DEPARTMENT OF HEALTH AND HUMAN SERVICES

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National Cancer Institute

Prostate Cancer Research Plan
FY 2003 – FY 2008

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NIH Prostate Cancer Research Plan
FY 2003 – FY 2008

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Executive Summary

The Prostate Cancer Research Plan for Fiscal Years 2003 – 2008 addresses a request from the Senate Committee on Appropriations (report No. 107-84, page 125) that the National Institutes of Health (NIH) prepare and submit a prostate cancer research plan to address concerns that prostate cancer research has not kept pace with scientific opportunities and the proportion of the male population afflicted with the disease.

As the lead institute for cancer research at the NIH, the NCI has prepared a prostate cancer research plan that serves as the core of this document. Research plans and activities of seven other NIH institutes and centers with significant prostate cancer research portfolios also are included.

The framework for NCI's portion of this plan comes primarily out of the recommendations of the National Cancer Institute's (NCI's) Prostate Cancer Progress Review Group as outlined in its 1998 report, *Defeating Prostate Cancer: Crucial Directions for Research*. This group consisted of representatives from the prostate cancer research and advocacy communities including scientific investigators, clinical researchers, advocates, and patients. Their report, augmented by the efforts of an internal NCI Prostate Cancer Working Group established in 2001, has provided the basis for this plan. Moreover, the prostate cancer research and advocacy organizations were provided with an opportunity to review initial drafts of this FY 2003 – FY 2008 plan, and many of their recommendations have been incorporated into this document.

The NCI plan outlines goals, objectives and near-term milestones in seven different scientific areas that span the continuum of research: 1) Biology, Progression and Metastasis; 2) Etiology and Prevention; 3) Early Detection, Diagnosis, and Prognosis; 4) Treatment; 5) Cancer Control, Survivorship, and Outcomes; 6) Laboratory and Preclinical Models; 7) Resources and Capacity Building.

The research plans from the seven other NIH institutes and centers with prostate cancer research outline their particular prostate cancer research foci and expertise that contribute significantly to the overall NIH prostate cancer research effort.

Increased funding over the past several years has allowed NIH to initiate dozens of new programs aimed at speeding progress in all areas of cancer research. Planning this research has enabled NCI and the other NIH Institutes and Centers to respond to discoveries and opportunities while ensuring the best use of resources. Through these efforts, we will achieve a future when prostate cancer is an uncommon and easily treatable disease.

Introduction

This report has been prepared by the National Institutes of Health (NIH) of the Department of Health and Human Services in response to the following request from Congress.

In its report on the Fiscal Year 2002 budget for the Department of Health and Human Services, the Senate Appropriations Committee made the following statement:

> "The Committee believes that prostate cancer research has not kept pace with the scientific opportunities and the proportion of the male population who are afflicted with the disease. This has resulted in significant gaps in scientific and clinical knowledge that contribute to the ongoing impact of prostate cancer on patients and their families. NIH has begun to address this shortcoming in the 5-year prostate cancer research strategy presented to Congress in June 1999. The Committee strongly urges the NIH to renew its commitment to prostate cancer research with special emphasis on accelerating new avenues for basic research, drug development and clinical research. The Committee further requests that NIH submit a prostate research plan for fiscal year 2003 to fiscal year 2008 by April 1, 2002. In developing this plan, the Committee urges the NIH to consult and work closely with the research community, clinicians, patient advocacy groups and the Congress." (Senate Report No. 107-84, page 125)

The National Cancer Institute has coordinated a comprehensive report addressing the NIH plans for accelerating prostate cancer research over the next six years.

Our Challenge

Prostate cancer is the most common type of cancer in men with the exception of skin cancers. In 2001, an estimated 198,100 men were diagnosed with the disease, and some 31,500 died from it. As the U.S. population ages, the impact of this cancer will increase. No other cancer rises in both incidence and mortality with increasing age as rapidly as prostate cancer. Furthermore, certain segments of the population are disproportionately affected. For example, African American men are far more likely to develop prostate cancer and twice as likely to die from it than are other Americans.

Although significant progress has been made over the past several years to improve our understanding of prostate cancer, there is still much to learn about its causes, early detection, diagnosis, treatment, and prevention. Over time, we have learned that prostate cancer is a very heterogeneous disease with a highly varied clinical course. Our inability to distinguish tumors that will lead to fatal disease from those that will remain clinically insignificant makes selecting optimal treatment regimens difficult.

It is critical that we:

- Elucidate the molecular and cellular processes that lead to prostate cancer initiation, progression, and metastasis.
- Discover genetic, biochemical, environmental, and lifestyle factors and their interactions that

define prostate cancer risk, play causal roles in prostate cancer initiation and progression, and inform the development of new strategies for prevention and early detection.

- Use knowledge gained about the molecular and cellular biology of prostate cancer to develop improved methods for detecting and diagnosing pre-malignant and malignant lesions and for better predicting disease progression and response to therapy.
- Accelerate development and validation of optimal treatments that target the molecular and cellular characteristics of prostate cancer.
- 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.
- Develop and validate accurate prostate cancer models and ensure that they are integrated into research on the biology, prevention, early detection and treatment of prostate cancer.
- Maximize the effectiveness and efficiency of prostate cancer scientists by providing them with essential resources and infrastructure for conducting their research.

Our Response

As the lead institute for cancer research at the National Institutes of Health (NIH), the National Cancer Institute (NCI) has developed a prostate cancer research plan that incorporates the numerous recommendations outlined by the Prostate Cancer Progress Review Group (PRG) in its 1998 report, *Defeating Prostate Cancer: Crucial Directions for Research,* as well as specific plans and recommendations of the other NIH Institutes and Centers with prostate cancer research portfolios. Prostate cancer research and advocacy organizations reviewed initial drafts of this FY 2003 –FY 2008 plan, and many of their suggestions and recommendations have been incorporated into this document.

The NCI Prostate Cancer PRG consisted of representatives from the prostate cancer research and advocacy communities including, scientific investigators, clinical researchers, advocates, and patients. As envisioned in 1999 following the publication of the PRG Report, NCI has initiated a process to report progress in implementing the PRG recommendations. An internal working group of prostate cancer experts has been assembled and is in the process of choosing measures of progress, collecting data, and preparing a progress report. When the progress report is complete, a group of scientists, clinicians, and advocates, including some former Prostate Cancer PRG members, will meet to review the Progress Report along with this six year prostate cancer research plan and, if indicated, recommend adjustments to NCI strategies.

NIH has long recognized that it is very difficult, if not impossible, to plan scientific discoveries and progress. Scientific knowledge evolves over time and can be influenced greatly by new technologies and breaking research findings. For example, the February 2002 issue of the journal *Nature Genetics* reports on research supported by NCI and the National Human Genome Research Institute that led to the identification of a second gene linked to hereditary prostate cancer. This finding will likely contribute to our understanding of prostate cancer biology and to the development of new treatments. Similarly, estimating specific funding amounts for research on a disease over a six-year period can be a challenge, requiring assumptions about budget growth coupled with predicting in what directions and how rapidly the science will advance over this period of time.

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. At a strategic level, this is our plan for scientific discovery and the application of knowledge related to prostate cancer over the Fiscal Years 2003–2008.

National Cancer Institute

On the basis of the Prostate Cancer PRG Report and the efforts of the internal Prostate Cancer Working Group, NCI has identified seven strategic areas that provide the framework for this plan:

1. Biology, Progression, and Metastasis
2. Etiology and Prevention
3. Early Detection, Diagnosis, and Prognosis
4. Treatment
5. Cancer Control, Survivorship, and Outcomes
6. Laboratory and Preclinical Models
7. Resource and Capacity Building

The goals, objectives, and strategies outlined for each of these seven areas identify critical needs for advancing basic scientific studies; identifying and tracking risk, incidence, and mortality information; developing evidence-based interventions; and testing those interventions in the clinical setting. As with current studies on prostate cancer, implementation of these plans will address gaps in knowledge, generate new research opportunities, and provide hope for better interventions in the future. As we carry out the plan, we will also improve our understanding of and ability to address prostate cancer-related health disparities, move research findings into clinical practice and public health programs, and leverage resources through collaborations and partnerships among individual investigators and across public and private sector organizations.

Biology, Progression, and Metastasis

Over the past decade, we have made significant progress in characterizing the molecular and cellular changes that underlie prostate cancer. 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. These findings raise hopes that we can improve the prevention, diagnosis, treatment, and control of prostate cancer.

Unfortunately, our understanding of the mechanisms that dictate prostate cancer initiation, progression, and metastasis is still quite limited. To make further progress, we need reliable experimental models that mimic the changes that occur in human prostate tumors (see priorities for model development ahead). In addition, basic research is needed to identify genes important in prostate cancer, the pathways they set in motion to produce and grow a tumor, and the relationships between these genes and pathways at various times in the cancer process. An equally important area of research is to understand the roles of the micro- and macro-environment of a tumor in the development and progression of prostate cancer. Such research includes identifying the biological changes influenced by biological, physical, and psychosocial factors.

