

**PROSTATE CANCER RESEARCH  
at the NATIONAL CANCER INSTITUTE**

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**Introduction**

Good morning, Congressman Burton and Members of the Committee. I am Richard Kaplan, M.D., of the National Cancer Institute (NCI). I am a Senior Investigator in the Cancer Therapy Evaluation Program and I coordinate NCI's extramural clinical research on prostate cancer treatment. I am accompanied today by Jeffrey White, M.D., Director of the NCI's Office of Cancer Complementary and Alternative Medicine.

I am pleased to appear before you today to describe NCI's prostate cancer research program and our growing interest in complementary and alternative approaches to prostate and other cancers. The Congress has asked NIH to make prostate cancer a top priority in allocating funding increases; to accelerate spending on prostate cancer; and to consult closely with the research community. Under Dr. Klausner's leadership, NCI has undertaken a vigorous effort to respond in all of these areas.

The nature and magnitude of the burden of prostate cancer has been tracked by NCI's surveillance program, and we estimate that about 180,000 men will be newly diagnosed with prostate cancer this year and about 37,000 will die. Prostate cancer exacts a particularly devastating toll on African American men; incidence rates are substantially higher among African Americans, and mortality rates in African American men remain more than twice as high as rates in white men.

This catalogue of statistics, while accurate, does little to convey the very real pain, fear, and uncertainty experienced by every man who is diagnosed with prostate cancer. Despite advances over the past decade, our treatments for prostate cancer are inadequate, the side effects of treatment are significant and often unacceptable, and troubling questions remain about the efficacy of early detection for the disease. Every day, too many men in the United States hear the life-changing words, "You have prostate cancer." Every day, too many men are faced with the agonizing decisions of how best to treat their prostate cancer. And every day, too many men are dying too young of this disease. The limited knowledge about the causes of prostate cancer, how it may be prevented, and how to treat it successfully demand a broad, robust, and clearly articulated approach to research.

At NCI, prostate cancer research funding increased significantly from a 1998 level of \$86.9 million to a current projection of \$141.5 million in 1999. At the request of Congress, NIH developed a plan for a coordinated, trans-NIH prostate cancer research initiative outlined in Planning for Prostate Cancer Research: Five Year Professional Judgment Estimates. A copy of this 5-Year Plan has been provided to you. This report describes prostate cancer research opportunities across NIH from 1999 through 2003. Without regard for economic constraints or other competing priorities of the NIH or the Federal government, we estimate NCI could support \$340 million, and NIH in total could support \$420 million worth of targeted prostate cancer research by FY 2003.

## Overview

The NCI is the lead NIH institute for prostate cancer research. Ongoing and future research initiatives have the potential to directly improve the length and quality of life of prostate cancer patients and survivors, as well as those at risk for the disease. Indeed, fully 70 percent of the research opportunities presented here are targeted at clinical or translational research that would have a direct impact on patients, survivors, and at-risk men.

The NCI has aggressively sought participation from non-government researchers, advocates, and patients in reviewing the prostate cancer research portfolio and charting a plan for a vigorous expansion of the prostate cancer research program. Over two years ago, we initiated a disease-specific planning process called a progress review group or PRG. The Prostate Cancer PRG involved scores of individuals from all over the country - scientists, clinicians, and advocates--and challenged the prostate cancer research community and the NCI to review our current prostate cancer research portfolio, to develop a prioritized set of questions that needed to be answered and resources that needed to be developed or applied, and to provide a vision and chart a course for research and progress in prostate cancer. The PRG report was presented to the NCI last September and in the 12 months since then we have acted to implement a plan that we believe will fulfill the vision of progress articulated by the PRG. A copy of the report has been provided to you.

In all of our planning phases we have involved a variety of members of the prostate cancer communities including researchers, clinicians and advocates. To ensure that the professional and advocacy groups were fully represented, the PRG invited the input of 32 "stakeholder" groups that represented both professional societies and advocacy organizations and groups.

We have begun, in an aggressive way, to accelerate funding for prostate cancer.

