuclear Receptors in Prostate Cancer	PAR-99-167	CA92131-Sub-03
Collins, Colin	Project 2: Genomics of Prostate Cancer	PAR-99-167	CA89520-Sub-02
Cuttitta, Frank	Identification of Peptide Growth Factors That Regulate Human Tumor Proliferation		SC00173
Delikatny, Edward	NMR Detection of Prostate Tumor Differentiation	PA-98-008	CA79718
Diamandis, Eleftherios P	Human Kallikrein 4 (HK4): A New Prostatic Biomarker?	PA-01-010	CA93492

Table B-21 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Duerk, Jeffrey	IMRI/SPECT Guided Prostate Cancer Biopsy and Therapy	CA-99-015	CA88144
Ellis, William	Genomic and Gene Expression Profiling of Disseminated Prostate Cancer	PAR-00-087	CA97186-Sub-02
Emmert-Buck, Michael R	Genetic Progression of Cancer		SC10437
Everson, Richard	Receptor Gene Polymorphisms in Prostate Cancer		CA81240
Feleppa, Ernest	Clinical Ultrasonic Characterization of the Prostate		CA53561
Ferrari, Anna	Molecular Staging of Lymph Nodes—Outcome of Prostate Cancer		CA79918
Fisher, Paul	Novel Prostate Cancer Gene and Monoclonal Antibody		CA74468
Frangioni, John	Low-Molecular Weight Ligands for Prostate Cancer	CA-99-015	CA88245
Gann, Peter	Project 5: Clinical Trial on Lycopene	PAR-99-167	CA90386-Sub-05
Garg, Pradeep	Androgen Receptor Mediated Detection of Prostate Cancer	CA-99-015	CA88146
Gerald, William	Molecular Classification of Prostate Cancer	CA-98-027	CA84999
Giovannucci, Edward	Genetic and Serologic Determinants of Prostate Cancer Risk and Progression	PAR-99-167	CA90381-Sub-01
Gleave, Martin	Characterization of Anti-Apoptotic Genes Induced during Androgen Independent Progression and Chemotherapy	PAR-00-087	CA97186-Sub-03
Glinsky, Gennadi	Transcriptome of Metastatic Prostate Cancer		CA89827
Glode, L	Molecular Markers for Prostate Cancer Detection		CA81073
Golub, Todd	Genomic Expression Analysis of Tumors after Radical Prostatectomy	PAR-99-167	CA90381-Sub-04
Griffith, Jeffrey	Prognostic Value of Telomere DNA in Prostate Biopsy	PAR-99-102	CA86136
Herschman, Harvey	The UCLA Center for In Vivo Imaging in Cancer Biology	CA-99-004	CA86306
Hood, Leroy	Transcriptome and Proteome Stratification of Prostate Adenocarcinoma Phenotypes	PAR-00-087	CA97186-Sub-04
Hricak, Hedvig	Imaging in Risk Assessment of Prostate Cancer Patients		CA76423
Huang, Tim	High Throughput Methylation Analysis in Cancer	PAR-98-067	CA84701
Isaacs, John T	Project 8: Down Regulation of Metastasis Suppressor Genes as Diagnostic Methods for Predicting the Biologic Behavior of Histologically Detectable Prostate Cancer	CA-94-031	CA58236-Sub-08
Jenkins, Robert	Biologic and Clinical Studies of Overrepresented 8q24 Region Associated with Prostate Cancer Progression	PAR-99-167	CA91956-Sub-03
Jiang, Yulei	Neural Network Prediction of Prostate Cancer Progression	PA-01-010	CA97308
Jones, Alun	Technetium and Rhenium in Nuclear Medicine		CA34970
Kattan, Michael	Natural History of Prostate Cancer, Prognostic Models, and Decision Making	PAR-99-167	CA92629-Sub-01
Lee, Chung	Project 1: Clusterin as a Negative Prognostic Indicator in Prostate Cancer	PAR-99-167	CA90386-Sub-01

Table B-21 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Lemkin, Peter F	Computer Aided Two-Dimensional Electrophoretic Gel Analysis (GELLAB)		BC08381
Linehan, W Marston	Molecular Genetics of Prostate Cancer		SC10095
Liotta, Lance	Laser Capture Microdissection Applied to Human Pathophysiology		SC09185
Livingston, David	Gene Expression Analysis of Prostate and Lung Cancer	CA-98-027	CA84995
Lizardi, Paul	Messenger RNA Profiling by Single Molecule Counting	PAR-98-067	CA81671
Ma, Haiching	Prostate Cancer Chip		CA97844
Malins, Donald	FT-IR/GC-MS Models for Predicting Prostate Cancer		CA79690
Marks, James	Project 4: Antibody Gene Diversity Libraries and Phage Display to Generate Recombinant Human Antibodies for Prostate Cancer Therapy	PAR-99-167	CA89520-Sub-04
Mason, Ralph	MR Measurement of Tumor pH, pO2, and Vascularity In Vivo		CA79515
McDonnell, Timothy	Project 3: Therapeutic Modulation of Apoptosis in Prostate Cancer Patients	PAR-99-167	CA90270-Sub-03
Mercola, Dan	Characterization of Early Stage Prostate Cancer	CA-98-027	CA84998
Michalopoulos, George	Molecular Reclassification of Prostatic Cancer	CA-98-027	CA88110
Morton, Ronald	E-Cadherin—Marker of Prostate Cancer Progression		CA74290
Mueller, Elisabetta	PPAR as a Target of Therapy for Prostate Cancer	PAR-99-167	CA90381-Sub-02
Ophir, Jonathan	Elastography: Clinical and Basic Science		CA64597
Ornstein, David K	Proteomic Study of Androgen Independent Prostate Cancer	PA-01-010	CA93759
Pandolfi, Pier Paolo	Molecular Analysis of Carcinogenesis in the Mouse and Human Prostate	PAR-99-167	CA92629-Sub-02
Parkos, Charles	Phage Display and Prostate Neoplasia Progression	PAR-99-102	CA91435
Pasqualini, Renata	Project 2: Targeting Prostate Cancer Bone Metastasis	PAR-99-167	CA90270-Sub-02
Piwnica-Worms, David	Molecular Imaging Center Planning Grant		CA86251
Rao, Chandra	Analysis of Circulating Cancer Cells Early in Disease	PAR-99-101	CA83598
Reiter, Robert	Prostate Stem Cell Antigen (PSCA) in the Biology and Therapy of Prostate Cancer	PAR-99-167	CA92131-Sub-01
Ross, Jeffrey	Human RNA Binding Protein as a Cancer Marker	PA-01-010	CA94082
Roy-Burman, Pradip	Pathogenesis of Human Prostate Carcinomas		CA59705
Sanghvi, Narendra	Quantitative Imaging and Treatment with Focused Ultrasound		CA83244
Sawyers, Charles	Targeted Therapy of PTEN Null Prostate Cancer	PAR-99-167	CA92131-Sub-02
Sellers, William	Single Nucleotide Repeat Polymorphism Analysis of Recurrent Prostate Cancer after Radiation Therapy	PAR-99-167	CA90381-Sub-03

Table B-21 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Shreve, Paul	C11 Acetate PET Imaging of Prostate and Renal Cancer		CA89448
Skelton, Timothy	Decoding Cancer Signature Glycoforms of Serum Tumor Mark	PAR-00-025	CA89730
Smith, Steven	DNA Methylation in Early Detection of Prostate Cancer	PAR-00-025	CA91234
Soff, Gerald	Project 3: Generation of, and Angiostatin Levels in, Prostate Cancer	PAR-99-167	CA90386-Sub-03
Stampfer, Meir J	Growth Factors and Prostate Cancer Risk		CA90598
Strom, Sara	Project 5: Clinical, Epidemiological, and Molecular Markers of Prostate Cancer Progression	PAR-99-167	CA90270-Sub-05
Thomas, Richard	Flow Cytometry of Nuclear Volume/Tumor Marker Expression		CA88530
Uhr, Jonathan	Early Detection/Characterization of Tumor Cells in Blood		CA78303
Van Dort, Marcian	Novel Radiotracers for Androgen Receptor Imaging		CA77287
Vigneron, Daniel	Metabolic Imaging of the Prostate Using 3D MRSI		CA59897
Volkert, Wynn	Center for Single Photo Emitting Cancer Imaging Agents	CA-99-002	CA86290
Wang, Zhou	Project 2: Suppressive Role of Androgen-Response Gene Calreticulin in Prostate Cancer	PAR-99-167	CA90386-Sub-02
Welch, Michael	Research Resource in Radionuclide Research		CA86307
Wheeler, Thomas	Project 1: Markers of Progression and Metastasis	PAR-00-087	CA58204-Sub-01
Windle, Bradford	hTERT Expression as a Marker for Early Cancer Detection	PA-98-022	CA90240
Xu, Jiangchun	Novel Markers for Prostate Cancer Diagnosis/Prognosis		CA80518
Yamamoto, Keith	Project 1: Mechanisms of Hormone Resistance in Prostate Cancer	PAR-99-167	CA89520-Sub-01
Yang, Catherine	Proteolytic Activity of Prostate Specific Antigen		CA89162
Ying, Shao-Yao	Novel Molecular Profiling of Prostate Cancer Signatures		CA85722
Young, Charles	Human Kallikreins as Novel Markers of Prostate Cancer	PAR-99-167	CA91956-Sub-02
Young, Charles	Novel Markers for Prostate Cancer		CA70892
Zagzebski, James	Accurate In Vivo Ultrasonic Scattering Assessments		CA39224
Zhao, Yingming	Identification of Prostate and Ovarian Cancer Markers	CA-98-028	CA85146

Table B-22
NCI Projects Supported in 2002 Addressing the PRG Priority: How should prognostic markers be validated?

Principal Investigator	Title	RFA or PA	Project ID
Aronson, William	The Role of Quantity and Composition of Dietary Fat in the Prevention of Prostate Cancer	PAR-99-167	CA92131-Sub-05
Balk, Steven	The Androgen Receptor in Hormone Refractory Disease	PAR-99-167	CA90381-Sub-05
Beach, Kirk	Tissue Pulsatility Imaging for Cancer Detection		CO07118
Brown, Patrick	A Cancer Taxonomy Based on Gene Expression Patterns	CA-98-027	CA85129
Carter, H Ballentine	Project 6: Longitudinal Studies of Men with and without Prostate Cancer	CA-94-031	CA58236-Sub-06
Ellis, William	Genomic and Gene Expression Profiling of Disseminated Prostate Cancer	PAR-00-087	CA97186-Sub-02
El-Zein, Randa	Molecular Biomarkers for Prostate Cancer Susceptibility		CA88301
Etzioni, Ruth	Statistical Methods for Prostate Cancer Research		CA70227
Gann, Peter	Project 5: Clinical Trial on Lycopene	PAR-99-167	CA90386-Sub-05
Giovannucci, Edward	Genetic and Serologic Determinants of Prostate Cancer Risk and Progression	PAR-99-167	CA90381-Sub-01
Golub, Todd	Genomic Expression Analysis of Tumors after Radical Prostatectomy	PAR-99-167	CA90381-Sub-04
Griffith, Jeffrey	Prognostic Value of Telomere DNA in Prostate Biopsy	PAR-99-102	CA86136
Hood, Leroy	Transcriptome and Proteome Stratification of Prostate Adenocarcinoma Phenotypes	PAR-00-087	CA97186-Sub-04
Jenkins, Robert	Biologic and Clinical Studies of Overrepresented 8q24 Region Associated with Prostate Cancer Progression	PAR-99-167	CA91956-Sub-03
Kattan, Michael	Natural History of Prostate Cancer, Prognostic Models, and Decision Making	PAR-99-167	CA92629-Sub-01
Kung, Hsing-Jien	ErbB Kinase Activation and Transformation		CA39207
Lee, Chung	Project 1: Clusterin as a Negative Prognostic Indicator in Prostate Cancer	PAR-99-167	CA90386-Sub-01
McDonnell, Timothy	Project 3: Therapeutic Modulation of Apoptosis in Prostate Cancer Patients	PAR-99-167	CA90270-Sub-03
Mercola, Dan	Characterization of Early Stage Prostate Cancer	CA-98-027	CA84998
Michalopoulos, George	Molecular Reclassification of Prostatic Cancer	CA-98-027	CA88110
Mueller, Elisabetta	PPAR as a Target of Therapy for Prostate Cancer	PAR-99-167	CA90381-Sub-02
Pandolfi, Pier Paolo	Molecular Analysis of Carcinogenesis in the Mouse and Human Prostate	PAR-99-167	CA92629-Sub-02
Sawyers, Charles	Targeted Therapy of PTEN Null Prostate Cancer	PAR-99-167	CA92131-Sub-02
Sellers, William	Single Nucleotide Repeat Polymorphism Analysis of Recurrent Prostate Cancer after Radiation Therapy	PAR-99-167	CA90381-Sub-03
Soff, Gerald	Project 3: Generation of, and Angiostatin Levels in, Prostate Cancer	PAR-99-167	CA90386-Sub-03
Stanford, Jean	Molecular Predictors of Prostate Cancer Progression and Mortality	PAR-00-087	CA97186-Sub-01
Stein, Cy A	Orthogonal Strategies for Specific Knockout Production		CA91058
Young, Charles	Human Kallikreins as Novel Markers of Prostate Cancer	PAR-99-167	CA91956-Sub-02
Young, Charles	Novel Markers for Prostate Cancer		CA70892