Recent Advances in Research:

Abnormalities on Chromosomes 8 and 10 May Be Associated with Prostate Cancer Development. NCI-supported researchers identified a mutation on chromosome 8 (8p21) in the tumors of approximately 80 percent of prostate cancer patients studied. This region overlaps a region that was identified as a locus for familial breast cancer. Deletions were also found in 63 percent of precancerous prostate lesions, suggesting that abnormalities on 8p21 may be associated with early stages of prostate cancer development. A map of this region is being constructed, and researchers have begun analyzing candidate genes that reside in this area.

Candidate Tumor Suppressor Genes Identified. In other NCI funded research, investigators are identifying new candidate tumor suppressor genes for study. One group of NCI-funded researchers used a combination of *in vitro* techniques and genetic database searches to determine that the gene *LZTS1* on chromosome 8 (8p22) is involved in the regulation of cell growth and may be a prostate tumor suppressor gene. Another group showed that the gene *KLF6*, located on chromosome 10p, is mutated in a subset of prostate cancer tumors, but not in normal prostate tissue from the same individuals. Their data suggest that *KLF6* is a tumor suppressor gene involved in human prostate cancer.

Osteoclasts Play an Important Role in Bone Metastasis of Prostate Cancer. Scientists have long known about the role of osteoclasts – cells that are the normal precursors to bone formation – in bone metastasis. They have more recently discovered the extensive, but little understood role of osteoclasts – cells that are normally involved in the breakdown of bone. To examine the contribution of osteoclasts to bone metastasis, NCI-funded researchers injected human prostate cancers cells both beneath the skin and into a leg bone of mice. Tumors easily grew at both injection sites when osteoclast activity was normal. When researchers used a drug called osteoprotegerin to block osteoclast activity at the same time as injecting the cancer cells, subcutaneous tumors would still grow, but tumor growth in the tibia was prevented. The results suggest that osteoclast activity is integrally involved in the establishment of prostate metastasis in bone and that inhibition of osteoclast activity may prevent or slow this growth.

Goal for Biology, Progression and Metastasis

Elucidate the molecular and cellular processes that lead to prostate cancer initiation, progression, and metastasis.

Objectives and Strategies

1. Identify the molecular pathways that cause prostate cancer and its progression and metastasis.

- Identify unique genes expressed during prostate cancer initiation and progression.
- Define the molecular pathways that cause prostate cancer by thoroughly characterizing genetic variations in molecular profiles. Relate these pathways to one another to understand the cascade of events that lead to and sustain prostate cancer.
- Determine the roles of nuclear receptors, their interactive proteins, and steroid-metabolizing enzymes in prostate development and tumorigenesis.
- Elucidate the molecular mechanisms associated with prostate cancer metastasis.

Selected Near-Term Milestones

– Use the Tumor Gene Index to build a complete index of prostate cancer-related genes.

- Extend the Genetic Annotation Initiative, a component of the Cancer Genome Anatomy Project, to characterize genetic variations in molecular profiles of prostate tissue.
- Continue to support research funded through the Role of Hormones and Growth Factors in Prostate Cancer Initiative to explore the underlying mechanism(s) of action of hormones and growth factors in the regulation of prostate development and tumorigenesis.
- Encourage new projects through the Biology, Development, and Progression of Malignant Prostatic Disease Initiative.
- Continue to study the molecular and cellular biology of metastatic prostate cells through the Molecular and Cellular Biology of Metastatic Tumor Cells Initiative.
- Continue to support research funded through the Innovative Molecular Analysis Technologies Program to differentiate phases of prostate cancer progression.

2. Understand the molecular mechanisms behind androgen-independent prostate cancer (AIPC).

- Determine the roles of mutations in the androgen receptor.
- Define the proteins that stimulate expression of the androgen receptor and that interact with it.
- Identify the changes in the expression of receptors, co-activators, and repressors involved in the androgen-response mechanism.
- Identify the biological mechanisms behind the side effects of treatment for AIPC.

Selected Near-Term Milestones

- Through the Role of Hormones and Growth Factors in Prostate Cancer Initiative, continue to explore the underlying mechanism(s) of action of hormones and growth factors in the regulation of prostate development and tumorigenesis.
- Support research on AIPC through the Pilot and Feasibility Program in Urology and the initiative entitled Complex Formation in Hormonal Regulation of Gene Expression.

3. Understand the role of the tumor micro<u></u>environment in the development of prostate cancer.

- Define the communications among stromal, endothelial, immune, and cancer cells that control or promote tumor growth.
- Characterize the role of stromal, epithelial, endothelial, and immune cells in the selective metastasis of prostate cancer cells to certain sites (especially bone), in the access of drugs to the malignant cells, and in the development of drug resistance.

Selected Near-Term Milestones

- Continue to study the molecular and cellular biology of metastatic prostate cells through the Molecular and Cellular Biology of Metastatic Tumor Cells Initiative.

- Fund the Molecular Interactions Between Tumor Cells and Bone Initiative to promote a better understanding of the pathophysiology of bone metastasis, especially as it relates to tumor cell-bone interactions and the delineation of the mechanisms of tumor metastasis to bone.

4. **Understand the role of the tumor macroenvironment in the development of prostate cancer.**

   - Identify the biological changes in prostate cells and tissues that are initiated by factors such as diet, stress, physical activity, and exposure to infectious and other environmental agents.
   - Identify the biological changes in prostate cells and tissues that are influenced by psychosocial factors such as attitudes, beliefs, and ethnic and cultural factors.

5. **Understand the relationship between the clinical course and biological features of prostate cancer to further understand the molecular and cellular underpinnings of the disease and improve prevention, detection, and treatment.**

   - Correlate the clinical behavior of prostate cancer with the molecular and cellular characteristics of prostate tumors.

   Selected Near-Term Milestones

   - Continue to support collaborations between basic scientists and clinical investigators to conduct correlative laboratory studies on patients participating in large prevention and treatment trials. The aims of these studies are to further the understanding of prostate cancer biology and improve prevention, detection, and treatment methods.

Etiology and Prevention

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. Increasing our understanding of causes is essential to the development of effective prevention methods. Currently, limited knowledge hinders prevention efforts and underscores the need to more fully identify these variables and determine how they interact to modify risk. Further research is also needed to determine what causes some prostate cancers to become particularly aggressive while others remain relatively harmless. Identifying risk factors and determining how they contribute not only to onset of the disease but also to progression will provide the foundation for effective prevention strategies.

Epidemiologic studies have documented that older age, family history, and race are risk factors for prostate cancer. These findings show that risk is greater among men with a family history of the disease, suggesting that genetic susceptibility contributes to its development. They also suggest that prostate cancer incidence and mortality rates vary among countries and racial and

ethnic groups. African Americans have the highest mortality rates for prostate cancer in the world, while Asian Americans have substantially lower rates. Although these family and racial/ethnic differences are well documented, how they influence risk is poorly understood. Even less is known about the influence of biochemical differences such as steroidal hormones and growth factors and the roles of environmental and lifestyle risk factors such as diet, exercise, and infectious diseases.

Recent Advances in Research:

Large Study Shows Positive Effects of Vitamin E in Preventing Prostate Cancer. A large cancer prevention trial conducted by the National Cancer Institute (NCI) in collaboration with the National Public Health Institute of Finland showed that daily use of a modest-dose vitamin E supplement led to a striking reduction in prostate cancer incidence. These promising results have enormous public health implications in that they describe the first time a simple, practical intervention has been shown to protect against the most common cancer in American men. How vitamin E works to prevent prostate cancer is the focus of ongoing research, such as the Selenium and Vitamin E Cancer Prevention Trial (SELECT), and may also have relevance to other cancers.

Researchers Identify Specific Gene Associated with Prostate Cancer in Some Families. Researchers from a consortium of 14 institutions, including the National Human Genome Research Institute (NHGRI) and investigators supported by the NCI, have found mutations that inactivate the RNASEL gene in some families with a history of prostate cancer. RNASEL is a gene that plays a role in defending cells from viruses and assists in normal cell turnover or programmed cell death. Inactivating this cellular self-destruct mechanism through genetic mutation may help scientists understand why some prostate cells become cancerous. This new discovery provides further proof that hereditary factors play a major role in prostate cancer risk. Investigators continue to aim at identifying all of the common contributing genes to hereditary susceptibility.

Genetic Mutation May Explain Higher Rates of Prostate Cancer in Certain Populations. NCI-supported researchers have identified a genetic mutation that may provide clues to the causes of prostate cancer and help to explain the much higher rates of prostate cancer among African American and Hispanic American men as compared to Caucasians. Because prostate cancer is known to "feed off" male hormones, this research team studied a gene for the enzyme steroid 5-alpha-reductase – that controls aspects of hormone metabolism. They identified a simple mutation on the *SRD5A2* gene that occurs rarely in most healthy African American and Hispanic American men, but much more frequently in those who have prostate cancer. The more advanced the cancer, the more often this mutation seems to be present. This intriguing finding requires further evaluation and confirmation, but it identifies a potential prostate cancer related gene that may be especially important for specific racial or ethnic groups.