- We have identified more than 20 initiatives through which high priority areas can be addressed and a special section of the NCI Web site serves to bring these to the attention of researchers and the public.
- We have further emphasized the importance of accelerating the pace of progress against prostate cancer by promising applicants that prostate cancer grant

applications will have priority for so-called exception funding. That is, every effort will be made to fund worthy applications in the identified high-priority research areas even when peer-review assigned priority scores are not quite high enough to fit within conventional grant award paylines

- NCI has met with the representatives of the prostate cancer research community, the PRG, and the leadership of professional societies, such as the American Urological Association, in order to communicate these initiatives and to enlist the research community's support in responding to these opportunities.
- Extensive outreach and advertising will alert the larger research community to these opportunities to energize their participation in this prostate cancer research program.

### **Research Initiatives**

The scientific opportunities we have identified fall into four major areas:

1. Clinical Science-- the near term direct testing of new interventions in patients or in those at risk for prostate cancer.
2. Translational Science -- moving ideas from the laboratory to the point of clinical testing, and determining how they should be applied and tested.
3. Risk, Burdens & Outcomes Science -- attempting to ask critical questions about cause, the unequal levels of cancer in different populations, outcomes and survivorship.
4. Basic research and discovery -- longer term investments in gaining insight into the development and biology of prostate cancer and the development of models for study.

Let me illustrate with a few examples of these new initiatives. In the area of clinical trials for patients with prostate cancer, we need to test new approaches and new agents aimed at a variety of clinical situations. We have established Prostate Cancer "Quick Trials," a new granting program to provide a rapid, streamlined funding mechanism for moving novel new ideas for therapeutic interventions into Phase I and II clinical trials for prostate cancer. This program has been set up in recognition of the urgent need for new types of interventions that are effective at different stages of prostate cancer, as well as the growing number of therapeutic ideas that are ready to be tested in patients.

In this type of project, where it is necessary to evaluate untested leads in the absence of preliminary data, conventional grant application and review procedures are not well suited. Quick Trials utilizes a process for rapid approval of early clinical trials. The NCI's goals are to increase the number of patients participating in early clinical trials by two to three-fold and to initiate 10-15 new trials per year through this accelerated mechanism. In addition, this year through NCI's Cancer Therapy Evaluation Program, we will initiate approximately 35 new Phase I/II trials in Prostate Cancer with agents directed against a number of particularly promising molecular targets and mechanisms. These targets include:

- angiogenesis and metastasis, the processes by which cancers induce new blood-vessel formation, invade these blood vessels, and spread throughout the body;
- growth factors and their receptors, which mediate growth signals to cancer cells; and
- tissue-specific genes expressed selectively in prostate or prostate cancer cells, thus allowing for the targeting of tumor-killing modalities to these cells.

We will test:

- Novel small molecule drugs
- Specific antibodies
- Vaccines
- Virus-based gene therapy
- Targeted radiation sensitizers

Compared to the current level of effort, this plan could more than double the number of early clinical trials in prostate cancer in the first year, with another doubling projected in the next four years as per the full professional judgment estimate presented by Dr. Klausner last June.

This year, we will activate at least 5 new multi-center phase III clinical trials in prostate cancer that will attempt to optimize and test new hormonal and chemotherapeutic approaches for the most common clinical presentations of the disease, including:

- adjuvant therapy in the setting of primary surgical or radiation treatment;
- neo-adjuvant therapy, which has shown promising results in reducing the mortality from locally advanced prostate cancer;
- treatment after hormone therapy;
- treatment in the setting of rising PSA levels after definitive local therapy; and
- advanced disease, particularly directed at bony metastases.

With this initial ramp up in clinical trials, we project the ability to double the number again over the following four years.

We have initiated a new program creating a drug development process that enables investigators to advance novel molecules to clinical trials when they have not yet found a pharmaceutical or biotechnology industry partner with the necessary resources. We do this by giving academic investigators access, on a competitive basis, to NCI's preclinical drug development resources and expertise. Investigators who have molecules that hold promise for cancer treatment, but without access to the development resources required for initiation of clinical studies, are invited to submit applications twice a year. Those selected for support are assisted with necessary development steps to enable Investigational New Drug Application (IND) filing with the Food and Drug Administration and to begin initiation of proof-of-principle clinical trials. For FY 1999, our goal is the development of three to five new therapeutic agents, each relevant to prostate cancer. Projects already approved include development of a bioreductive

compound with potential as a radio- and chemo-sensitizer, and a gene-therapy approach that will convert inactive pro-drugs into toxic agents within prostate cancer cells. Over five years, 15 new therapeutic agents for prostate cancer could potentially be developed if sufficient resources are available.