Table B-23

NCI Projects Supported in 2002 Addressing the PRG Priority: What biologic determinants characterize the growth rate and/or tumor-doubling time during the progression of prostate cancer?

Principal Investigator	Title	RFA or PA	Project ID
Beach, Kirk	Tissue Pulsatility Imaging for Cancer Detection		CO07118
Brown, Patrick	A Cancer Taxonomy Based on Gene Expression Patterns	CA-98-027	CA85129
Chakrabarti, Ratna	Molecular Markers for Prostate Cancer	PA-98-022	CA81329
Cheng, Leo	Characterization of Prostate Cancer with HRMAS 1HMRS	PA-98-022	CA80901
Fisher, Paul	Novel Prostate Cancer Gene and Monoclonal Antibody		CA74468
Giovannucci, Edward	Genetic and Serologic Determinants of Prostate Cancer Risk and Progression	PAR-99-167	CA90381-Sub-01
Glode, L	Molecular Markers for Prostate Cancer Detection		CA81073
Heeb, Mary	Forms of Prostate Specific Antigen and HK2 in Cancer		CA59979
Jenkins, Robert	Biologic and Clinical Studies of Overrepresented 8q24 Region Associated with Prostate Cancer Progression	PAR-99-167	CA91956-Sub-03
Kung, Hsing-Jien	ErbB Kinase Activation and Transformation		CA39207
Mason, Ralph	MR Measurement of Tumor pH, pO2, and Vascularity In Vivo		CA79515
McDonnell, Timothy	Project 3: Therapeutic Modulation of Apoptosis in Prostate Cancer Patients	PAR-99-167	CA90270-Sub-03
Mercola, Dan	Characterization of Early Stage Prostate Cancer	CA-98-027	CA84998
Michalopoulos, George	Molecular Reclassification of Prostatic Cancer	CA-98-027	CA88110
Morton, Ronald	E-Cadherin—Marker of Prostate Cancer Progression		CA74290
Pretlow, Thomas	Cytogenetics and Biochemistry of Prostate Cancer		CA57179
Thomas, Richard	Flow Cytometry of Nuclear Volume/Tumor Marker Expression		CA88530
Uhr, Jonathan	Early Detection/Characterization of Tumor Cells in Blood		CA78303
Windle, Bradford	hTERT Expression as a Marker for Early Cancer Detection	PA-98-022	CA90240

Table B-24

NCI Projects Supported in 2002 Addressing the PRG Priority: Does early detection change mortality from prostate cancer?

Principal Investigator	Title	RFA or PA	Project ID
Beach, Kirk	Tissue Pulsatility Imaging for Cancer Detection		CO07118
Etzioni, Ruth	PSA Screening and U.S. Prostate Cancer Trends	CA-99-013	CA88160
Griffith, Jeffrey	Prognostic Value of Telomere DNA in Prostate Biopsy	PAR-99-102	CA86136
Kattan, Michael	Natural History of Prostate Cancer, Prognostic Models, and Decision Making	PAR-99-167	CA92629-Sub-01
Morton, Ronald	E-Cadherin—Marker of Prostate Cancer Progression		CA74290
Rhoads, George	PSA Screening and Prostate Cancer Mortality		CA71734
Tsodikov, Alexander	Survival Effects of Prostate Cancer Surveillance	CA-02-010	CA97414
Young, Charles	Novel Markers for Prostate Cancer		CA70892

Table B-25

NCI Projects Supported in 2002 Addressing the PRG Priority: What are the effects of early detection on morbidity and quality of life?

Principal Investigator	Title	RFA or PA	Project ID
Etzioni, Ruth	PSA Screening and U.S. Prostate Cancer Trends	CA-99-013	CA88160
Rhoads, George	PSA Screening and Prostate Cancer Mortality		CA71734

Table B-26
Additional NCI Projects Supported in 2002 in Early Detection, Diagnosis, and Prognosis

Principal Investigator	Title	RFA or PA	Project ID
Alam, Sheikh	Diagnostic Freehand Elastographic Imaging of Cancer	PA-98-008	CA84274
Chance, Britton	2 and 3D Imaging of Contrast Agents in Animal Models		CA72895
Degrado, Timothy R	Automated Synthesis of F-18 Fluorocholine	PAR-00-090	CA94387
Difilippo, Frank	Improved Medium-Energy and High-Energy SPECT		CA88373
Frederickson, Christopher J	Zinc-Based Diagnostic for Prostate Cancer		CA96354
Gambhir, Sanjiv	UCLA Imaging Resource for Mouse Cancer Models	CA-01-012	CA92865
Giusti, Ruthann	Israeli Prostate Cancer		CP10144-Sub-08185
Gmitro, Arthur F	Confocal Microendoscope for In Vivo Molecular Imaging	PAR-00-089	CA94287
Gunter, Donald	Prostate Gamma Probe		CA90149
Haas, Gabriel P	Postmortem PSA: Role in Epidemiology of Prostate Cancer	PA-01-021	CA97751
Hainfeld, James F	Improved MRI Contrast Agents		CA94495
Henrichs, P Mark	Optoacoustic Rectal Probe for Prostate Cancer Imaging		CA96153
Kurhanewicz, John	Improved MRI/MRSI for Biopsy Guidance of Prostate Cancer	CA-99-015	CA88214
Mourant, Judith	Light Scattering and Normal Tissue Models		CA71898
Piwnica-Worms, David R	Washington University Molecular Imaging Center	CA-01-014	CA94056
Sommer, F	Precise MRI Directed Sonic Ablation of Prostate Cancer	CA-99-015	CA88205
Stoianovici, Dan	Multi-Imager Compatible Robot for Prostate Access	PAR-00-089	CA88232
Taylor, John-Stephen	Nucleic Acid Triggered Prodrug and Probe Activation		CA92477
Watabe, Kounosuke	Tumor Metastasis Suppressor Gene on Human Chromosome 16		CA79473
Zipfel, Warren R	Nonlinear Intrinsic Microspectroscopy of Cancer	PAR-00-089	CA94311

FY 2002 Scientific Model Systems Projects

Table B-27

NCI Projects Supported in 2002 Addressing the PRG Priority: Can models be designed to display the carcinogenic characteristics of human prostate cancer (i.e., genetics, host–tumor interactions, microenvironment, angiogenesis, and progression)? Importantly, can models that mimic bone marrow metastases be developed?

Principal Investigator	Title	RFA or PA	Project ID
Abate-Shen, Cory	A Mouse Model for Prostate Cancer	CA-98-013	CA84294
Abdulkadir, Sarki A	Modeling Prostate Cancer by Conditional Gene Targeting		CA94858
Agus, David	The Role of the Her-Kinase Axis in Emergence of Androgen Independence in Human Prostate Cancer	PAR-99-167	CA92131-Sub-04
Balk, Steven	The Androgen Receptor in Hormone Refractory Disease	PAR-99-167	CA90381-Sub-05
Balmain, Allan	Project 5: Identification of Prostate Tumor Susceptibility Genes Using Mouse Models for Prostate Cancer	PAR-99-167	CA89520-Sub-05
Borgstrom, Per	VEGF and Prostate Cancer Angiogenesis		CA79004
Chen, Ching-Shih	Testing of Novel Apoptotic Agents in Prostate Cancer	PA-99-081	CA92307
Clohisy, Denis	Bone Cancer and Skeletal Pain		CA90434
Cohen, Pinchas	Interactions between IGFBPs and Nuclear Receptors in Prostate Cancer	PAR-99-167	CA92131-Sub-03
Gleave, Martin	Characterization of Anti-Apoptotic Genes Induced during Androgen Independent Progression and Chemotherapy	PAR-00-087	CA97186-Sub-03
Glinsky, Gennadi	Transcriptome of Metastatic Prostate Cancer		CA89827
Greenberg, Norman	Androgen Independent Prostate Cancer—A Transgenic Model		CA73747
Greenberg, Norman	KGF in Prostate Cancer—A Transgenic Animal Model		CA64851
Greenberg, Norman	Project 6: Prostate-Specific Gene Expression in Transgenic Animals	PAR-00-087	CA58204-Sub-06
Hay, Nissim	PI3K/PTEN/Akt (PKB), Signaling, and Genesis of Cancer		CA90764
Hayward, Simon	Hormonal Carcinogenesis in Rb-Knockout Mouse Prostate		CA96403
Kraft, Andrew	Regulation of Prostate Cancer Programmed Cell Death		CA78631
Languino, Lucia	Integrin Signaling Pathways in Prostate Cancer	PA-99-081	CA89720
Matusik, Robert	Transgenic Mouse Model for Prostate Cancer		CA76142
McKeon, Frank	Murine p73 in Tumorigenesis		CA75340
Mundy, Gregory	Tumors' Effects on the Skeleton		CA40035
Muschel, Ruth	Molecular Mechanisms of Metastasis		CA46830
Norris, James	Induction and Analysis of Prostate Cancer		CA69598
Pandolfi, Pier Paolo	Molecular Analysis of Carcinogenesis in the Mouse and Human Prostate	PAR-99-167	CA92629-Sub-02
Parsons, Ramon	PTEN Tumor Suppressor and Signal Transduction		CA82783
Petros, John A	Mitochondrial DNA in Mutations in Prostate Cancer		CA96994
Pienta, Kenneth	Project 5: Inhibition of Human Prostate Cancer Metastasis	CA-94-031	CA69568-Sub-05

Table B-28

NCI Projects Supported in 2002 Addressing the PRG Priority: Can models be designed to display the hormone responsiveness of human prostate cancer and its progression to hormone independence?