Goal for Etiology and Prevention

Discover genetic, biochemical, environmental, and lifestyle factors and their interactions that define prostate cancer risk, play causal roles in its initiation and progression, and inform the development of new strategies for prevention and early detection.

Objectives and Strategies

1. **Identify the role of biochemical and environmental risk factors, susceptibility genes, and their interactions in prostate cancer causation and progression.**

   - Develop tools for the study of gene and environment interactions.
   - Investigate the role of biochemical factors, including steroidal hormones and growth factors, in prostate cancer causation.
   - Investigate the role of environmental and life style factors, such as environmental

exposures, infectious agents, diet, and physical activity in promotion and inhibition of prostate carcinogenesis and cancer progression.

- Identify high-penetrance cancer-predisposing genes in high-risk families and investigate how these genes and other more common genetic polymorphisms inter-relate with environmental factors to modify prostate cancer risk.

Selected Near-Term Milestones

- Pool high quality environmental exposure and biologic specimen data available through the NCI Cohort Consortium to identify critical gene-environment interactions in endogenous hormone pathways for over 7,000 cases of prostate cancer.
- Extend the Genetic Annotation Initiative to identify new gene variants relevant to prostate cancer in clinically and epidemiologically defined populations, and for various molecular applications.
- Continue promotion of collaborations such as the International Consortium for Prostate Cancer Genetics (ICPCG) to address such issues as identifying the most important regions of the genome for prostate cancer.
- Fund scientifically meritorious applications submitted in response to the recently released request for applications entitled: *Molecular Targets for Nutrients in Prostate Cancer Prevention*.
- Support studies through the Cancer Genetics Network (CGN), such as the Prostate Cancer Gene Discovery Pilot, to recruit families with multiple members with a prostate cancer diagnosis, to accelerate studies of hereditary and environmental factors that may increase prostate cancer risk.
- Collaborate with the National Institute on Aging (NIA) to fund scientifically meritorious applications received in response to the request for applications titled: *Interdisciplinary Studies in the Genetic Epidemiology of Cancer*.

2. Identify genetic, environmental, and life style factors responsible for incidence and mortality variations among groups defined by race, ethnicity, and geography.

- Continue to support development of studies to address mechanisms underlying racial and ethnic disease disparities.
- Stimulate epidemiologic research to study the determinants of geographic disease patterns.

Selected Near-Term Milestones

- Support efforts to understand mechanisms underlying disparities through projects such as the Southern Community Cohort Study, a long-term prospective cohort study which should help to elucidate causes of disparities in prostate cancer incidence and mortality across racial groups.
- Through prostate Specialized Programs of Research Excellence (SPOREs), continue the design and development of tissue microarrays for studies of special populations.
- Continue development of the international case-control study of prostate cancer in African and U.S. populations, focusing on disease origins.

3. **Identify and evaluate promising preventive agents and strategies that target cancer causes.**

   - Use discoveries about causal factors to develop targeted prevention strategies, including the use of chemopreventive agents and control of environmental and life style risk factors through behavioral interventions.
   - Evaluate the full range of promising preventive agents, alone and in combinations, in Phase I, II, and III clinical trials.

   Selected Near-Term Milestones

   Continue to expedite movement of novel molecules and concepts from the laboratory to the clinic for clinical trials of efficacy through programs such as Rapid Access to Preventive Intervention Development (RAPID). (Examples include the following agents: isoflavones (from soy), polypheolic (from tea), COX2 antagonists, vitamin D analogs, selenium analogs, and triterpenoid analogs.)

   – Evaluate potential chemopreventive agents from such categories as: natural products, anti-androgens, selective estrogen receptor modulators, receptor tyrosine kinase inhibitors, anti-proliferative/differentiation inducers, and non-steroidal anti-inflammatory agents.
   – Continue support for a full spectrum of prevention trials, including large studies such as SELECT and the Prostate Cancer Prevention Trial (PCPT), and smaller Phase III trials.

Early Detection, Diagnosis, and Prognosis

Current prostate cancer screening and early detection results pose serious dilemmas for men and their health care providers. This is because many more prostate cancers are present in men over age 50 than ever become clinically apparent or significant. Although early detection, primarily through PSA screening, may have decreased prostate cancer mortality, the test does not differentiate between tumors that will lead to fatal disease and those that will remain clinically insignificant. In the recent American Society of Clinical Oncologists (ASCO) meeting new research was presented that might lead to changes in the clinical practice as related to monitoring person's PSA levels.

Recent research is providing important information that is expanding our understanding of prostate cancer biology, a prerequisite to developing diagnostic tools and identifying new targets for prevention, early diagnosis, and treatment. In addition, new technologies such as microarrays and proteomics are providing improved means of identifying diagnostic markers. The challenge will be to select the most promising markers and to determine how to validate and develop them into diagnostic tests.

Recent Scientific Advances

Thymosin beta 15 may be a new prognostic marker. A newly discovered protein, thymosin beta 15, that stimulates cell motility and invasion of surrounding tissues has been found to be present in much higher amounts in prostate cancer cells and in those patients who fail therapy. Thymosin beta 15 is currently being tested in a clinical trial as a potential prognostic test for prostate cancer.

PSA levels in White and African American men are similar. In an effort to understand why prostate cancer rates are higher in African Americans than in other American men, researchers measured PSA levels in the blood of African American and White American men. PSA levels were found to be comparable and therefore do not explain the disparity.

New PSA monitoring protocols. In the recent American Society of Clinical Oncologists new research was presented suggesting annual screening of men with PSA between 2-4 and once every five years for those with PSA of 1 or less.

New information on the value and use of PSA screening. Findings from the Baltimore Longitudinal Study of Aging have provided several insights into the value and use of Prostate Serum Antigen (PSA) screening, including data on levels of risk related to age, PSA level, and rates of change in PSA level.

Two new imaging agents for detecting prostate cancer are under study. One is a contrast agent that enhances positron emission tomography (PET). The second is a probe that can improve the accuracy with which magnetic resonance imaging can detect the earliest stages of angiogenesis accompanying tumor development.

Magnetic Resonance Spectroscopy Imaging(MRI) will be tested in a multi-institutional clinical trial to determine its value in identifying active tumors in the prostate following positive screening tests.

Goal for Early Detection, Diagnosis, and Prognosis

Use knowledge gained about the molecular and cellular biology of prostate cancer to develop improved methods for detecting and diagnosing pre-malignant and malignant lesions and for better predicting disease progression and response to therapy.

Objectives and Strategies

1. Identify and validate biologic markers of pre-malignant, early stage, latent and potentially aggressive disease.

- Use information on the basic biology of prostate cancer and emerging technologies to identify candidate diagnostic markers.
- Use statistically appropriate models to validate biological markers including both innovative pilot approaches and large studies of diagnostic markers.

Selected Near-Term Milestones

- Expand programs such as the NCI Intramural Program on Translational Research: Molecular Markers for Early Detection, Prognosis Prediction, and Intervention to identify and validate epigenetic markers of prostate cancer.
- Expand validation programs for prostate cancer markers as results emerge from the Director's Challenge, Early Detection Research Network (EDRN), the Cancer

Biomarkers Research Group, Prostate Cancer Specialized Programs of Research Excellence (SPOREs), Cancer Genome Anatomy Project (CGAP), and other programs.
- Develop applied algorithms and statistical methods to analyze multiple biomarkers and patterns of molecular changes and link those changes with clinical outcomes.
- Continue to develop clinical applications of tests specific to prostate cancer through the Clinical and Epidemiologic Centers of the EDRN.
- Develop an expansive prostate tissue resource through the establishment of the Shares Pathology Informatics Network (SPIN) and encourage communication and collaborative efforts between Prostate Cancer SPOREs.

2. Use knowledge of etiology and molecular profiles at different stages of development to improve tumor classification and identify patient subgroups.

- Use new knowledge on the biology of prostate cancer and data from powerful new technologies, such as microarray and proteomic analysis, to develop schemes for improved tumor classification and prediction of tumor behavior.
- Develop informatics resources to facilitate the pooling of molecular profiling data in order to increase the statistical power of these analyses.