The NCI is moving very quickly in important directions to develop CAM information and expand research opportunities for CAM investigators. These activities are broad in scope and include strengthening our relationship with the National Center for Complementary and Alternative Medicine (NCCAM), the careful evaluation of CAM therapies, and the development of accurate CAM information for the public. One goal shared by the NCI, NCCAM, and other Institutes is to establish Centers for CAM Research that would provide the resources necessary for the rigorous scientific study of CAM approaches, as well as Specialized Research Centers to investigate the biological effects of botanicals, including those that are available as dietary supplements.

Several studies of CAM approaches are already underway. NCI - sponsored projects recently have suggested that both vitamin E and selenium supplements can safely prevent prostate and other cancers. More investigation is indicated and NCI continues to support several studies addressing effectiveness in the prevention of prostate cancer by lycopene and dietary soy, as well as vitamin E and selenium.

To enhance our collaboration with the CAM community toward bringing effective prevention strategies and therapies to cancer patients we worked with NCCAM to establish the federally-chartered Cancer Advisory Panel (CAP-CAM). The CAP-CAM meets 2 to 3 times a year and draws its 15 members from a broad range of experts from the conventional and CAM cancer research community. This group will review and evaluate summaries of evidence for CAM cancer approaches submitted by practitioners, make recommendations on whether and how these evaluations should be followed up, and be available to observe and provide advice about studies supported by the NCCAM and NCI, and about communication of the results of those studies. The panel affords CAM practitioners the opportunity to submit retrospective analyses of data from patients treated with a specific modality and to allow an expert panel of CAM and conventional scientists to assess possible therapeutic benefit. This is formally known as the Best Case Series (BCS). The CAPCAM held its first meeting on July 8-9, 1999, in Bethesda, MD. Panel members discussed the scope of their advisory role and assessed presentations of two Best Case Series. The CAPCAM's recommendations were: additional study of a specific dietary supplement as a treatment for non-small cell lung cancer, currently provided by the Connecticut Institute of Aging and Cancer; and further exploration of homeopathic cancer treatments, provided by the PB Homeopathic Research Foundation, Calcutta, India. We are enthusiastic that this group can work collaboratively in a new partnership between the conventional and CAM cancer research communities.

### **Direction of Future Efforts**

A number of additional central questions about prostate cancer have been identified, as well as potential strategies to address them. These include:

1. Testing promising preventive agents, particularly in high risk individuals;
2. Developing new, predictive molecular diagnostics;
3. Validating current and new early detection markers;
4. The linkage of new imaging technology to directing therapy and assessing its effects without invasive procedures;
5. Epidemiologic studies to attempt to systematically identify correlates of the profound geographic and population differences in prostate cancer rates; and
6. Developing new animal models that faithfully reproduce human prostate cancer in order to better understand tumor development and spread, and to better test preventive and therapeutic interventions.

All of these opportunities build on a strong base of existing prostate cancer research including:

1. The Cancer Genome Anatomy Project (CGAP), the goals of which are to build an index of all genes that are expressed in tumors and support development of new technologies that will allow high throughput analysis of gene and protein expression as well as mutation detection. The tumor type with the highest representation in the early stages of the CGAP effort is prostate cancer. NCI has facilitated investigator collaborations of interdisciplinary studies following the recent discovery of a susceptibility gene on chromosome 1. Leads from this effort may help to clarify genetic and gene-environment interactions responsible for black-white differences in risk.
2. NCI funded (in total or in part) 246 clinical trials in prostate cancer, including 80 Phase III studies and 37 Phase II studies. NCI clinical studies in prostate cancer have significant African-American participation. One NCI study shows that 14.7 percent of men enrolled onto NCI sponsored prostate cancer treatment trials are African American while 10.3 percent of Americans diagnosed with prostate cancer are African American.
3. NCI's ongoing Prostate Cancer Prevention Trial (PCPT) involves 18,000 healthy men over the age of 55 to determine if the drug finasteride can prevent prostate cancer.
4. NCI's ongoing Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) is assessing the efficacy of prostate cancer screening. New PLCO sites are being added to enhance minority patient accrual. NCI also is co-sponsoring with the Veterans Administration the PIVOT trial in which "watchful waiting" is being compared in terms of outcome with surgical removal of the prostate. This

trial is intended to determine whether conservative treatment of localized disease may be an acceptable alternative to surgery.