Principal Investigator	Title	RFA or PA	Project ID
Abate-Shen, Cory	A Mouse Model for Prostate Cancer	CA-98-013	CA84294
Balk, Steven	The Androgen Receptor in Hormone Refractory Disease	PAR-99-167	CA90381-Sub-05
Bosland, Maarten	Hormonal Induction Animal Model of Prostate Cancer		CA75293
Brodie, Angela	Androgen Synthesis Inhibitors for Prostate Cancer		CA27440
Gleave, Martin	Characterization of Anti-Apoptotic Genes Induced during Androgen Independent Progression and Chemotherapy	PAR-00-087	CA97186-Sub-03
Hayward, Simon	Hormonal Carcinogenesis in Rb-Knockout Mouse Prostate		CA96403
Ho, Shuk-Mei	Prostatic Differentiation and Sex Hormone Metabolism		CA15776
Hochberg, Richard	Biologically Active Steroid Analogs		CA37799
Sanda, Martin	Modulating Tolerance for Prostate Cancer Antigen Vaccine		CA82419
Wang, Zhou	Project 2: Suppressive Role of Androgen-Response Gene Calreticulin in Prostate Cancer	PAR-99-167	CA90386-Sub-02

Table B-29

NCI Projects Supported in 2002 Addressing the PRG Priority: Can laboratory models be used to screen potential chemotherapeutic agents, clarify dose / response relationships, and understand chemotherapy resistance and mechanisms of therapeutic response?

Principal Investigator	Title	RFA or PA	Project ID
Agus, David	The Role of the Her-Kinase Axis in Emergence of Androgen Independence in Human Prostate Cancer	PAR-99-167	CA92131-Sub-04
Brodie, Angela	Androgen Synthesis Inhibitors for Prostate Cancer		CA27440
Chang, Esther H	Targeting Stealth Liposome for Cancer Gene Therapy		CA91660
Cohen, Pinchas	Interactions between IGFBPs and Nuclear Receptors in Prostate Cancer	PAR-99-167	CA92131-Sub-03
Davidson, Bradley	New Antimicrotubule Agents from Marine Organisms		CA81388
Day, Billy	Validation and Optimization of Tubulin Targeted Drugs		CA88833
Figg, William D	Development of Pharmacokinetic Models to Characterize the Disposition of New Anticancer Agents		SC06537
Gleave, Martin	Characterization of Anti-Apoptotic Genes Induced during Androgen Independent Progression and Chemotherapy	PAR-00-087	CA97186-Sub-03
Jones, Terence	Peptide Antagonists of Urokinase Plasminogen Activator	CA-98-022	CA86150
Kadmon, Dov	Project 4: Biological Therapy for Prostate Cancer	PAR-00-087	CA58204-Sub-04
Lazo, John	Combinatorial Approaches for Novel Anticancer Agents	CA-97-006	CA78039
Lee, Yue-Wei	SAR of Novel Topo I Inhibitor against Prostate Cancer		CA81002
McCormick, David L	Efficacy Studies of Chemopreventive Agents		CN95113
McCormick, David	Efficacy Studies of Chemopreventive Agents in Animal Models, WS 94		CN25017
McDonnell, Timothy	Project 3: Therapeutic Modulation of Apoptosis in Prostate Cancer Patients	PAR-99-167	CA90270-Sub-03
Mueller, Elisabetta	PPAR as a Target of Therapy for Prostate Cancer	PAR-99-167	CA90381-Sub-02
Needham, David	Thermally Sensitive Drug Delivery System for Tumors		CA87630
Nelson, William	Project 9: Mechanisms of Sensitivity and Drug Resistance in Prostate Cancer	CA-94-031	CA58236-Sub-09
Ratliff, Timothy	Host/Tumor Interactions in Immunotherapy of Prostate Cancer	PA-99-081	CA89062
Sherman, David	Combinatorial Creation of New Anticancer Agents	CA-98-009	CA83155
Thompson, Timothy	Project 5: Gene Therapy for Prostate Cancer	PAR-00-087	CA58204-Sub-05
Von Hoff, Daniel	Novel A Ring and E Ring Modified Camptothecin Analogs		CA76563
Wientjes, M	Intraprostatic Doxorubicin Therapy	PA-92-27	CA74179
Yang, Meng	GFP Imaging for In Vivo High-Throughput Drug Screening	PAR-00-030	CA89779

Table B-30

NCI Projects Supported in 2002 Addressing the PRG Priority: Can models be used to test novel therapeutic approaches (e.g., cancer vaccines, gene therapy, and immunological therapies)?

Principal Investigator	Title	RFA or PA	Project ID
Abrams, Scott	Host Immune Responses to Human Carcinoma Antigens Induced by Peptide Vaccines		BC09029
Beer, Tomasz	Pulse Calcitriol for Prostate Cancer Prevention	PA-98-042	CA82504
Borgstrom, Per	VEGF and Prostate Cancer Angiogenesis		CA79004
Chatta, Gurkamal	Immunologic Therapy of Prostate Cancer		CA76033
Chung, Leland	Ad-OC-TK/Val Gene Therapy Clinical Correlates		CA85555
Dahut, William L	The Evaluation of Novel Therapeutics for Genitourinary Malignancies		SC10098
Denardo, Gerald	Synergistic Multimodality Antibody Therapy		CA47829
Donovan, Gerald P	Development of PSMA-Based Vaccines for Prostate Cancer		CA91746
Feldman, David	Androgen-Independent Prostate Cancer: Mechanisms and Treatment	PA-99-081	CA92238
Frelinger, John	Targeted CTL Mediated Immunity for Prostate Cancer		CA70218
Gardner, Jason P	Alphavirus Prime-Boost Vaccines for Prostate Cancer	PA-01-091	CA95928
Green, Jeffrey E	Transgenic Models for Prostate and Breast Cancer		BC05740
Houghton, Alan	The Development of DNA Vaccines against Prostate Cancer with PSMA as a Target	PAR-99-167	CA92629-Sub-03
Kasahara, Noriyuki	Cellular Transduction by Retrotransposon-Adenovirus Hybrid Vector		CA93709
Lee, Chung	Clusterin—An Anti-Apoptotic Mediator in Prostate Cancer		CA80953
Margalit, Ruth	Development of Novel Adenovirus-Lentivirus Hybrid Vector		CA96410
McCormick, Frank	Project 3: Viral Therapy for Prostate Cancer	PAR-99-167	CA89520-Sub-03
McDonnell, Timothy	Project 3: Therapeutic Modulation of Apoptosis in Prostate Cancer Patients	PAR-99-167	CA90270-Sub-03
Morris, John	Gene Therapy of Prostate Cancer Using Radioiodine	PAR-99-167	CA91956-Sub-06
Pardoll, Drew	Project 10: Transgenic Models of Prostatic Cancer and Autoimmunity	CA-94-031	CA58236-Sub-10
Pastan, Ira	Immunotoxin Therapy of Solid and Hematopoietic Tumors: Preclinical Studies		BC08753
Peace, David	A Pilot Phase Ib Trial of a PSA Peptide Vaccine	PA-99-070	CA88062
Pretlow, Thomas	Cytogenetics and Biochemistry of Prostate Cancer		CA57179
Ratliff, Timothy L	Enhancement of Gene Transfer and Prostate Cancer Immunity		CA96691
Reiter, Robert	Prostate Stem Cell Antigen (PSCA) in the Biology and Therapy of Prostate Cancer	PAR-99-167	CA92131-Sub-01
Sanda, Martin	Modulating Tolerance for Prostate Cancer Antigen Vaccine		CA82419
Schlom, Jeffrey	Cytokines as Biologic Adjuvants		BC10428
Schlom, Jeffrey	Design and Development of Novel Immunotherapeutics and Strategies for Cancer Immunotherapy		BC05190

Table B-30 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Schlom, Jeffrey	Development of Vaccines and Vaccine Strategies for Human Cancer		BC10425
Schlom, Jeffrey	Mechanism of Human T-Cell Activation		BC10427
Schlom, Jeffrey	Novel Recombinant Immunoglobulin Forms for Cancer Therapy and Diagnosis		BC10429
Schlom, Jeffrey	T-Cell Costimulation in the Design of Cancer Vaccines		BC10426
Small, Eric	Project 6: Anti-CTLA4 Antibody Immunologic Therapy for Prostate Cancer	PAR-99-167	CA89520-Sub-06
Thompson, Timothy	Project 5: Gene Therapy for Prostate Cancer	PAR-00-087	CA58204-Sub-05
Uhr, Jonathan	Early Detection/Characterization of Tumor Cells in Blood		CA78303
Vile, Richard	Use of Fusogenic Membrane Glycoproteins for Gene Therapy of Prostate Cancer	PAR-99-167	CA91956-Sub-05
Zanetti, Maurizio	Targeted Therapeutic Vaccination in Prostate Cancer		CA84062

Table B-31

Additional NCI Scientific Models Research Projects Supported in 2002

Principal Investigator	Title	RFA or PA	Project ID
Felton, James S	Carcinogenic Significance of Heterocyclic Amines		CA55861
Gambhir, Sanjiv	UCLA Imaging Resource for Mouse Cancer Models	CA-01-012	CA92865
Greenberg, Norman	Transgenic Mouse Models of Prostate Cancer	CA-98-013	CA84296

FY 2002 Treatment Projects

Table B-32

NCI Projects Supported in 2002 Addressing the PRG Priority: What new technologies can detect clinically significant metastases prior to treatment? What is the clinical significance of circulating prostate cells detected by molecular techniques and their relationship to treatment failure and metastases?

Principal Investigator	Title	RFA or PA	Project ID
Beitz, Alvin J	In Vivo Analysis of Tumor Peptide Secretion	PAR-01-106	CA86330
Cheng, Leo	Characterization of Prostate Cancer with HRMAS 1HMRS	PA-98-022	CA80901
Dahl, Thomas	Automated Microscopy for Rare Cancer Cell Detection		CA94454
Ellis, William	Genomic and Gene Expression Profiling of Disseminated Prostate Cancer	PAR-00-087	CA97186-Sub-02
Gallagher, Robert	Arsenic Trioxide in Advanced Prostate Cancer	PA-99-070	CA86794
Ganju-Krishan, Awtar T	Flow Cytometry to Detect Human Tumor Cells in Body Fluid		CA97335
Gerald, William	Molecular Classification of Prostate Cancer	CA-98-027	CA84999
Karczmar, Gregory S	High Spectral and Spatial Resolution MRI of Rodent Tumors	PA-01-030	CA89408
Kattan, Michael	Natural History of Prostate Cancer, Prognostic Models, and Decision Making	PAR-99-167	CA92629-Sub-01
Livingston, David	Gene Expression Analysis of Prostate and Lung Cancer	CA-98-027	CA84995
Mason, Ralph	MR Measurement of Tumor pH, pO2, and Vascularity In Vivo		CA79515
Morton, Ronald	E-Cadherin—Marker of Prostate Cancer Progression		CA74290
Pretlow, Thomas	Cytogenetics and Biochemistry of Prostate Cancer		CA57179
Rao, Chandra	Analysis of Circulating Cancer Cells Early in Disease	PAR-99-101	CA83598
Uhr, Jonathan	Early Detection/Characterization of Tumor Cells in Blood		CA78303
Windle, Bradford	hTERT Expression as a Marker for Early Cancer Detection	PA-98-022	CA90240
Woodson, Karen	Gene Methylation in Prostate Cancer		BC10459
Young, Charles	Novel Markers for Prostate Cancer		CA70892

Table B-33

NCI Projects Supported in 2002 Addressing the PRG Priority: What technologies (e.g., new, irradiation therapy and localization techniques) can be developed to decrease morbidity and enhance efficacy of therapy for the primary tumor?