Selected Near-Term Milestones

- Validate new diagnostic approaches and results of the Director's Challenge through the Program for Assessment of Clinical Cancer Tests (PACCT) and the Cancer Biomarkers Research Group
- Perform analyses of prospective clinical data collected through the Director's Challenge to correlate molecular profiles with prostate tumor characteristics.
- Through the NCI-FDA Clinical Proteomics Program, use innovative proteomics technologies and mass spectrometry to identify additional proteins and proteomic signatures in prostate cancer microdissected tissue samples and in serum.
- Expand collaboration between NCI and private partners to identify different tumor types and their respective characteristics important in devising novel therapeutics.
- Develop a Comprehensive Protein Fingerprinting (proteomics) Program for identifying earlier stages of disease and risk of prostate cancer.
- Initiate a Comprehensive Molecular Technology Program for prostate cancer detection.
- Support the development of high-yield technologies for isolating exfoliated tumor cells in seminal fluid and urine.
- Continue to support the development of the NCI Center for Bioinformatics, the Tissue Micro-Array Database Initiative, and other similar initiatives so that investigators can share results that can be rapidly translated for tumor classification.

3. Develop, evaluate, and apply new technologies that more precisely characterize the biological properties of prostatic lesions and will aid in predicting clinical behavior.

- Develop imaging technologies to provide non-invasive methods for biologically characterizing prostatic lesions.

- Develop improved reagents and probes that will enhance positron emission tomography (PET) scanning and magnetic resonance imaging (MRI).
- Develop computer and mathematical modeling techniques that will improve our ability to diagnose and predict tumor progression using imaging methodologies.
- Integrate functional imaging methods into clinical trials to predict disease progression.

Selected Near-Term Milestones

- Support the development of non-invasive imaging agents and technologies through NCI programs such as the In-vivo Cellular and Molecular Imaging Centers (ICMICs), Small Animal Imaging Resource Programs (SAIRPs), Interdisciplinary Research Teams for Molecular Target Assessment, Molecular Target Drug Discovery, and Molecular Target Laboratories.
- Increase the number of promising imaging agents supported by the Development of Clinical Imaging Drugs and Enhancers Program (DCIDE).
- Establish data banks of standardized digital image data associated with known clinical outcomes for prostate cancer.
- Work through the Innovative Molecular Analysis Technologies (IMAT) Program to develop and apply novel technologies that will enable molecular analysis for distinguishing cancerous from normal prostate cells and aiding in the development of more effective strategies for detection and diagnosis and in predicting responsiveness to treatment.
- Fund grants to develop and test image processing and analysis algorithms using standardized data sets.
- Continue to support protocols for testing functional imaging methods through the American College of Radiology Imaging Network Cooperative Group (ACRIN).

Treatment

Although genuine options are available for curing prostate cancer when it is localized, we do not have reliable ways to predict the behavior of an individual cancer, nor do we know how to predict whether an individual cancer will respond well to one particular treatment compared to another. Moreover, while treatments for localized prostate cancer usually are effective, they are not *always* effective, nor are they free from troublesome side effects. We need to develop optimal treatments for the continuum from early stage disease to advanced lethal prostate cancer.

We will focus attention on the new paradigm of targeting and controlling cancer rather than a seek and destroy or "killing" paradigm that aims treatment at eradication of all cancer cells. This new paradigm has been referred to as a "regulatory model" of cancer, viewing cancer as a maladaptive, evolving process with cancer cells differing from normal cells as a consequence of critical genetic changes leading to dysregulation of growth. Under the regulatory model, standard therapies would be combined with additional therapies to control the growth and spread of remaining cancer cells by targeting the multiple molecular pathways involved in dysregulation. Examples of important pathways include: growth signaling mediated by oncogenes, growth inhibition mediated by tumor suppressor genes, promotion of DNA repair,

promotion of cell death (apoptosis), and formation of new blood vessels (angiogenesis). We should study the integration of therapies to attack multiple pathways in the cascade of events that lead to and sustain malignant disease, using current therapies, such as radiation and hormone therapy, together with molecular therapies, such as those directed at BCL-2 or P53.

Recent Scientific Advances

New Drugs Provide Hope for Prostate Cancer Patients with Bone Metastases
When prostate cancer spreads, it often invades the bones, where it causes severe, debilitating pain. However, several drugs currently under study may combat bone metastases, slowing the spread of the cancer and improving the patient's quality of life. Clodronate, a bisphosphonate, has shown activity against prostate cancer metastasis, opening the door for further studies involving more potent bisphosphonates, or higher doses of the drug. A second drug, Atrasentan, targets the protein endothelin-1, which promotes cell growth in bone and which is overactive in prostate cancer cells.

Radiation Plus Hormone Treatments Extend Lives of Prostate Cancer Patients
NCI-supported investigators conducted a randomized clinical trial in which men who had been treated with surgery for early-stage prostate cancer were assigned either to receive immediate hormonal therapy or to simply be observed until their disease progressed. All of the men had microscopic tumor metastases in their lymph nodes (node positive), putting them at high risk for recurrence of their cancer. The results of this trial, together with evidence from previous studies, support the hypothesis that early hormonal therapy may prolong survival. The trial has changed the standard of care for node-positive prostate cancer patients, and the dramatic results also suggest that early administration of hormonal therapy could extend the lives of many other prostate cancer patients.

Translational Research Promises to Yield New Targets for Treating Prostate Cancer
At this time, our knowledge of exploitable targets for prostate cancer is still developing. NCI is currently funding a number of projects to enhance this knowledge by examining targets in prostate cancer cell lines. These studies may help scientists find ways to block cancer metastasis, suppress the growth of cancer cells by interfering with nuclear proteins, and block tumor growth by controlling expression of certain genes.

Goal for Treatment

Accelerate development and validation of optimal treatments that target the molecular and cellular characteristics of prostate cancer.

Objectives and Strategies

1. **Identify and validate new targets, novel therapeutic agents, and optimal intervention approaches by disease stage in a clinical setting**.

   - Support studies of molecularly targeted agents that influence key pathways implicated in such prostate cancer-related processes as: growth signaling, DNA repair, tumor suppression, cell death (apoptosis), blood vessel formation (angiogenesis), and metastasis.
   - Support rapid movement of promising new agents from academic and other laboratories through clinical trials and into the clinic.
   - Support studies to identify the optimal time to administer therapeutic agents.
   - Accelerate the development and validation of novel technologies, including nanotechnology and advanced imaging for use in delivering therapeutic agents.

- Investigate immunological approaches to prostate cancer, including the development of vaccines that target specific markers expressed by tumors.
- Improve understanding of the technical aspects of treatment (i.e., surgical and radiation technique, post operative care) that lead to decreased complications and improved clinical outcomes in select settings by working with data generated by CanCORS or other groups reporting outcome and treatment data.

Selected Near-term Milestones

- Continue efforts of NCI clinical trials staff and Cooperative Group investigators to ensure that all promising prostate cancer treatment agents undergo phase II evaluation and that safe, effective agents or combination of agents move to phase III evaluations quickly.
- Continue support of large (phase III) trials in prostate cancer, including studies: comparing alternative methods of primary treatment for localized disease; optimizing 3-D radiation therapy as a primary treatment for localized cancers; optimizing the combination of hormonal therapy with radiation for patients at substantial risk of recurrence; adding adjuvant chemotherapy for patients at intermediate to high risk of recurrence; testing new classes of agents that can be effective in delaying clinical progression for symptomatic or asymptomatic patients with rising PSA after initial treatment; and determining if agents and approaches that target bone delay the onset of metastatic disease or improve the treatment of established metastatic cancer.
- Support strategic planning efforts such as NCI State-of-the-Science workshops and other meetings to improve clinical strategies and identify pilot studies of novel approaches.
- Familiarize more investigators with and support prostate cancer trials through "Quick Trials," a relatively new grant mechanism created to support a single clinical trial, which was initially piloted in prostate cancer as a means of stimulating research in this area.
- Through NCI's intramural Center for Cancer Research, continue support of prostate cancer clinical trials, including studies of chemotherapeutic agents; new regiments that combine chemotherapeutic agents with hormonally active drugs; promising drugs that inhibit formation of blood vessels feeding prostate tumors (angiogenesis); and immuneotherapeutic approaches.
- Using both data from the Cancer Genome Anatomy Project (CGAP) and proteomic techniques, discover novel vaccine treatments for prostate cancer.
- Through the Molecular Target Drug Discovery (MTDD) program, identify new molecularly targeted drugs for prostate cancer.
- Support translational research through the prostate cancer Specialized Programs of Research Excellence (SPOREs), with an emphasis on developing novel therapeutic agents and optimal interventions. Several new therapeutic agents are targeting specific prostate cancer cells that regulate tumor growth and cell proliferation. Clinical studies include a proteasome inhibitor (ps-341), a new treatment modality using situ gene therapy combined with anitandrogen therapy for metastatic prostate cancer.

- Using the Rapid Access to Intervention Development (RAID) program, continue to provide resources and services for the pre-clinical development of novel, meritorious prostate cancer agents.

2. Identify promising tools for enhancing and evaluating the effectiveness of new therapies.

- Develop novel techniques to monitor radiation dose in real time, allowing more precise delivery to the tumor and minimizing radiation injury to normal tissue.
- Assess and validate technologies that facilitate and enable image-guided therapy.
- Integrate functional imaging technologies into the design of therapeutic interventions and monitoring of treatment outcomes.