5. NCI staff analyzing the Surveillance and End Results (SEER) Program data have shown that there are tremendously differing patterns of care among black and white men with prostate cancer. Encouragingly, however, NCI staff and the Department of Defense have collaborated in a study of treatment data and shown that equal treatment yields equal outcome within disease stages. This finding suggests that NCI efforts to improve prevention, diagnosis, and treatment of this disease have the potential to benefit all patients equally.
  
6. NCI, along with the American Cancer Society and the Centers for Disease Control and Prevention sponsored a Leadership Conference on Prostate Cancer in the African-American Community in November of 1997. Developed in cooperation with the 100 Black Men of America, the Intercultural Cancer Council, the National Black Leadership on Cancer, and the National Prostate Cancer Coalition, the conference represented a significant step toward developing a strategy for the full participation of African Americans in prostate cancer research and control.
  
7. In addition, NCI recently conducted a large interview-based study of prostate cancer in African Americans and whites. Analysis of the results has not thus far revealed any specific factor that could explain the racial differences in risk. However, further studies are underway, including an extensive evaluation of the role of different components of the diet.

### **Public Understanding**

Communicating with cancer patients, individuals at high risk for cancer, the general public, and the health care community is a central component of NCI's mission and mandate. For prostate cancer, the institute communicates information to all of those groups, as well as to the cancer research community.

Materials available from NCI, including print, video, and web products, range from basic information about the disease, information about research now ongoing to improve understanding and management of the disease, and information for men about early detection and treatment options.

One of the most recent communications initiatives is a partnership with the prostate cancer advocacy organization, US TOO, to develop a national communications initiative,

called Know Your Options, to better inform men and their families about the disease. The initiative is based on an information package or kit that provides a solid base of information about prostate cancer to help US TOO chapters work with their hometown media. The media, in turn, use the information provided by US TOO with the NCI endorsement to keep their readers, listeners, and viewers informed about the disease. The kit includes the latest medical and scientific information available, as well as information about where US TOO chapter leaders can go for more information, advice, and help.

In addition, information specialists from the NCI-sponsored Cancer Information Service provide more than 60,000 people annually with information about prostate cancer, information about research on the disease, information about screening and treatment options, and information about coping with physical and psychological side effects of the disease and its treatment. The NCI web site provides information about prostate cancer clinical trials as well as information about treatment options for every stage of the disease.

NCI is currently working with the Centers for Disease Control and Prevention and with the Health Care Financing Administration to develop an educational video for men on issues they could face with regard to prostate cancer screening, diagnosis, and treatment. The video, intended to be relevant to a general male audience, will be developed to have special relevance to African-American men. The video will provide educational material on what men need to know about prostate cancer screening options, what they need to know about diagnostic follow-up if a screening test is positive, and what they need to know about treatment options if the diagnosis is positive.

NCI's basic print product about the disease, What You Need to Know about Prostate Cancer, is now available on the web as well. It provides information about prostate cancer; its symptoms, diagnosis, staging and treatment; clinical trials; side effects of treatment; nutrition and other support for prostate cancer patients; and what prostate cancer research holds for the future. A new publication from NCI, Understanding Prostate Changes: A Health Guide for All Men, will soon be available on the web too. It covers all aspects of prostate cancer in more depth than the basic booklet, but also describes non-cancerous prostate conditions. Another product in development, called Prostate Cancer Treatment: Know Your Options, will be published in print format soon and will also be available on the NCI web site.

NCI is communicating vigorously with the cancer research community. Earlier this year, NCI staff described all of the prostate cancer research initiatives that exist at the institute, and placed that information on its web site. The institute then promoted the availability of that information and issued an invitation for grant applications from the scientific community. The promotion of the information on the web site included the placement of advertisements in major scientific journals, the distribution of packets of information to the nation's cancer centers, and the distribution of information through direct mail to cancer investigators. Since the promotion began in late February, the web page listing prostate cancer grant opportunities has had thousands of hits from those seeking information about the grant opportunities.

Mr. Chairman, I appreciate the level of interest this Committee has shown in prostate cancer. I hope my testimony demonstrates NCI's commitment to advancing our knowledge about prostate cancer as rapidly as possible. Our activities, and specifically Dr. Klausner's leadership efforts, over the past year have invigorated the prostate cancer research community. It is this essential partnership between NIH, other funders and that research community that will successfully accomplish the ambitious goals of this plan. I would be pleased to answer any questions you may have.