Principal Investigator	Title	RFA or PA	Project ID
Ahmed, Mansoor	EGR-1 and Apoptosis in Prostate Cancer		CA78471
Bischof, John	Establishment of Mechanisms of Cryodestruction		CA75284
Blasberg, Ronald	MSKCC Center for In Vivo Molecular Imaging in Cancer	CA-99-004	CA86438
Burdette, Everette	Real-Time Robotic Image-Guided Prostate Brachytherapy	PAR-99-149	CA88139
Camphausen, Kevin	The Synergy between Radiotherapy and Angiogenesis Inhibitors		SC10373
Cetas, Thomas	Dosimetric Markers for Image Guided Radiation Therapy		CA91039
Cho, Paul	Seed Localizer for Image Guided Prostate Brachytherapy	PA-98-008	CA89061
Dahut, William L	The Evaluation of Novel Therapeutics for Genitourinary Malignancies		SC10098
Deasy, Joseph	Intensity Modulated Radiotherapy—Computational Studies		CA85181
Denardo, Gerald	Synergistic Multimodality Antibody Therapy		CA47829
Dent, Paul	Carcinoma Cell Radiosensitization by MAPK Inhibition		CA88906
DeWeese, Theodore	Project 14: Determinants of Radiosensitivity in Prostate Cancer	CA-94-031	CA58236-Sub-14
Duerk, Jeffrey	IMRI/SPECT Guided Prostate Cancer Biopsy and Therapy	CA-99-015	CA88144
Dumoulin, Charles	MR Guided Focused Ultrasound Ablation of Prostate Cancer	CA-99-015	CA88102
Duncan, James	Automatic Image Registration for Prostate Radiotherapy	PAR-99-009	CA80894
Epstein, Alan	TNT Imaging to Monitor the Efficacy of Cancer Therapy	CA-98-024	CA83001
Ettinger, Gil	Dynamic Dosimetry Planning for Ultrasound Brachytherapy		CA88378
Feleppa, Ernest	Novel Ultrasonic Imaging of Brachytherapy Seeds		CA88231
Fidler, Isiah	Project 1: The Biology of Human Prostate Cancer Metastasis	PAR-99-167	CA90270-Sub-01
Freytag, Svend	Combined Suicide Gene Therapy/Radiotherapy for Cancer		CA75456
Gudkov, Andrei	Stress Induced Bystander Effect in Cancer Treatment		CA88071
Hahn, Stephen	Phase I Trial of PDT in Patients with Prostate Carcinoma	PA-99-070	CA88064
Hasan, Tayyaba	Physical and Biological Determinants for Optimal PDT		CA84203
Hasegawa, Bruce	Improved Prostate Cancer Staging with Dual Mode Imaging	PA-98-008	CA86893
Jankun, Jerzy	Computer Directed Photodynamic Therapy of Prostate Cancer		CA90524
King, Ivan	Bacterial Gene Delivery Vectors for Cancer Therapy		CA77963
Koch, Tad	New Drugs Targeted to Metastatic Cancer and Angiogenesis		CA92107
Kurhanewicz, John	Improved MRI/MRSI for Biopsy Guidance of Prostate Cancer	CA-99-015	CA88214
Kurhanewicz, John	Metabolic Studies of Response to Prostate Cancer Therapy		CA64667
Kurhanewicz, John	Monitoring Radiation Therapy of Prostate Cancer by MRSI		CA79980
Lasser, Marvin E	Speckle-Free Attenuation Ultrasound Prostate Imaging		CA96149
Lattanzi, Joseph	Ultrasound Image Guided Stereotactic Navigational System	CA-99-015	CA88337

Table B-33 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Lee, Chung	Project 1: Clusterin as a Negative Prognostic Indicator in Prostate Cancer	PAR-99-167	CA90386-Sub-01
Line, Bruce	Diagnostic Imaging and Guide Therapy in Prostate Cancer	CA-99-015	CA91770
Ling, Clifton	3D Conformal Radiation Therapy		CA59017
Lizzi, Frederic	Integrated Ultrasonic Systems for Noninvasive Therapy	PAS-00-006	CA84588
Mason, Ralph	MR Measurement of Tumor pH, pO2 and Vascularity In Vivo		CA79515
McCormick, Frank	Project 3: Viral Therapy for Prostate Cancer	PAR-99-167	CA89520-Sub-03
McDonnell, Timothy	Project 3: Therapeutic Modulation of Apoptosis in Prostate Cancer Patients	PAR-99-167	CA90270-Sub-03
McNichols, Roger	Interactive Image Guided Closed Loop Thermal Therapy		CA79282
McVary, Kevin	Project 4: Molecular Mechanisms of Neuropathic Erectile Dysfunction	PAR-99-167	CA90386-Sub-04
Mehta, Minesh	Improving Cancer Outcome—Adaptive Helical Tomotherapy		CA88960
Mitchell, James B	Modulation of Therapeutic Response		SC06321
Nakaar, Valerian	Potentiating the Anti-Tumor Activity of Salmonella		CA94699
Needham, David	Thermally Sensitive Drug Delivery System for Tumors		CA87630
Oleinick, Nancy	Phototherapy of Prostate Cancer—Pro and Anti Apoptosis		CA83917
Peng, Yongren	Production of Y-90 Microspheres for Radiation Therapy		CA79225
Peng, Yongren	Timed-Bioresorbable Radioseeds for Prostate Cancer		CA86567
Piwnica-Worms, David R	Washington University Molecular Imaging Center	CA-01-014	CA94056
Pizer, Stephen M	Medical Image Presentation: Structural Image Analysis		CA47982
Pogue, Brian	Oxygen Dosimetry in Photodynamic Therapy		CA78734
Samant, Sanjiv	KCD Based System for Megavoltage Portal Imaging		CA76061
Sanghvi, Narendra	High Intensity Ultrasound for Prostate Treatment		CA81340
Sanghvi, Narendra	Quantitative Imaging and Treatment with Focused Ultrasound		CA83244
Sawyers, Charles	Targeted Therapy of PTEN Null Prostate Cancer	PAR-99-167	CA92131-Sub-02
Saxena, Indu	Fiber Temperature Sensor for Hyperthermia Treatment		CA78114
Schneiderman, Martin	Tumor-Targeted Radiosensitizers in Cancer Therapy		CA72411
Schultheiss, Timothy	Normal Tissue Dose Volume Response in Radiation Therapy		CA73766
Sioshansi, Piran	Linear PD Sources for Prostate Brachytherapy		CA78005
Sommer, F	Precise MRI Directed Sonic Ablation of Prostate Cancer	CA-99-015	CA88205
Sommer, F	Prostate Cancer and BPH Ablation Using HIFU Waveguide	PA-98-008	CA79931
Sterzer, Fred	Microwave Treatment of Localized Prostate Cancer		CA86656
Thompson, Timothy	Project 5: Gene Therapy for Prostate Cancer	PAR-00-087	CA58204-Sub-05
Thornton, Kenneth	Dynamic Prostate Brachytherapy		CA88150

Table B-33 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Vaughn, James	Improving ErbB2 Antisense Efficacy for Cancer Therapy		CA83953
Vigneron, Daniel	Metabolic Imaging of the Prostate Using 3D MRSI		CA59897
Welch, Michael	Research Resource in Radionuclide Research		CA86307
Wientjes, M	Intraprostatic Doxorubicin Therapy	PA92-27	CA74179
Williamson, Jeffrey	Brachytherapy Dosimetry Using Plastic Scintillator		CA57222
Williamson, Jeffrey	Heterogeneity Corrections in Brachytherapy Dosimetry		CA46640
Woynarowska, Barbara	DNA Damaging Agents and Apoptosis in Prostate Cancer		CA78706
Wu, Ed	Sodium MRI for Assessing Early Chemotherapy Response	PA-98-008	CA85594
Yan, Di	Adaptive Radiation Therapy		CA71785
Yu, Cedric	Treatment Uncertainty—Implication on Conformal Therapy		CA66075
Yu, Yan	Piper: Prostate Implant Planning Engine for Radiotherapy		CA78115
Zakian, Kristen	Monitoring Chemotherapy in Prostate Cancer by Proton NMR	PA-98-042	CA84258
Zheng, Gang	Photodynamic Therapy for Prostate Cancer	PAR-01-045	CA95330
Zipfel, Warren R	Nonlinear Intrinsic Microspectroscopy of Cancer	PAR-00-089	CA94311

Table B-34

NCI Projects Supported in 2002 Addressing the PRG Priority: What critical features of the primary tumor determine treatment success? What clinical, pathological, and molecular determinants can be used as markers of aggressiveness and "indolent" prostate cancer? How can multiple test results be combined using informatics?

Principal Investigator	Title	RFA or PA	Project ID
Agus, David	The Role of the Her-Kinase Axis in Emergence of Androgen Independence in Human Prostate Cancer	PAR-99-167	CA92131-Sub-04
Camphausen, Kevin	Molecular Imaging of the Proliferating Endothelium		SC10372
Ellis, William	Genomic and Gene Expression Profiling of Disseminated Prostate Cancer	PAR-00-087	CA97186-Sub-02
Emmert-Buck, Michael R	Genetic Progression of Cancer		SC10437
Etzioni, Ruth	PSA Screening and U.S. Prostate Cancer Trends	CA-99-013	CA88160
Etzioni, Ruth	Statistical Methods for Prostate Cancer Research		CA70227
Fidler, Isiah	Project 1: The Biology of Human Prostate Cancer Metastasis	PAR-99-167	CA90270-Sub-01
Gelmann, Edward	Apoptosis in Prostate Cancer		CA79912
Ghosh, Malay	Bayesian Neural Networks for Prostate Cancer Study		CA85414
Golub, Todd	Genomic Expression Analysis of Tumors after Radical Prostatectomy	PAR-99-167	CA90381-Sub-04
Hood, Leroy	Transcriptome and Proteome Stratification of Prostate Adenocarcinoma Phenotypes	PAR-00-087	CA97186-Sub-04
Jiang, Yulei	Neural Network Prediction of Prostate Cancer Progression	PA-01-010	CA97308
Karczmar, Gregory S	High Spectral and Spatial Resolution MRI of Rodent Tumors	PA-01-030	CA89408
Kattan, Michael	Natural History of Prostate Cancer, Prognostic Models, and Decision Making	PAR-99-167	CA92629-Sub-01
King, Jean A	NMR Imaging of Prostate Cancer Using Ligands	PAR-01-101	CA95876
Lee, Chung	Project 1: Clusterin as a Negative Prognostic Indicator in Prostate Cancer	PAR-99-167	CA90386-Sub-01
McDonnell, Timothy	Project 3: Therapeutic Modulation of Apoptosis in Prostate Cancer Patients	PAR-99-167	CA90270-Sub-03
Pandolfi, Pier Paolo	Molecular Analysis of Carcinogenesis in the Mouse and Human Prostate	PAR-99-167	CA92629-Sub-02
Pretlow, Thomas	Cytogenetics and Biochemistry of Prostate Cancer		CA57179
Sawyers, Charles	Targeted Therapy of PTEN Null Prostate Cancer	PAR-99-167	CA92131-Sub-02
Scher, Howard	Mechanism Based Therapy for Prostate Cancer	PAR-99-167	CA92629-Sub-04
Sellers, William	Single Nucleotide Repeat Polymorphism Analysis of Recurrent Prostate Cancer after Radiation Therapy	PAR-99-167	CA90381-Sub-03
Simons, Jonathon	Project 5: Cellular and Molecular Basis of Prostate Metastasis to Bone	CA-94-031	CA58236-Sub-05
Spielman, Daniel	Magnetic Resonance Spectroscopic Neoplasm Imaging		CA48269
Stanford, Janet	NSAIDs and Other Medications in Prostate Cancer Etiology	PA-00-080	CA92579
Wheeler, Thomas	Project 1: Markers of Progression and Metastasis	PAR-00-087	CA58204-Sub-01
Wilson, Michael S	Antibody Microarray for Detection of Tumor Markers		CA96250

Table B-35

NCI Projects Supported in 2002 Addressing the PRG Priority: Which gene therapies, including immunotherapeutic approaches, appear most suitable for localized and systemic prostate cancer treatment?