Selected Near-term Milestones

- Enhance programs for image-guided therapy research within programs such as the Prostate Cancer SPOREs and NCI's biological imaging program that emphasize an interdisciplinary problem-solving approach. Projects underway include those aimed at using imaging to better guide external or internal (brachy-radiation beam therapy of prostate cancer, magnetic resonance imaging (MRI) to guide thermal ablation of prostate cancer, and the development of molecular imaging probes to better image prostate cancer through radionuclide techniques.
- Increase collaborations among Clinical Trials Cooperative Groups for testing promising, minimally invasive, image-guided interventions
- Continue development and testing of more precise techniques for radiation delivery through NCI's Center for Cancer Research.

3. Identify and validate intermediate endpoints for clinical trials of local and systemic therapies.

- Identify and validate intermediate endpoints, in addition to PSA, that can serve, in initial trials of a new agent, to provide a signal of a potentially useful biologic effect against prostate cancer.
- Identify and validate intermediate endpoints as reliable indicators of genuine patient benefit and as a basis for Food and Drug Administration (FDA) drug approval.
- Support novel clinical trial designs that focus on and test clinically relevant end points.

Selected Near-term Milestones

- Use the Translational Research Fund (TRF) contract mechanism to support studies aimed at correlating the biological features of prostate cancer with clinical outcomes. This correlation will enable better assessment of response to treatment.
- Expand studies of serum proteomic profiling, a new technology that may prove more accurate than PSA testing.
- Facilitate maker validation through the Program for the Assessment of Clinical Cancer Tests (PACCT).

- Continue development of tools for use in clinical trials to assess whether novel agents are affecting intended targets through programs such as the Interdisciplinary Research Teams for Molecular Target Assessment (IRT/MTA).

4. **Strengthen clinical trial infrastucture including design and patient recruitment to increase the number of rigorous clinical trials that are pivotal to developing and testing novel therapeutics.** (See page 28, Resources and Capacity Building, Objective 3 for strategies and near-term milestones.)

Cancer Control, Survivorship and Outcomes

New approaches to early detection as well as improvements in treatment have resulted in a dramatic rise in the long-term survival rate of prostate cancer patients. Most patients can now expect to live more than 10 years after diagnosis. However, the same treatments that have enabled long-terms survival can also cause potentially disabling effects ranging from minor alterations in day-to-day activities to major functional loss involving critical organs. Furthermore, the true effect on mortality from specific screening and treatment measures remains uncertain. Therefore, more data about all aspects of treatment outcome and quality of life are needed to provide a more comprehensive and complete perspective on the needs of the long-term cancer survivor. Increased surveillance of the early detection, treatment, and outcomes of prostate cancer in the population are required. Better qualitative and quantitative measures of the risk factors, use of interventions, cost of treatment, and quality of life among prostate cancer patients and survivors also are crucial. Major efforts still are needed to stimulate research on prostate cancer survivorship.

Pronounced racial disparities in prostate cancer have led to studies to try to better understand the reasons for differences in prostate cancer incidence, aggressiveness, mortality, and treatment patterns among men in different racial and ethnic groups. Information from NCI's Surveillance, Epidemiology and End Results (SEER) Program has been essential in assessing prostate cancer incidence and mortality trends with a focus on differences among population subgroups. With the participation of SEER registries, the Prostate Cancer Outcomes Study (PCOS) has provided valuable information on health outcomes, such as long-term complications and quality of life, following various treatments for prostate cancer. Follow up of the PCOS cohort is expected to provide the most detailed data ever collected on factors associated with prostate cancer treatments.

Recent Scientific Advances

The Prostate Cancer Outcomes Study - This ongoing study is enabling comparisons of treatment modalities in various combinations in terms of their success medically and on quality of life, and has produced more than a dozen of peer-reviewed publications along with citations throughout much of the prostate cancer outcomes literature.

Estimates of Long-term Treatment Complications Are Higher Than from Previous Studies - Investigators have found that among patients with clinically localized cancer, men receiving radical prostatectomy were more likely than those receiving radiotherapy to be incontinent (10% versus 4%) and to have higher rates of impotence (80% vs. 62%), although large, statistically significant declines in sexual function were observed in both treatment groups.

Diagnosis of Prostate Cancer Is Similar in Different Health Care Settings - In one study comparing treatment and outcomes among Medicare recipients in HMOs and FFS settings, researchers looked at the same geographic area and found that 10-year survival following a diagnosis of non-metastatic prostate cancer diagnosis was similar for men treated in each setting, although there were significant differences in treatment between the FFS and one of the HMOs.

The Races Differ in Their Use of Prostate Cancer Treatment - Despite the increased use of aggressive treatment overall, only 17.2 percent of black men received radical prostatectomies versus 27.7 percent of white men while 49.0 percent of black men had conservative therapy versus 38.1 percent white men.
Study of Cancer Survival Rates in Underserved Populations - Research is demonstrating that differences in cancer morbidity and mortality previously attributed to race are not due to supposed biological differences between populations or between the tumors individuals develop.

Goal for Cancer Control, Survivorship and Outcomes

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.

Objectives and Strategies

1. **Conduct, apply, and disseminate surveillance research to describe and understand trends in the burden of prostate cancer, in screening and in medical practice.**

   - Improve registry data by expanding coverage, improving the quality and coordination of all population-based cancer registries, and enhancing research data resources.
   - Expand systems and methods to enhance the quality of data on risk, health and behaviors; to link screening practices to high quality data on outcomes; to enhance exploration of causes of prostate cancer; to generate new hypotheses on risk; and to identify opportunities for prostate cancer control interventions.
   - Improve dissemination of information on trends and progress in cancer control and care to all interested audiences.
   - Enhance training opportunities in surveillance, health services, and applied research.

   Selected Near-Term Milestones
   - Conduct surveillance research to describe and understand trends in the prostate cancer burden, screening, and medical practice: Because changes in prostate cancer incidence, treatments, and PSA testing in the population continue to occur, we will continue collecting extensive new information through PCOS and other studies such as the California Health Interview, including more minority patients to compare treatment patterns and quality of life.
   - Offer traineeships and Intergovernmental Personnel Act positions in surveillance, with opportunities specifically associated with prostate cancer.

2. **Assess quality of life for prostate cancer survivors and interventions to ameliorate**

symptoms associated with treatment and survival.

- Assess the impact of "watchful waiting" on patient lifestyle and behavior.
- Assess the impact of disease- and treatment-related morbidities on quality of life.
- Examine methods of pain control and their effect on quality of life.
- Examine the impact of prostate cancer on patients' social support systems.
- Assess the population prevalence and health-related quality of life (HRQOL) outcomes of emerging initial therapies for early stage disease, particularly brachytherapy and androgen deprivation therapy.
- Assess the population prevalence and HRQOL outcomes of different treatment approaches for managing asymptomatic biochemical failure, or symptomatic progression of disease.

Selected Near-Term Milestones

- Support research to improve the theory and practice of patient-centered outcomes measurement in cancer, including the development and testing of new instruments, item banking, and computer adaptive testing to improve the efficiency and accuracy of data collection as well as statistical studies to facilitate the "cross-walking" of scores between competing instruments.
- Continue to participate in and provide supplemental funding for the National Quality Forum in order to identify core process measures of cancer care quality.

3. Evaluate the outcomes of screening and treatment interventions, with special emphasis on the impact of the quality of cancer care.

- Improve process and outcome measures, methods and the empirical foundation for assessing the quality of screening and cancer care, in all clinical settings, including clinical trials.
- Enhance the influence of state-of-the-science assessments on screening, care delivery, coverage, and regulation.
- Improve the quality and scope of screening and cancer care by strengthening the quality of cancer communications.

Selected Near-Term Milestones

- Conduct interim analyses of results from the Prostate Cancer Outcomes Study (PCOS), which has provided valuable information on health outcomes, such as long-term complications and quality of life, following various treatments for prostate cancer. This is expected to provide the most detailed data ever collected on factors associated with prostate cancer treatments.
- Evaluate, in collaboration with the research and clinical community, the potential of a PCOS II, which would permit more detailed and up-to-date treatment and outcome comparisons, including, for example, brachytherapy and newer forms of radiation therapy. Such a study could also address, longitudinally, the consequences of various screening interventions.
- Through sustained support for Cancer Care Outcomes Research and Surveillance Consortium (CanCORS), conduct studies of the dissemination of state-of-the-science

therapies and palliative care into community practice, the influence of modifiable risk factors, and disparities in the delivery of quality cancer care. These studies are currently limited to lung and colorectal cancer. If the interim results justify doing so, expand the studies to include prostate cancer.

- Sustain support for Cancer Research Network population laboratories for cancer control research, with additional emphasis on studies of the quality of cancer care in community settings. Provide results of this research to assist in monitoring the success of prostate cancer initiatives as well.
- Evaluate quality of life for prostate cancer survivors, and interventions to ameliorate symptoms associated with treatment and survival: NCI will evaluate the long-term physical effects of survivorship and the context of the prostate cancer survivorship experience across different age groups and ethnic, cultural, and socioeconomic status categories. In addition, there is a need to better understand the impact of prostate cancer on the well-being of family members affected by this illness.
- Initiate the National Quality Forum's Quality of Cancer Care measurement project (CanQual), which will identify a set of core measures of cancer care quality that will be applied to prostate and other cancers.
- Develop standardized instruments to assess prostate intervention outcomes. A Cancer Outcomes Measurement Working Group (COMWG), convened by NCI in 2000 will continue its work to identify standardized measures of outcomes for major cancer sites, including prostate cancer.

4. Conduct biobehavioral research to understand how patient preferences and behaviors affect treatment decisions and outcomes and test interventions based on findings.

- Conduct studies to better understand the biological correlates and consequences of patient environment, attitudes and behaviors.
- Continue to discover and refine metrics of the relationship of patient knowledge, attitudes and behavior to treatment decisions and disease outcomes.
- Develop interventions and best practices to assist physicians and other care providers in recognizing and, to the degree possible, modifying patient attitudes and behaviors that may inhibit the effectiveness of treatment.
- Improve the understanding and quality of national and targeted campaigns for better consumer decisions regarding prevention, screening and treatment

Selected Near-Term Milestones

- Gather and analyze nationally representative data to assess the current status of cancer communications and their use in cancer care decision making. This study places special emphasis on the leading cancers, including prostate cancer.
- Within the Centers of Excellence in Cancer Communications Research, support projects to improve patients' understanding of the risks, benefits, and costs of curative therapies and palliative interventions for prostate cancer.
- Building on the success of new NCI-supported multimedia tools, such as an Emmy-nominated television special on prostate cancer choices, to enhance prostate cancer decisions by patients, to create new communications products and tools to improve the accuracy, clarity and timeliness of cancer care decision making.

- To accelerate the adoption of important prostate cancer patient interventions, convene an interdisciplinary group of scholars, organization gatekeepers, and funders to identify research strategies and opportunities for collaboration.
- Set and implement an inter-institutional research agenda for improving information campaigns to promote better prostate-cancer related behaviors and decisions.

5. Expand the channels for dissemination and diffusion of cancer research findings

- Expand support for training of public health personnel, voluntary association staff and volunteers.
- Establish and maintain local and regional partnerships.
- Support researchers in the dissemination of evidence-based interventions.

Selected Near-Term Milestones

- Continue to build and strengthen the NCI-sponsored Special Populations Networks for Cancer Awareness Research and Training (SPNs), established at 18 research institutions in 2000, which will build relationships with community-based programs to foster cancer awareness activities and the development of researchers in minority and underserved communities.
- Continue to support interagency demonstration projects organized through the Quality of Cancer Care Committee, a forum for coordinating Federal activities to improve the quality of cancer care.
- Continue work with the Agency for Healthcare Research and Quality to fund research on decision aids ("Making Quality Count for Consumers and Patients").
- Assess the status of low-literacy research and national initiatives in order to develop a strategic plan for low-literacy programs and materials.
- Build and sustain the Translating Research into Improved Outcomes (TRIO) program recently initiated by NCI to: 1) better communicate cancer intervention research and surveillance data, 2) expand partnerships with other Federal agencies and national voluntary and philanthropic organizations, 3) identify special regional and local partnership opportunities for model infrastructure programs.

Laboratory and Preclinical Models

In its quest to rapidly advance prostate cancer research, NCI is committed to developing more accurate models of prostate cancer. Prostate cancer researchers will use these models to screen drug candidates, conduct preclinical studies of new drugs, and better understand the biology of human prostate cancer. Currently, multiple models are available to the scientific community such as xenograft, cell lines, transgenic, reconstitution, spontaneous tumor, and hormonally induced models. However, limitations within each of these model systems have prompted NCI to support the development of additional models that more faithfully imitate the human disease.

NCI's strategic plans to develop more accurate prostate cancer models focus on five major areas: (1) mouse models, (2) models in other species, (3) transplantation technologies in model development, (4) models for studying prostate epithelium and underlying stroma, and (5) computational and in-silico mathematical models of prostate cancer.

Advances in Research

Researchers use mouse models in which certain genes have been altered or inactivated to advance studies on several aspects of prostate cancer.

- The normally functioning *PTEN* gene – whose mutated form is found in a large percentage of prostate and other cancers – plays a critical role in regulating cell growth and specialization and acts as a tumor suppressor gene. Researchers are using mouse models to study how and when the loss of PTEN protein function fits into the chain of genetic mutations that can lead to tumor development. One research group has designed a mouse model that lacks PTEN and another important protein, p27. These mice develop spontaneous tumors in the prostate and other organs.
- A mouse model that carries a defect known as the "*TRAMP* transgene" permits investigators to analyze sequential genetic changes that occur during the multi-step process in prostate carcinogenesis. Researchers use this model to study hormone-independent tumor growth, which occurs in humans with the failure of androgen-ablation therapy. The model has been used in several chemoprevention and chemotherapy studies.

X***enografts model the late stages of prostate cancer progression***. A model has been developed to study tumors that stop responding to androgen ablation therapy. For this model, investigators first isolated a special cell line from a patient with advanced prostate cancer. When some of these cells are transferred to the prostate of mice, they metastasize to a number of organs, including the lymph nodes and skeleton. The pattern of metastasis is similar to that seen in human prostate cancer.

Research using micro-PET is expected to reveal new avenues for human therapy. Scientists involved in developing mouse models for prostate cancer have teamed with colleagues from the NCI-funded Small Animal Imaging Resource Program to use positron emission tomography (micro-PET, when it is used on mice) to study prostate cancer development, from its beginnings in the prostate to its metastasis (spread) to bone and other organs.

Goal for Laboratory and Preclinical Models

Develop and validate accurate prostate cancer models and ensure that they are integrated into research on the biology, prevention, early detection and treatment of prostate cancer.

Objectives and Strategies

1. Identify and design models that can accurately mimic the natural progression of human prostate cancer, namely its genetic characteristics, interactions with the host, microenvironment, progression and metastasis.

- Create and validate *in vitro* models to address unmet research needs.
- Develop and validate prostate cancer models in the mouse and other species.
- Create models to study prostate epithelium, the underlying stroma, and metastasis.

Selected Near-Term Milestones

Fund supplements to encourage research that designs, derives, and uses organotypic models--multi-cell culture systems that attempt to reproduce in cell culture some of the aspects of cancer behavior that can now be studied only in animals.

- To better characterize mouse models of prostate cancer, foster collaboration among prostate researchers from the Director's Challenge initiative, the Early Detection Research Network, the prostate SPOREs (Specialized Programs of Research Excellence), and the NCI Center for Cancer Research to evaluate specimens from the best current mouse prostate cancer models and from human prostate cancers to determine what genes and proteins they express.
- Use program announcements to encourage development and use of alternate mammalian model systems such as multiple cell types from a particular tissue, studied together, as reconstituted multi-cellular systems, or as tissue explants in culture or in animals as transplants. These would more closely resemble normal tissue or emerging tumors than do dispersed cells cultured on plastic.
- Support human/mouse cross-comparisons to determine stage-specific validation using innovative technologies for the molecular analysis of cancer through the program announcement process.

2. Use mouse and other models to characterize molecular and cellular processes in human prostate cancer and disseminate this information widely to the research community.

- Support disease site-specific discovery groups of mouse modelers, population scientists and statistical geneticists to employ mouse models to find the genes, pathways, and environmental exposures that determine human cancer susceptibility and affect response to therapy.

Selected Near-Term Milestones

Use the MMHCC, the Cancer Genetics Network (CGN), and the Cancer Family Registries (CFR) to assemble disease-site specific discovery groups to apply a newly described gene identification method to mouse models. Integrating human and mouse studies ensure that as the human genes are identified, their functions can be rapidly assessed in the mice. The mouse models also permit investigators to distinguish the contributions of multiple genes to cancer susceptibility from the environmental interactions that confound human genetic studies.

- Through the NCI Center for Bioinformatics, store data about prostate cancer mouse models in relevant databases to enable information dissemination to the entire research community and support use of research findings for further discovery.
- Encourage innovation in translational application of the models and in-depth characterization through reissuing the MMHCC RFA.

3. Use validated models to identify and test preventive, detection and therapeutic agents.

- Use genetically engineered mice and other models to identify and test new molecular target-based approaches for prevention, detection, and therapy.
- Design and conduct appropriate preclinical trials using these models.

Selected Near-Term Milestones

Encourage studies that use genetically engineered mouse cancer models for cancer therapy-related objectives. Provide special funding consideration to high quality applications that involve prostate cancer models.