Principal Investigator	Title	RFA or PA	Project ID
Abrams, Scott	Host Immune Responses to Human Carcinoma Antigens Induced by Peptide Vaccines		BC09029
Allison, James	T Cell Costimulation in Antitumor Responses		CA57986
Banchereau, Jacques	Dendritic Cell Vaccine in Metastatic Prostate Cancer	PA-00-047	CA91556
Celis, Esteban	Immune Based Therapeutic Approach for Prostate Cancer		CA82677
Celis, Esteban	An Immune-Based Therapeutic Approach for Prostate Cancer	PAR-99-167	CA91956-Sub-04
Chang, Esther	Immunoliposome Mediated Gene Therapy for Prostate Cancer		CA80449
Chang, Esther H	Targeting Stealth Liposome for Cancer Gene Therapy		CA91660
Chatterjee, Malaya	HER-2/Neu—A Target for Cancer Immunotherapy		CA91878
Chung, Leland	Ad-OC-TK/Val Gene Therapy Clinical Correlates		CA85555
Dahut, William L	The Evaluation of Novel Therapeutics for Genitourinary Malignancies		SC10098
Disis, Mary	HER2 Vaccination for the Treatment of Cancer		CA85374
Donovan, Gerald P	Development of Anti-PSMA Antibodies for Prostate Cancer		CA92927
Donovan, Gerald P	Development of PSMA-Based Vaccines for Prostate Cancer		CA91746
Donovan, Gerald P	Human Anti-PSMA Antibodies for Prostate Cancer Therapy	PA-01-091	CA96075
Freytag, Svend	Combined Suicide Gene Therapy/Radiotherapy for Cancer		CA75456
Gardner, Jason P	Alphavirus Prime-Boost Vaccines for Prostate Cancer	PA-01-091	CA95928
Gilboa, Eli	Tumor RNA Transfected Dendritic Cell Vaccines		CA85307
Greenberg, Norman	Project 6: Prostate-Specific Gene Expression in Transgenic Animals	PAR-00-087	CA58204-Sub-06
Houghton, Alan	The Development of DNA Vaccines against Prostate Cancer with PSMA as a Target	PAR-99-167	CA92629-Sub-03
Humphreys, Robert	Prostate Cancer Vaccine by Suppressing II Protein		CA85100
Kasahara, Noriyuki	Cellular Transduction by Retrotransposon-Adenovirus Hybrid Vector		CA93709
Lee, Byungkook	Molecular Modeling and Bioinformatics		BC08759
Margalit, Ruth	Development of Novel Adenovirus-Lentivirus Hybrid Vector		CA96410
Margalit, Ruth	Retroviral Vectors for Cancer Gene Therapy		CA91659
McCready, Victor	Radionuclide Therapy of Skeletal Metastases from Cancer	PA-99-070	CA86784
Morris, John	Gene Therapy of Prostate Cancer Using Radioiodine	PAR-99-167	CA91956-Sub-06
Norris, James	Viral Vector CORE Facility	PAR-99-127	CA88163
Pastan, Ira	Immunotoxin Therapy of Solid and Hematopoietic Tumors: Preclinical Studies		BC08753
Peace, David	A Pilot Phase Ib Trial of a PSA Peptide Vaccine	PA-99-070	CA88062
Ratliff, Timothy L	Enhancement of Gene Transfer and Prostate Cancer Immunity		CA96691

Table B-35 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Reiter, Robert	Prostate Stem Cell Antigen (PSCA) in the Biology and Therapy of Prostate Cancer	PAR-99-167	CA92131-Sub-01
Sanda, Martin	Project 6: Vaccinia PSA for Androgen-Modulated, Post-Surgical Recurrence of Prostate Cancer	CA-94-031	CA69568-Sub-06
Schlom, Jeffrey	Cytokines as Biologic Adjuvants		BC10428
Schlom, Jeffrey	Design and Development of Novel Immunotherapeutics and Strategies for Cancer Immunotherapy		BC05190
Schlom, Jeffrey	Development of Vaccines and Vaccine Strategies for Human Cancer		BC10425
Schlom, Jeffrey	Mechanism of Human T-Cell Activation		BC10427
Schlom, Jeffrey	Novel Recombinant Immunoglobulin Forms for Cancer Therapy and Diagnosis		BC10429
Schlom, Jeffrey	T-Cell Costimulation in the Design of Cancer Vaccines		BC10426
Simons, Jonathon	Project 11: Gene Therapy for Human Prostate Cancer	CA-94-031	CA58236-Sub-11
Small, Eric	Project 6: Anti-CTLA4 Antibody Immunologic Therapy for Prostate Cancer	PAR-99-167	CA89520-Sub-06
Thompson, Timothy	Project 5: Gene Therapy for Prostate Cancer	PAR-00-087	CA58204-Sub-05
Topalian, Suzanne L	Specific Immune Recognition of Tumor-Associated Antigens by Human T Cells		SC06664
Vaughn, James	Improving ErbB2 Antisense Efficacy for Cancer Therapy		CA83953
Vieweg, Johannes W	Telomerase RNA Transfected Dendritic Cell Vaccines	PA-99-046	CA93910
Vile, Richard	Use of Fusogenic Membrane Glycoproteins for Gene Therapy of Prostate Cancer	PAR-99-167	CA91956-Sub-05
Zanetti, Maurizio	Targeted Therapeutic Vaccination in Prostate Cancer		CA84062

Table B-36

NCI Projects Supported in 2002 Addressing the PRG Priority: What are the mechanisms associated with resistance to hormone therapy, immunotherapy, radiation, and chemotherapy?

Principal Investigator	Title	RFA or PA	Project ID
Agus, David	The Role of the Her-Kinase Axis in Emergence of Androgen Independence in Human Prostate Cancer	PAR-99-167	CA92131-Sub-04
Balk, Steven	The Androgen Receptor in Hormone Refractory Disease	PAR-99-167	CA90381-Sub-05
Cheng, Yung-Chi	Nucleoside Analogs as Anticancer Compounds		CA63477
Chinnadurai, Govindaswamy	Oncogenesis and Chemoresistance by Bcl-2		CA73803
Dalton, James	Nonsteroidal Affinity Ligands for the Androgen Receptor		CA68096
Frelinger, John	Targeted CTL Mediated Immunity for Prostate Cancer		CA70218
Gleave, Martin	Characterization of Anti-Apoptotic Genes Induced during Androgen Independent Progression and Chemotherapy	PAR-00-087	CA97186-Sub-03
Golde, David	Memorial Sloan-Kettering Cancer Gene Therapy Program		CA59350
Liao, Shutsung	Molecular Mechanisms of Growth Control—Prostate Cancer		CA58073
Lu, Michael L	Molecular Regulation of Androgen Receptor Activation	PA-99-081	CA87997
Nelson, William	Project 9: Mechanisms of Sensitivity and Drug Resistance in Prostate Cancer	CA-94-031	CA58236-Sub-09
Schor, Nina	Targeted Therapy for Chemoresistant Tumors		CA74289
Tew, Kenneth	Determinants of Estramustine Resistance and Response		CA83778
Yamamoto, Keith	Project 1: Mechanisms of Hormone Resistance in Prostate Cancer	PAR-99-167	CA89520-Sub-01

Table B-37

NCI Projects Supported in 2002 Addressing the PRG Priority: What is the role of gene and cellular therapy for prostate cancer?

Principal Investigator	Title	RFA or PA	Project ID
Abrams, Scott	Host Immune Responses to Human Carcinoma Antigens Induced by Peptide Vaccines		BC09029
Baldwin, Albert	Antiapoptotic Mechanisms in Prostate Cancer		CA75080
Banchereau, Jacques	Dendritic Cell Vaccine in Metastatic Prostate Cancer	PA-00-047	CA91556
Beer, Tomasz	Calcitriol in Recurrent Prostate Cancer		CA85585
Beer, Tomasz	Pulse Calcitriol for Prostate Cancer Prevention	PA-98-042	CA82504
Bystryn, Jean-Claude	Polypeptide Vaccine in Il-2 Liposomes for Prostate Cancer		CA90562
Celis, Esteban	An Immune-Based Therapeutic Approach for Prostate Cancer	PAR-99-167	CA91956-Sub-04
Chang, Esther	Immunoliposome Mediated Gene Therapy for Prostate Cancer		CA80449
Chang, Esther H	Targeting Stealth Liposome for Cancer Gene Therapy		CA91660
Chatta, Gurkamal	Immunologic Therapy of Prostate Cancer		CA76033
Chung, Leland	Ad-OC-TK/Val Gene Therapy Clinical Correlates		CA85555
Curiel, David	Replicative Adenoviruses with Enhanced Infectivity		CA83821
Donovan, Gerald P	Development of Anti-PSMA Antibodies for Prostate Cancer		CA92927
Donovan, Gerald P	Development of PSMA-Based Vaccines for Prostate Cancer		CA91746
Donovan, Gerald P	Human Anti-PSMA Antibodies for Prostate Cancer Therapy	PA-01-091	CA96075
Freytag, Svend	Combined Suicide Gene Therapy/Radiotherapy for Cancer		CA75456
Gardner, Jason P	Alphavirus Prime-Boost Vaccines for Prostate Cancer	PA-01-091	CA95928
Gilboa, Eli	Tumor RNA Transfected Dendritic Cell Vaccines		CA85307
Golde, David	Memorial Sloan-Kettering Cancer Gene Therapy Program		CA59350
Houghton, Alan	The Development of DNA Vaccines against Prostate Cancer with PSMA as a Target	PAR-99-167	CA92629-Sub-03
Humphreys, Robert	Prostate Cancer Vaccine by Suppressing Il Protein		CA85100
Kao, Chinghai	Tissue Specific Gene Therapy for Human Prostate Cancer		CA74042
Kasahara, Noriyuki	Cellular Transduction by Retrotransposon-Adenovirus Hybrid Vector		CA93709
Kasahara, Noriyuki	Transcriptional Targeting of Retroviral Replication		CA85908
King, Ivan	Bacterial Gene Delivery Vectors for Cancer Therapy		CA77963
Margalit, Ruth	Development of Novel Adenovirus-Lentivirus Hybrid Vector		CA96410
Margalit, Ruth	Retroviral Vectors for Cancer Gene Therapy		CA91659
Morris, John	Gene Therapy of Prostate Cancer Using Radioiodine	PAR-99-167	CA91956-Sub-06
Norris, James	Viral Vector CORE Facility	PAR-99-127	CA88163
Pasqualini, Renata	Targeted Delivery of Genes to Angiogenic Vasculature	PAR-98-096	CA88106
Pastan, Ira	Immunotoxin Therapy of Solid and Hematopoietic Tumors: Preclinical Studies		BC08753