- In alliance with representatives from the pharmaceutical and biotechnology sectors, sponsor a Preclinical Trials Roundtable that is open to the research community. The Roundtable will set specific goals for using genetically engineered models to identify new therapeutic targets; test new, targeted agents; design appropriate preclinical trials using these models; and define the genetic determinants of response or resistance to therapy.
- Convene a meeting with pharmaceutical biotech company executives, academic licensing office heads, and the FDA to discuss MTAs that restrict testing of multiple proprietary agents in a single preclinical model.
- MMHCC and other NCI funded mouse modelers, will partner with the NCI Molecular Targets Laboratories and the Prostate Cancer SPOREs to test agents under development.

Resource and Capacity Building

The infrastructure for tissue acquisition, storage, and use; data sharing across disciplines; and information sharing to link the efforts of various initiatives and programs are challenges to prostate cancer research. The scientific community has witnessed an incredible surge in the development of new biomedical technologies, and in the next few years, tissue-based and bioinformatics systems for prostate cancer research will expand greatly. NCI has played a critical role in developing and applying a wide variety of novel technologies, but there is room for improvement in the dissemination and application of such new technologies for prostate cancer research.

Equally critical is the need to provide the kind of research infrastructure that will support multidisciplinary, collaborative efforts and promote translational research. Substantial and sustained investments in the infrastructures that allow the development and testing of emerging basic science discoveries into clinically useful products are essential.

We must also work to ensure the adequacy of our clinical trials system. Over the last several years, the scope of NCI drug development for prostate cancer has grown several fold. The number of NCI-funded prostate cancer clinical trials ongoing at any one time is now in the range of 250-300 phase I, II, and III studies, making it one of the most active segments of the clinical trials portfolio. A clinical trials mechanism that is adapted to the special needs and opportunities in prostate cancer can play a major role in accelerating progress.

People are our most valuable resource, and it is absolutely critical that we prepare experienced and new researchers to work in multidisciplinary, collaborative environments and to effectively use the full range of tools available to them. Prostate cancer researchers must also have the necessary funding to enable the finest quality research efforts to thrive.

Ongoing Initiatives That Support Resource and Capacity Building

The NCI **Tissue Expediter** provides information on sources of human tissue specimens and helps prostate cancer and other researchers locate the tissue and related data they need. The tissue expediter is a scientist with contacts in the resources community who can rapidly relate investigator needs to appropriate resources. The **Specimen Resource Locator** is an invaluable database with query tools to help prostate cancer researchers locate resources such as tissue banks and tissue procurement services with access to normal, benign, pre-cancerous and/or cancerous human tissue.

The **Cancer Genome Anatomy Project** (CGAP) is a multi-initiative NCI program to build a complete profile of genes expressed in normal, precancerous, and cancer cells and help cancer researchers elucidate major steps of tumor development, develop molecular diagnostic techniques, and identify molecules that can be used for early detection or drug discovery. Researchers throughout the world have started mining CGAP databases to identify molecular signatures of prostate and other cancers and are discovering new potentially cancer-causing genes, identifying candidates for molecular targets research, and helping to build microarrays for cancer cell signature research.

NCI has expanded the **Prostate Cancer Specialized Programs of Research Excellence** (SPOREs) for translational research, from four funded Prostate Cancer SPOREs in 2000 to from six to nine SPOREs in 2003. The programs provide valuable infrastructure for translational research to develop new scientific approaches in early detection, diagnosis, treatment, and prognosis of human prostate cancer. An expanded network of prostate SPOREs is scheduled to bring about Inter-SPORE scientific studies that will conduct innovative pilot and early phase clinical interventions.

A **new national system for Cancer Clinical Trials** involves a fundamental change in how NCI develops, reviews, conducts, and supports prostate and other cancer clinical trials. The overall goal of the new system is to accelerate the pace of all clinical research to more rapidly answer important research questions. The revitalized system is more flexible and promises to speed new ideas from lab to clinic, increase physician and patient participation, and streamline administration and data reporting.

NCI is building **Minority Institution/Cancer Center Partnerships** to link Minority-Serving Institutions with NCI Cancer Centers to increase the number of minority students engaged in prostate and other cancer research; strengthen the research capabilities of minority institutions; and reduce incidence and mortality in minority populations. NCI has also collaborated with Minority-Serving Institutions to increase access to and involvement in clinical trials by underrepresented populations, minority researchers, and patients and physicians. These efforts are especially critical for prostate cancer because of the high incidence and mortality rates among certain minority populations.

Goal for Resource and Capacity Building

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

Objectives and Strategies

1. Build an integrated suite of research resources that enable the scientific community to enhance discovery and readily translate findings into clinical applications.

- Establish and make widely available tissue resources that are closely linked with

appropriate clinical, pathology, and epidemiologic information.

- Create a national informatics network that enhances information and resource exchange among researchers and within and among NCI-supported research initiatives.
- Develop and apply novel approaches that take advantage of new biomedical technologies such as advanced imaging, biosensors, nanotechnology, microarrays, molecular biomarker analysis, laser capture microdissection, and protein pattern analysis.

Selected Near-Term Milestones

- Work through programs such as the Cooperative Prostate Cancer Tissue Resource and large prostate cancer related clinical trials to procure and distribute well-characterized prostate tissue and link clinical and patient outcome information to collected tissue.
- Expand tissue-based and bioinformatics systems in Prostate Cancer SPOREs and large randomized prostate cancer prevention and screening trials to support tissue acquisition, storage, and use and provide the necessary support to ensure data system integration across multiple platforms and projects.
- Support biosensor and nanotechnology/nanoscience research that holds promise for less invasive early detection, real time diagnosis, real time patient care, treatment, and monitoring of response to treatment for prostate cancer.
- Use programs such as the *In Vivo* Cellular and Molecular Imaging Centers and the Early Detection Research Network to support development of technologies for discovering and measuring molecular biomarkers of prostate cancer, identifying the biological properties of a precancerous or cancerous prostate cells, and predicting clinical behavior.

2. Continue to improve the infrastructure needed to promote interdisciplinary research and collaborations and develop the expertise needed to move discoveries to application.

- Continue to enhance the rapid movement of basic research findings into clinical interventions through translational research.
- Increase support for collaborative research projects with other Federal, non-profit, and for profit organizations.
- Expand the capacity of NCI centers, networks, and consortia to engage in newly developing areas of research and technology and to act as platforms for translating discoveries into interventions.
- Encourage collaborations and partnerships to improve access of minority populations to clinical and population studies and state-of-the-art prostate cancer treatments, technologies, and care.

Selected Near-Term Milestones

- Support additional Prostate Cancer Specialized Programs of Research Excellence (SPOREs).
- Continue the NCI Intramural Genitourinary Malignancy Faculty collaboration to facilitate the transfer of knowledge on the biology of human prostate cancer to the development of new treatments or how the effects of treatments can be improved.
- Support multidisciplinary research collaborations between Prostate Cancer SPOREs and other NCI-supported translational research centers, networks, and consortia such

as the Mouse Models of Human Cancers Consortium, the American College of Radiology Imaging Network, and the Early Detection Research Network.
  - Integrate NCI-designated Cancer Centers, including Prostate SPOREs, and Minority Institution/Cancer Center partnerships with the NCI Special Populations Networks for Cancer Awareness Research and Training.
  - Continue to support and maintain the SPORE Web Site as a way to enhance collaboration among researchers with differing expertise, expand cross-disciplinary communication, and increase the pace of progress.

3. **Strengthen the infrastructure needed for the increasing number of clinical trials that are pivotal to validating prognostic markers and developing new preventive agents and novel therapeutics.**

   - Enhance the ability and flexibility of the clinical trials system to respond quickly and effectively to scientific opportunities emerging from the vast expansion of molecular targets discovery, new drug discovery, and translational research.
   - Improve accrual of individuals at high risk of developing prostate cancer and accelerate the rate at which Phase III clinical trials are completed.
   - Increase access for underserved populations to state-of-the-art clinical trials in prevention and treatment.

   Selected Near-Term Milestones
   - Create flexible collaborations and integrate scientific strategic planning among investigators to facilitate multi-institutional and cross-disciplinary prostate cancer clinical trials.
   - Incorporate behavioral, epidemiologic, outcomes, and other relevant research to effectively address specific prostate cancer questions and patient populations and utilize the clinical trials infrastructure more broadly.
   - Expand the Clinical Trials Support Unit to consolidate the administrative tasks associated with prostate cancer clinical trials and to provide a single interface for investigators enrolling patients.
   - Work through newly established clinical trial units at Minority-Serving Institutions and minority-based community oncology sites to increase enrollment of minority men in prostate cancer clinical trials.

4. **Build a stable cadre of basic, clinical, biobehavioral, and population scientists who can work together effectively in a multidisciplinary environment.**

   - Support research training and career development for talented investigators across all disciplines and from diverse racial and ethnic backgrounds. Ensure that investigators are trained in new technologies.
   - Commit to sustained funding for investigators of proven productivity or potential. Allocate research funds to qualified young investigators to initiate independent research.

   Selected Near-Term Milestones
   - Continue to support prostate cancer research training through Prostate Cancer

SPOREs.