Table B-37 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Peace, David	A Pilot Phase Ib Trial of a PSA Peptide Vaccine	PA-99-070	CA88062
Ratliff, Timothy	Host/Tumor Interactions in Immunotherapy of Prostate Cancer	PA-99-081	CA89062
Ratliff, Timothy L	Enhancement of Gene Transfer & Prostate Cancer Immunity		CA96691
Sanda, Martin	Project 6: Vaccinia PSA for Androgen-Modulated, Post-Surgical Recurrence of Prostate Cancer	CA-94-031	CA69568-Sub-06
Schlom, Jeffrey	Cytokines as Biologic Adjuvants		BC10428
Schlom, Jeffrey	Design and Development of Novel Immunotherapeutics and Strategies for Cancer Immunotherapy		BC05190
Schlom, Jeffrey	Development of Vaccines and Vaccine Strategies for Human Cancer		BC10425
Schlom, Jeffrey	Mechanism of Human T-Cell Activation		BC10427
Schlom, Jeffrey	Novel Recombinant Immunoglobulin Forms for Cancer Therapy and Diagnosis		BC10429
Schlom, Jeffrey	T-Cell Costimulation in the Design of Cancer Vaccines		BC10426
Schor, Nina	Targeted Therapy for Chemoresistant Tumors		CA74289
Simons, Jonathon	Project 11: Gene Therapy for Human Prostate Cancer	CA-94-031	CA58236-Sub-11
Spencer, David	Regulated Apoptosis in the Treatment of Prostate Cancer		CA77266
Tempero, Margaret	Mechanism Based Evaluations of ErbB Targeted Agents	CA-00-001	CA90788
Thompson, Timothy	Project 5: Gene Therapy for Prostate Cancer	PAR-00-087	CA58204-Sub-05
Vaughn, James	Improving ErbB2 Antisense Efficacy for Cancer Therapy		CA83953
Vieweg, Johannes W	Telomerase RNA Transfected Dendritic Cell Vaccines	PA-99-046	CA93910
Vile, Richard	Use of Fusogenic Membrane Glycoproteins for Gene Therapy of Prostate Cancer	PAR-99-167	CA91956-Sub-05
Zhang, Wei-Wei	Complementary Adenoviral Vectors for Treatment of Cancer	CA-98-022	CA83156

Table B-38

NCI Projects Supported in 2002 Addressing the PRG Priority: What are the relevant endpoints for clinical trials of systemic therapies (e.g., PSA levels, time to progression, quality of life, and survival)? How can endpoints be validated? What is the impact of treatment on survival?

Principal Investigator	Title	RFA or PA	Project ID
Beer, Tomasz	Calcitriol in Recurrent Prostate Cancer		CA85585
Carducci, Michael	Phenylbutyrate Bioactivity Assessment in Prostate Cancer		CA75525
Cohen, Pinchas	Interactions between IGFBPs and Nuclear Receptors in Prostate Cancer	PAR-99-167	CA92131-Sub-03
Etzioni, Ruth	PSA Screening and U.S. Prostate Cancer Trends	CA-99-013	CA88160
Fidler, Isiah	Project 1: The Biology of Human Prostate Cancer Metastasis	PAR-99-167	CA90270-Sub-01
Gallagher, Robert	Arsenic Trioxide in Advanced Prostate Cancer	PA-99-070	CA86794
Hood, Leroy	Transcriptome and Proteome Stratification of Prostate Adenocarcinoma Phenotypes	PAR-00-087	CA97186-Sub-04
Kufe, Donald	Phase I Trials of New Anticancer Agents		CA62490
Sanda, Martin	Project 6: Vaccinia PSA for Androgen-Modulated, Post-Surgical Recurrence of Prostate Cancer	CA-94-031	CA69568-Sub-06
Smith, David	Phase II Trial of Tetrathiomolybdate in Prostate Cancer	PA-00-047	CA94510
Tempero, Margaret	Mechanism Based Evaluations of ErbB Targeted Agents	CA-00-001	CA90788

Table B-39

NCI Projects Supported in 2002 Addressing the PRG Priority: How can new targets be identified and what is the role of novel therapeutic agents directed at these targets?

Principal Investigator	Title	RFA or PA	Project ID
Agus, David	The Role of the Her-Kinase Axis in Emergence of Androgen Independence in Human Prostate Cancer	PAR-99-167	CA92131-Sub-04
Aoki, Masahiro	Nuclear Targets of Akt Oncoproteins		CA93837
Arap, Wadih	Project 4: Exploring the Molecular Diversity of Blood Vessels for Diagnostic and Therapeutic Targeting in Prostate Cancer	PAR-99-167	CA90270-Sub-04
Balk, Steven	The Androgen Receptor in Hormone Refractory Disease	PAR-99-167	CA90381-Sub-05
Beranova-Giorgianni, Sarka	Cancer Relevant Proteins in the Human Prostate Proteome	PAR-00-025	CA91254
Bojanowski, Krzysztof	Development of a New Antiangiogenic Tumor Blocker SBD.1	PA-01-091	CA96058
Boothman, David	Exploiting IR Inducible NQ01 Levels Using Beta Lapachone		CA92250
Borgstrom, Per	VEGF and Prostate Cancer Angiogenesis		CA79004
Borrello, Melinda	New Target Antigens for Prostate Cancer Vaccines		CA82948
Cantley, Lewis	The Role of PTEN and the PI3K Pathway in Prostate Cancer		CA89021
Caprioli, Richard M	Molecular Analysis of Cancer—Imaging Mass Spectrometry	PAR-99-102	CA86243
Celis, Esteban	An Immune-Based Therapeutic Approach for Prostate Cancer	PAR-99-167	CA91956-Sub-04
Chang, Esther	Immunoliposome Mediated Gene Therapy for Prostate Cancer		CA80449
Chatta, Gurkamal	Immunologic Therapy of Prostate Cancer		CA76033
Chatterjee, Malaya	HER-2/Neu—A Target for Cancer Immunotherapy		CA91878
Chen, Ching-Shih	Apoptosis Regulation by Lipid Signals in Prostate Cancer	PA-99-081	CA94829
Chen, Ching-Shih	Testing of Novel Apoptotic Agents in Prostate Cancer	PA-99-081	CA92307
Cheng, Jin	Akt1 Oncogene in Carcinogenesis		CA89242
Cheng, Yung-Chi	Nucleoside Analogs as Anticancer Compounds		CA63477
Christman, Judith	De Novo DNA Methyltransferases as Anticancer Drug Targets	PAR-00-060	CA91315
Chung, Leland	Extracellular Matrix Integrin Signaling in Prostate Cancer		CA76620
Cohen, Pinchas	Interactions between IGFBPs and Nuclear Receptors in Prostate Cancer	PAR-99-167	CA92131-Sub-03
Corey, David	Consequences of Inhibition of Cellular Telomerase		CA85363
Counter, Christopher M	Targeting Functional Domains in Telomerase	PAR-01-045	CA95155
Davar, Gudarz	Endothelin 1 Induced Pain and Metastatic Prostate Cancer		CA80153
Denardo, Gerald	Synergistic Multimodality Antibody Therapy		CA47829
Disis, Mary	HER2 Vaccination for the Treatment of Cancer		CA85374
Dou, Q	Tea Targeting Proteasome—A Role in Cancer Prevention	PAR-00-025	CA91282
Ellis, William	Genomic and Gene Expression Profiling of Disseminated Prostate Cancer	PAR-00-087	CA97186-Sub-02

Table B-39 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Fidler, Isiah	Project 1: The Biology of Human Prostate Cancer Metastasis	PAR-99-167	CA90270-Sub-01
Figg, William D	Development of Angiogenesis Inhibitors Using Prostate Cancer as a Tumor Model		SC06538
Finstad, Connie	LHRH Synthetic Peptide Vaccine for Prostate Cancer		CA83450
Fletterick, Robert J	Inhibition of Androgen Receptor Activation	PAR-01-045	CA95324
Foster, Barbara A	Vitamin D Analogs for Chemoprevention of Prostate Cancer		CA95367
Glazer, Robert I	Structure Based Discovery of Akt Inhibitors	PAR-01-045	CA95378
Gleave, Martin	Characterization of Anti-Apoptotic Genes Induced during Androgen Independent Progression and Chemotherapy	PAR-00-087	CA97186-Sub-03
Glode, L M	Cytotoxic Gonadotropin Releasing Hormone Derivatives	PA-01-091	CA96049
Glode, L	GnRH Analog Toxins for Targeted Gonadotroph Ablation		CA75662
Gudkov, Andrei	Stress Induced Bystander Effect in Cancer Treatment		CA88071
Hainfeld, James F	Improved MRI Contrast Agents		CA94495
Honn, Kenneth V	Formulation and Evaluation of a Prostate Cancer Drug		CA97863
Hood, Leroy	Transcriptome and Proteome Stratification of Prostate Adenocarcinoma Phenotypes	PAR-00-087	CA97186-Sub-04
Houghton, Alan	The Development of DNA Vaccines against Prostate Cancer with PSMA as a Target	PAR-99-167	CA92629-Sub-03
Jenkins, Robert	Biologic and Clinical Studies of Overrepresented 8q24 Region Associated with Prostate Cancer Progression	PAR-99-167	CA91956-Sub-03
Johnson, Candace	Antitumor Mechanisms and Therapeutic Effects of Vitamin D		CA67267
Jones, Alun	Technetium and Rhenium in Nuclear Medicine		CA34970
Jones, Peter	De Novo DNA Methylation in Bladder Cancer		CA83867
Jones, Terence	Peptide Antagonists of Urokinase Plasminogen Activator	CA-98-022	CA86150
Kadmon, Dov	Project 4: Biological Therapy for Prostate Cancer	PAR-00-087	CA58204-Sub-04
King, Jean A	NMR Imaging of Prostate Cancer Using Ligands	PAR-01-101	CA95876
Koch, Tad	New Drugs Targeted to Metastatic Cancer and Angiogenesis		CA92107
Kwon, Eugene	CTLA-4 Blockade Immunotherapy for Prostate Cancer		CA82185
Lazo, John	Combinatorial Approaches for Novel Anticancer Agents	CA-97-006	CA78039
Lee, Byungkook	Molecular Modeling and Bioinformatics		BC08759
Lee, Yue-Wei	SAR of Novel Topo I Inhibitor against Prostate Cancer		CA81002
Lemkin, Peter F	Computer Aided Two-Dimensional Electrophoretic Gel Analysis (GELLAB)		BC08381
Lewis, Kevin C	Systems-Based Modeling of Retinoid—Drug Interactions		BC00162
Lin, Sue-Hwa	Regulation of Angiogenesis by C-CAM1		CA86342

Table B-39 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Lokeshwar, Balakrishna	Control of Metastatic Progression of Prostate Cancer		CA61038
Marks, James	Project 4: Antibody Gene Diversity Libraries and Phage Display to Generate Recombinant Human Antibodies for Prostate Cancer Therapy	PAR-99-167	CA89520-Sub-04
Maslak, Peter	Inhibition of Histone Deacetylase as Anti Cancer Therapy		CA82740
McDonnell, Timothy	Project 3: Therapeutic Modulation of Apoptosis in Prostate Cancer Patients	PAR-99-167	CA90270-Sub-03
Merajver, Sofia	Prevention of Mammary Cancer in HER-2/Neu Transgenic Mice		CA77612
Meyn, Raymond	Anticancer Drug Resistance by Bcl-2 Oncogene Expression		CA69003
Mikovits, Judy	Development of Inhibitors of the DNA Methylation Process		CA90013
Mikovits, Judy A	Development of DNA Methyltransferase Inhibitors as Anti*	PA-01-091	CA92828
Mitchell, James B	Nitroxides as Protectors against Oxidative Stress		SC06387
Molinski, Tadeusz F	Natural Product Antitumor Inducers of Apoptosis		CA85602
Morris, John	Gene Therapy of Prostate Cancer Using Radioiodine	PAR-99-167	CA91956-Sub-06
Moses, Marsha	Novel Angiogenesis Inhibitor from Cartilage	PAR-98-096	CA83106
Mueller, Elisabetta	PPAR as a Target of Therapy for Prostate Cancer	PAR-99-167	CA90381-Sub-02
Mulder, Kathleen	Mechanisms of TGF-Beta Production in Human Cancer Cells		CA90765
Mundy, Gregory	Tumors' Effects on the Skeleton		CA40035
Nakaar, Valerian	Potentiating the Anti-Tumor Activity of Salmonella		CA94699
Ornstein, David K	Proteomic Study of Androgen Independent Prostate Cancer	PA-01-010	CA93759
Pan, Xing	Folate Conjugates for Prostate Cancer Imaging	PAR-00-090	CA81975
Parchment, Ralph	Stable Stereoisomer Analogs of Topo II-Beta Inhibitors		CA90088
Pasqualini, Renata	Project 2: Targeting Prostate Cancer Bone Metastasis	PAR-99-167	CA90270-Sub-02
Pasqualini, Renata	A Receptor for Tumor Homing Peptides in Vasculature		CA78512
Pastan, Ira	Gene Discovery		BC10298
Pienta, Kenneth	Project 5: Inhibition of Human Prostate Cancer Metastasis	CA-94-031	CA69568-Sub-05
Piwnica-Worms, David R	Washington University Molecular Imaging Center	CA-01-014	CA94056
Pommier, Yves	DNA Repair and Cell Cycle Checkpoints as Targets for Anticancer Drugs		BC06150
Rangnekar, Vivek	Mechanism of Apoptosis by Par4	PA-99-081	CA60872
Reiter, Robert	Prostate Stem Cell Antigen (PSCA) in the Biology and Therapy of Prostate Cancer	PAR-99-167	CA92131-Sub-01
Romanov, Victor	Peptide Inhibitors of Prostate Cancer Cells Adhesion		CA92931
Sanda, Martin	Project 6: Vaccinia PSA for Androgen-Modulated, Post-Surgical Recurrence of Prostate Cancer	CA-94-031	CA69568-Sub-06
Sarkar, Fazlul	Molecular Mechanism of Genistein in Prostate Cancer		CA83695

Table B-39 (cont.)

Principal Investigator	Title	RFA or PA	Project ID
Sawyers, Charles	Targeted Therapy of PTEN Null Prostate Cancer	PAR-99-167	CA92131-Sub-02
Scher, Howard	Biologic Effects of 17AA Geldanamycin		CA85506
Scher, Howard	Mechanism Based Therapy for Prostate Cancer	PAR-99-167	CA92629-Sub-04
Shankar, Geetha	Lysophospholipid Receptors as Targets for Cancer Therapy		CA92925
Sherman, David	Combinatorial Creation of New Anticancer Agents	CA-98-009	CA83155
Sherman, Merry R	Pegylated Prolactin Receptor Antagonists as Cancer Drugs		CA96283
Shih, Charles	Anti-Androgenic Mechanism of a New Compound		CA97647
Shih, Charles	Cell-Based High Throughput Screening for Anti-Androgens		CA96189
Shuman, Marc	Proteases in Cancer—Biology and Drug Development		CA72006
Simons, Jonathon	Project 5: Cellular and Molecular Basis of Prostate Metastasis to Bone	CA-94-031	CA58236-Sub-05
Small, Eric	Project 6: Anti-CTLA4 Antibody Immunologic Therapy for Prostate Cancer	PAR-99-167	CA89520-Sub-06
Smith, David	Phase II Trial of Tetrathiomolybdate in Prostate Cancer	PA-00-047	CA94510
Soff, Gerald	Project 3: Generation of, and Angiostatin Levels in, Prostate Cancer	PAR-99-167	CA90386-Sub-03
Spencer, David	Regulated Apoptosis in the Treatment of Prostate Cancer		CA77266
Taylor, John-Stephen	Nucleic Acid Triggered Prodrug and Probe Activation		CA92477
Tempero, Margaret	Mechanism Based Evaluations of ErbB Targeted Agents	CA-00-001	CA90788
Tew, Kenneth	Determinants of Estramustine Resistance and Response		CA83778
Topalian, Suzanne L	Specific Immune Recognition of Tumor-Associated Antigens by Human T Cells		SC06664
Trump, Donald L	Vitamin D in Prostate Cancer: Tumor Vasculature Effects		CA95045
Vaughn, James	Improving ErbB2 Antisense Efficacy for Cancer Therapy		CA83953
Vile, Richard	Use of Fusogenic Membrane Glycoproteins for Gene Therapy of Prostate Cancer	PAR-99-167	CA91956-Sub-05
Woods, Catherine	Novel Prostate Homing Peptides as Potential Diagnostics		CA92933
Woynarowska, Barbara	DNA Damaging Agents and Apoptosis in Prostate Cancer		CA78706
Yang, Meng	GFP Imaging for In Vivo High-Throughput Drug Screening	PAR-00-030	CA89779
Zhang, Wei-Wei	Complementary Adenoviral Vectors for Treatment of Cancer	CA-98-022	CA83156
Zheng, Gang	Photodynamic Therapy for Prostate Cancer	PAR-01-045	CA95330

Table B-40

NCI Projects Supported in 2002 Addressing the PRG Priority: What is the optimal treatment for androgen-independent disease?

Principal Investigator	Title	RFA or PA	Project ID
Balk, Steven	The Androgen Receptor in Hormone Refractory Disease	PAR-99-167	CA90381-Sub-05
Celis, Esteban	An Immune-Based Therapeutic Approach for Prostate Cancer	PAR-99-167	CA91956-Sub-04
Dahut, William L	The Evaluation of Novel Therapeutics for Genitourinary Malignancies		SC10098
Figg, William D	Development of Angiogenesis Inhibitors Using Prostate Cancer as a Tumor Model		SC06538
Fletterick, Robert J	Inhibition of Androgen Receptor Activation	PAR-01-045	CA95324
Foster, Barbara A	Vitamin D Analogs for Chemoprevention of Prostate Cancer		CA95367
Gallagher, Robert	Arsenic Trioxide in Advanced Prostate Cancer	PA-99-070	CA86794
Gleave, Martin	Characterization of Anti-Apoptotic Genes Induced during Androgen Independent Progression and Chemotherapy	PAR-00-087	CA97186-Sub-03
Hood, Leroy	Transcriptome and Proteome Stratification of Prostate Adenocarcinoma Phenotypes	PAR-00-087	CA97186-Sub-04
Houghton, Alan	The Development of DNA Vaccines against Prostate Cancer with PSMA as a Target	PAR-99-167	CA92629-Sub-03
Imperato-Mc Ginley, Julianne	Androgens Regulate IGF Pathway and Prostate Diseases	PAR-98-023	CA85435
Johnson, Candace	Glucocorticoids and Vitamin D: Role in Anti-Tumor Effects		CA85142
Koch, Tad	New Drugs Targeted to Metastatic Cancer and Angiogenesis		CA92107
Kufe, Donald	Phase I Trials of New Anticancer Agents		CA62490
Lee, Chung	Project 1: Clusterin as a Negative Prognostic Indicator in Prostate Cancer	PAR-99-167	CA90386-Sub-01
Morris, John	Gene Therapy of Prostate Cancer Using Radioiodine	PAR-99-167	CA91956-Sub-06
Ratliff, Timothy L	Enhancement of Gene Transfer and Prostate Cancer Immunity		CA96691
Reiter, Robert	Prostate Stem Cell Antigen (PSCA) in the Biology and Therapy of Prostate Cancer	PAR-99-167	CA92131-Sub-01
Sawyers, Charles	Targeted Therapy of PTEN Null Prostate Cancer	PAR-99-167	CA92131-Sub-02
Scher, Howard	Mechanism Based Therapy for Prostate Cancer	PAR-99-167	CA92629-Sub-04
Sellers, William	Single Nucleotide Repeat Polymorphism Analysis of Recurrent Prostate Cancer after Radiation Therapy	PAR-99-167	CA90381-Sub-03
Shih, Charles	Anti-Androgenic Mechanism of a New Compound		CA97647
Shih, Charles	Cell-Based High Throughput Screening for Anti-Androgens		CA96189
Wang, Zhou	Project 2: Suppressive Role of Androgen-Response Gene Calreticulin in Prostate Cancer	PAR-99-167	CA90386-Sub-02

Table B-41

NCI Projects Supported in 2002 Addressing the PRG Priority: At what point in the progression of prostate cancer should novel therapeutic agents be initiated (e.g., anti-angiogenic and anti-metastatic agents)?

Principal Investigator	Title	RFA or PA	Project ID
Dahut, William L	The Evaluation of Novel Therapeutics for Genitourinary Malignancies		SC10098
Jenkins, Robert	Biologic and Clinical Studies of Overrepresented 8q24 Region Associated with Prostate Cancer Progression	PAR-99-167	CA91956-Sub-03
Kadmon, Dov	Project 4: Biological Therapy for Prostate Cancer	PAR-00-087	CA58204-Sub-04
Kufe, Donald	Phase I Trials of New Anticancer Agents		CA62490
Merajver, Sofia	Prevention of Mammary Cancer in HER-2/Neu Transgenic Mice		CA77612
Pasqualini, Renata	Targeted Delivery of Genes to Angiogenic Vasculature	PAR-98-096	CA88106
Ratliff, Timothy	Host/Tumor Interactions in Immunotherapy of Prostate Cancer	PA-99-081	CA89062
Sanda, Martin	Project 6: Vaccinia PSA for Androgen-Modulated, Post-Surgical Recurrence of Prostate Cancer	CA-94-031	CA69568-Sub-06
Shoji, Mamoru	Inhibition of Tissue Factor Mediated Angiogenesis		CA82995

Table B-42

NCI Projects Supported in 2002 Addressing the PRG Priority: When should a patient with a rising PSA be treated?

Principal Investigator	Title	RFA or PA	Project ID
Beer, Tomasz	Calcitriol in Recurrent Prostate Cancer		CA85585
Rhoads, George	PSA Screening and Prostate Cancer Mortality		CA71734
Young, Charles	Human Kallikreins as Novel Markers of Prostate Cancer	PAR-99-167	CA91956-Sub-02

Table B-43
Additional NCI Treatment Projects Supported in 2002

Principal Investigator	Title	RFA or PA	Project ID
Gallo, James	Optimized Cancer Chemotherapy via Pharmacodynamic Models		CA76254
Glazer, Robert I	Structure Based Discovery of Akt Inhibitors	PAR-01-045	CA95378
Petereit, Daniel G	Enhancing Native American Participation in RT Trials	CA-02-002	CA99010
Trump, Donald L	Vitamin D in Prostate Cancer: Tumor Vasculature Effects		CA95045

FY 2002 Cancer Control, Survivorship, and Outcomes Projects

Table B-44

NCI Projects Supported in 2002 Addressing the PRG Priority: What is the impact of treatment on outcomes? How do the benefits differ in subsets of patients by age, morbidity, race, etc.? What are the outcomes in the community setting compared with those from clinical trials or centers of excellence? How do provider characteristics (e.g., volume and expertise) affect outcomes? How do patients value tradeoffs between length of survival and quality of life?

Principal Investigator	Title	RFA or PA	Project ID
Bokhour, Barbara	Prostate Cancer Survivor Narratives and Doctors' Responses	PAR-99-006	CA91737
Deimling, Gary	Quality of Life of Older Long-Term Cancer Survivors	CA-97-018	CA78975
Denberg, Thomas D	Disparities in Prostate Cancer Decision-Making and QOL	PAR-02-037	CA99505
Diefenbach, Michael A	A Multimedia Prostate Cancer Intelligent Expert System	PA-99-163	CA90904
Etzioni, Ruth	PSA Screening and U.S. Prostate Cancer Trends	CA-99-013	CA88160
Ferrans, Carol	Quality of Life of African American Cancer Survivors		CA89418
Kattan, Michael	Natural History of Prostate Cancer, Prognostic Models, and Decision Making	PAR-99-167	CA92629-Sub-01
McCarthy, Ellen	Patterns of Care for Cancer Patients at End of Life		CA79052
McClellan, Mark	Economics of Cancer		CA74760
McVary, Kevin	Project 4: Molecular Mechanisms of Neuropathic Erectile Dysfunction	PAR-99-167	CA90386-Sub-04
Meltzer, David	Cost-Effectiveness of Prostate Cancer Screen/Treatment		CA92443
Northouse, Laurel	Prostate Cancer—Family Care for Patients and Spouses		CA90739
Sanda, Martin G	Survivor QOL/Spouse Satisfaction after Prostate Therapy		CA95662
Scott, Charles	QOL and LENT in Survivors of Head and Neck/Prostate Cancer		CA79034
Troxel, Andrea	Clinical Trials with Quality of Life and Compliance Data		CA79470
Zabora, James	Family Dynamics and Problem Solving Education for Caregivers		CA88769

Table B-45

NCI Projects Supported in 2002 Addressing the PRG Priority: How are different types of outcomes defined and standardized (e.g., quality of life, morbidity, and patient satisfaction)?

Principal Investigator	Title	RFA or PA	Project ID
Carver, Charles	Quality of Life in Adult Cancer Survivors	CA-97-018	CA78995
Cella, David	Project 6: QOL Item Banking and Adaptive Testing in Prostate Cancer	PAR-99-167	CA90386-Sub-06
Deimling, Gary	Quality of Life of Older Long-Term Cancer Survivors	CA-97-018	CA78975
Meltzer, David	Cost-Effectiveness of Prostate Cancer Screen/Treatment		CA92443
Sanda, Martin G	Survivor QOL/Spouse Satisfaction after Prostate Therapy		CA95662
Troxel, Andrea	Clinical Trials with Quality of Life and Compliance Data		CA79470

Table B-46

NCI Projects Supported in 2002 Addressing the PRG Priority: What is the impact of early detection and screening on outcomes?

Principal Investigator	Title	RFA or PA	Project ID
Etzioni, Ruth	PSA Screening and U.S. Prostate Cancer Trends	CA-99-013	CA88160
Phillips, Kathryn	Use of Cancer Screening in a Managed Care Environment	PA-99-014	CA81130
Rhoads, George	PSA Screening and Prostate Cancer Mortality		CA71734
Tsodikov, Alexander	Survival Effects of Prostate Cancer Surveillance	CA-02-010	CA97414

Table B-47
Additional NCI Cancer Control, Survivorship, and Outcomes Projects Supported in 2002

Principal Investigator	Title	RFA or PA	Project ID
Antoni, Michael	Center for Psycho-Oncology Research	OD-99-005	CA84944
Bass, Sarah	Use of Internet Health Information by Cancer Patients		CA90145
Berry, Donna	Nursing Support of Decisions by Men with Prostate Cancer		CA77372
Bowman, Karen	Family Members and the Survivorship Phase of Cancer	PAR-99-006	CA91577
Brink, Susan	Interactive Prostate Cancer Decision Support System		CA75801
Brink, Susan	Recurrent Prostate Cancer: Decision Support Guide		CA88557
Davar, Gudarz	Endothelin 1 Induced Pain and Metastatic Prostate Cancer		CA80153
Demark-Wahnefried, Wendy	Promoting Health in Prostate and Breast Cancer		CA81191
Dodd, Marylin	Exercise—An Intervention for Fatigue in Cancer Patients		CA83316
Earp, Shelton	NCCU/UNC Lineberger Partnership in Cancer Research	CA-01-008	CA92075
Guadagnoli, Edward	Managed Care Penetration and Cancer Care	PA-99-015	CA92588
Harewood, Kenneth	NCCU-BBRI/UNC-Lineberger Partnership in Cancer Research	CA-01-008	CA92077
Matthews, Alicia	Information Needs of African American Cancer Patients		CA77525
Partridge, Edward	Deep South Network for Cancer Control	CA-99-003	CA86128
Redd, William	East Harlem Partnership for Cancer Awareness (EHPCA)	CA-99-003	CA86107
Roth, Andrew	Psychostimulants for Fatigue in Ambulatory Men with PC		CA85229
Schildkraut, Joellen	Carolina and Georgia Genetics Network Center		CA78157
Snyder, Brian	Biomechanics of Metastatic Defects in Bone		CA40211
Weber, Bryan	Dyadic Social Support for Men with Prostate Cancer	PAR-99-006	CA96204
Wilkie, Diana	Computerized Pain Report and Nursing Pain Consult Protocol		CA62477
Wilkie, Diana	Computerized Symptom Report Consult for Cancer Patients	CA-98-014	CA81918

APPENDIX C

U.S. Patents Resulting from NCI-Funded Research on Prostate Cancer: 1998–2002

U.S. Patents Resulting from NCI-Funded Research on Prostate Cancer

Year	Patent Title
Pending as of 2002[a]	◆ Alpha-difluoromethylornithine (DFMO) suppresses polyamine levels in the human prostate (Serial No. 938846) ◆ Anti-tumor effects of prostate carcinoma tumor antigen-1 (Serial No. 948227) ◆ Chimeric prostate-homing peptides with pro-apoptotic activity (Serial No. 765086) ◆ Chromosome 17p-linked prostate cancer susceptibility gene and a paralog and orthologous genes (Serial No. 988626 and Serial No. 988687) ◆ Compounds for cancer imaging and therapy (Patent No. 6,517,811)[b] ◆ Genetic markers for breast, ovarian, and prostatic cancer (Patent No. 6,512,091)[b] ◆ Human thymosin beta15 gene, protein, and uses thereof (Serial No. 726422) ◆ Methods for detecting prostate cancer (Serial No. 957376) ◆ Novel discalamide compounds and their use as antiproliferative agents (Serial No. 835692) ◆ Novel prostate cancer cell lines (Serial No. 919196) ◆ Oligonucleotide inhibitors of cancer cell proliferation (Serial No. 141263) ◆ Prostate cancer-related compositions, methods, and kits based on DNA macroarray proteomics platforms (Serial No. 813380) ◆ Real-time mechanical imaging of the prostate (Serial No. 819419) ◆ Reversal of cancer phenotype by inhibiting expression of prostate tumor inducing gene (Serial No. 263178) ◆ Roles for Nkx3.1 in prostate development and cancer (Serial No. 756151) ◆ RTVP-based compositions and methods for the treatment of prostate cancer (Serial No. 876225) ◆ Sequences for targeting metastatic cells (Serial No. 151055 and Serial No. 797969) ◆ Suppressors of human breast cancer cell growth (Serial No. 972758) ◆ Use of retinoids plus histone deacetylase inhibitors to inhibit the growth of solid tumors (Serial No. 061101)
2002	◆ 17-azolyl steroids useful as androgen synthesis inhibitors (Patent No. 6,444,683) ◆ Benzamide compounds for cancer imaging and therapy (Patent No. 6,447,748) ◆ Circulating insulin-like growth factor-I and prostate cancer risk (Patent No. 6,410,335) ◆ Discalamide compounds and their use as anti-proliferative agents (Patent No. 6,476,065) ◆ Method for detection of micrometastatic prostate cancer (Patent No. 6,479,263) ◆ Methods for diagnosing cancer or precancer based upon hnRNP protein expression (Patent No. 6,500,625) ◆ Prostate cancer assays and related methods (Patent No. 6,352,834) ◆ Thymosin beta-15 promoter and uses thereof (Patent No. 6,489,463)

[a] The U.S. Patent database only includes data on Published Applications in accordance with the 18 month pre-grant publication rules. Pending patent applications where the applicant has elected to not publish prior to grant remain confidential.
[b] These patents were granted in 2003.

U.S. Patents Resulting from NCI-Funded Research on Prostate Cancer (cont.)

Year	Patent Title
2001	◆ 17-azolyl steroids useful as androgen synthesis inhibitors (Patent No. 6,200,965) ◆ Antibodies specific for human thymosin beta15 protein and uses thereof (Patent No. 6,300,479) ◆ Chromosome 17p-linked prostate cancer susceptibility gene and a paralog and orthologous genes (Patent No. 6,333,403) ◆ CYP3A4 NFSE variant and methods of use therefore (Patent No. 6,174,684) ◆ Detection of metatstatic cancer cells using PCTA-1 (Patent No. 6,255,049) ◆ Epithelial protein and DNA thereof for use in early cancer detection (Patent No. 6,251,586) ◆ Immortalized and malignant human prostatic cell lines (Patent No. 6,255,058) ◆ Molecules that home to various selected organs or tissues (Patent No. 6,232,287) ◆ Prostate implant planning engine for radiotherapy (Patent No. 6,200,255) ◆ Sequences for targeting metastatic cells (Patent No. 6,252,058) ◆ Tumor suppressor designated TS1023.3 (Patent No. 6,262,242) ◆ Therapeutic methods for prostate cancer (Patent No. 6,177,410) ◆ Ultrasonic tissue-type classification and imaging methods and apparatus (Patent No. 6,238,342)
2000	◆ Benzamide compounds containing a heterocyclic ring for tumor imaging and therapy (Patent No. 6,015,543) ◆ Discodermolide compounds and methods of use (Patent No. 6,127,406) ◆ Method for diagnosis of cancer (Patent No. 6,150,117) ◆ Method of inhibiting cancer growth (Patent No. 6,100,248) ◆ Prediction of prostate cancer progression by analysis of selected predictive parameters (Patent No. 6,025,128) ◆ Prostate-specific regulatory nucleic acid sequences and transgenic non-human animals expressing prostate-specific antigen (Patent No. 6,100,444) ◆ Use of inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase as a modality in cancer therapy (Patent No. 6,040,334)
1999	◆ 17-azolyl steroids useful as androgen synthesis inhibitors (Patent No. 5,994,335) ◆ Benzamide compounds for cancer imaging and therapy (Patent No. 5,993,777) ◆ Epithelial protein and DNA thereof for use in early cancer detection (Patent No. 5,994,062) ◆ Isolated nucleic acid molecule encoding alternatively spliced prostate-specific membrane antigen and uses thereof (Patent No. 5,935,818) ◆ Methods for cancer imaging and therapy using benzamine compounds (Patent No. 5,911,970) ◆ Method for molecular staging of prostate cancer (Patent No. 5,976,794) ◆ Nomograms to aid in the treatment of prostatic cancer (Patent No. 5,993,388) ◆ Treatment of cancer with human chorionic gonadotropin (Patent No. 5,877,148) ◆ Method for prognosis of prostate cancer (Patent No. 5,858,681)

U.S. Patents Resulting from NCI-Funded Research on Prostate Cancer (cont.)

Year	Patent Title
1998	◆ Bone and prostate-derived protein factors affecting prostate cancer growth, differentiation, and metastasis (Patent No. 5,728,815) ◆ Genetic markers for breast, ovarian, and prostatic cancer (Patent No. 5,821,328) ◆ Human prostate tumor inducing gene-1 and uses thereof (Patent No. 5,851,764) ◆ Human prostatic cell lines immortalized by adenovirus 12-simian virus 40 (AD12/SV40) hybrid virus (Patent No. 5,814,452 and Patent No. 5,716,830) ◆ Human thymosin beta15 (Patent No. 5,721,337) ◆ Human thymosin beta15 gene, protein, and uses thereof (Patent No. 5,831,033) ◆ Immortalized and malignant human prostatic cell lines (Patent No. 5,824,488) ◆ Method for detecting prostate cancer using a reagent which binds prostate cancer-1 protein (Patent No. 5,824,490) ◆ Method of inhibiting cancer growth (Patent No. 5,837,696) ◆ Method for molecular staging of prostate cancer (Patent No. 5,840,494)

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