- Use established partnerships with Minority-Serving Institutions to implement a fellowship training program for health care providers focused on prostate cancer and provide forums for minority scientist input into the development of prostate cancer clinical trials that address issues of importance for minority and special populations.

National Institute of Diabetes and Digestive and Kidney Diseases

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is firmly committed to play an important role in a broad NIH approach to the problem of prostate cancer. Particular research strengths of the Institute are in the basic biology of the prostate, the mechanisms of androgen action, clinical and basic research studies of benign disease of the prostate, longitudinal studies of the natural history of prostate disease progression, data bases which focus on the health care burden of all urological diseases, and epidemiology of urologic disorders. These strengths provide a compelling base for major expansion, and position the NIDDK to attack critical questions as part of a broad NIH approach to this major health problem. NIDDK efforts are intended to integrate with and to complement the plans of the National Cancer Institute (NCI). The Institute will work to ensure continued integration of its programs with those of the NCI and other NIH institutes with active programs in this area.

While *clinical* research on prostate cancer is not within the NIDDK's mission, there are two major components of prostate cancer research in which NIDDK has unique strengths and special responsibilities: research on benign prostatic diseases and studies of androgen action. The NIDDK is the NIH Institute with primary responsibility for research into benign diseases of the prostate, particularly benign prostatic hyperplasia (BPH). Since prostate cancer and BPH occur together, all clinical approaches to the benign disease need to consider their possible impact on the malignant disease. One major basic focus is to understand the relationship between benign prostate growth and malignant change. There are key clinical issues as well, as strategies for treatment of BPH are showing rapid progress. As treatment improves, it is critical to clarify how the changes in the medical management of this very common benign condition will impact on all aspects of prostate cancer, including detection, progression, and treatment.

A second major area of program focus for NIDDK is the study of androgen action. The NCI's Prostate Cancer Progress Review Group identified as a major high priority a full molecular understanding of the mechanisms of androgen action, including identification of all gene targets and interacting nuclear proteins. Investigation of these issues is a major area of strength of NIDDK-supported endocrine programs.

Program Planning Process

The NIDDK planning process for development of prostate cancer programs has been undertaken with advice from the NIDDK Advisory Council. In March 1998, the Institute convened an International Symposium on Prostate Growth, which resulted in the identification of a number of priorities for new research directions. To ensure continued external advice, in July 1999, the Institute convened a special Ad Hoc Prostate Planning Group to provide overview of existing programs and ongoing input into the development of new programs. A recent NIDDK scientific

workshop, entitled "Coactivators and Corepressors in Gene Expression," presented new evidence on the roles of nuclear accessory proteins in the regulation of hormone receptor action. Since this workshop included discussion of the androgen receptor, the data presented were helpful in formulating initiatives to expand NIDDK efforts to understand this area of research and how it may be relevant to disease.

Institute leadership meets regularly with members of the urology community, particularly the leadership of the American Urological Association, the American Foundation for Urological Disease, and the Society for Basic Urological Research, as well as leaders in the field of endocrine research, and actively solicits the advice and input of these societies. The Institute's planning process also has been carefully integrated with planning activities undertaken by NCI. As a result, the priority items in this plan are areas also identified as important in the *Report of the Prostate Cancer Progress Review Group*.

Targeted Areas of Emphasis

Through the program planning process described above, and building on existing program strengths, the NIDDK has identified five key areas to target for emphasis over the next five years. The Institute anticipates that its programs will lead to discoveries critical for improved outcomes in prostate cancer by addressing scientific opportunities in these five areas:

Benign Prostatic Disease and Prostate Cancer: Prostate cancer typically develops in the setting of underlying benign prostatic disease. The medical treatment of BPH is changing, as there is widespread use of alternative medications, standard medical therapy is evolving and improving, and a wide range of new surgical interventions are available. All of these changes may potentially impact on detection, treatment of progression of prostate cancer. All aspects of these changes need careful study.

Basic Developmental Biology and Cell Biology: Basic developmental biology and cell biology are proving to be important sources of clues about disease and the genes that cause disease. An understanding is needed of the developmental program for formation of the prostate and of the lineage of the cells that make up the gland. A greater understanding is needed of the processes that cause growth of the prostate with age, their relationship to development, and the relevance of these growth processes to malignant change. The outcome of cancer depends not just on the behavior of the tumor cell, but also on the normal surrounding cells that are not themselves cancerous. More must be known about the normal prostate cells and the genes they express, in order to identify new targets for disease intervention, and also about the interactions between prostate cancer cells and bone, in order to understand the determinants of metastasis. Systematic approaches, such as genomics and proteomics to identify genes and gene products important to prostate growth, development , and disease, are increasingly being applied to these problems.

Androgen Action: Full understanding of all aspects of androgen action is expected to increase therapeutic possibilities. Consistent with the *Report of the Prostate Cancer Progress Review Group*, the NIDDK is encouraging research on the action of androgen, and specifically on the search for intracellular signal transduction pathways that govern ligand-dependent or independent activation of hormone receptors or other factors that affect androgen sensitivity (*Report* pages 21-22). What are the actions of androgens, the genes controlled, and the

mechanisms by which they turn genes on and off? With full sequencing of the human genome, it now becomes possible to dissect at a larger systemic level the short-and long-term elements that control gene expression. This new information needs to drive understanding of the responses to androgens. Answers to these critical basic questions can be broadly anticipated to yield the basis for new therapeutic approaches.

Prostate cancer is hormone-responsive, and the major forms of treatment of advanced prostate cancer involve pharmacologic blockade of gonadotropin release or antagonism of the androgen receptor. There are new and emerging opportunities to develop a range of molecular targets focused on different components of the androgen pathway to create treatments having greater specificity.

Epidemiological Trends: Little is known about the variation in susceptibility of different populations to the diseases of the prostate. Careful monitoring of epidemiological trends in the burden of benign and malignant prostate disease is an important priority. In particular, the enhanced susceptibility of certain racial groups to prostate cancer–and the relative protection of other groups–are phenomena that need to be understood.

Complications of Prostate Surgery: Better strategies are urgently needed to prevent the two feared complications of surgery on the prostate, urinary incontinence and impotence. Although new surgical approaches for both benign prostatic hypertrophy and prostate cancer have reduced the rate of these complications, further progress is needed.

Current Prostate Research Program Areas of Emphasis

The NIDDK has substantially increased support of prostate research since 1998, and plans to continue efforts to develop, encourage, and fund new and innovative research projects that utilize "cutting edge" approaches to the study of prostate disease. The following are specific examples of research areas that the NIDDK is currently supporting in its investigator-initiated portfolio:

- Characterization of the cellular and molecular events that occur during prostate development
- Development and use of array technology and bioinformatics to characterize profiles of gene expression in normal and abnormal prostate
- Identification of novel signaling molecules and pathways involved in prostate development, differentiation, transcription and function
- Targeted development of additional tools for study of prostate biology, such as identification of promoter sequences that dictate cell specific expression
- Expansion of support for development of surrogate markers, particularly characterization of proteins secreted by prostate tissues
- Expanded epidemiologic studies of prostate disorders in minority populations
- Identification of regulatory elements in androgen-regulated genes
- The intersection of other hormone signals with the androgen receptor to effect regulated and specific expression of genes
- The involvement of altered signaling components of the androgen receptor/gene complex in the development of prostate cancer
- Elucidation of the mechanism of regulation of transactivation by ligand-bound androgen receptors

- Use of information about androgen receptor complex formation in the nucleus to design selective receptor modulators (SRMs) for treatment of hormone-responsive or -unresponsive tumors
- Characterization of growth factors critical for normal prostate tissue maturation and growth, and their contributions to tumor growth
- Detailed studies of steroid metabolism in the prostate, centering on conversion of testosterone to dihydrotestosterone

Progress in Pursuit of Our Goals
Following are brief descriptions of selected recent advances in prostate research supported by the NIDDK:

Treatment of Benign Prostatic Hypertrophy: A large interventional, randomized, controlled clinical trial supported by NIDDK, called the Medical Therapy of Prostatic Symptoms (MTOPS) trial, was completed in 2001. The trial assessed the effect of two different pharmacological agents—finasteride and doxazosin—on the prevention of progression of symptomatic BPH in 3,047 men, and correlated those clinical effects with molecular and genetic actions on prostate biopsy tissue from participants in the study. The two drugs were found to be more effective in combination than alone to prevent progression of BPH. Together, finasteride and doxazosin reduced the risk of BPH progression by 67 percent. The risk of progression was reduced by 39 percent with doxazosin alone and by 34 percent with finasteride alone. The results of the MTOPS trial were presented at the annual meeting of the American Urological Association in May 2002, in Orlando, Florida. It is anticipated that the study results will have major implications for the treatment of BPH across the country.

Mechanisms of Androgen Action: In the *Report of the Prostate Cancer Review Group*, the mechanism(s) of androgen action was highlighted as a major area in need of intensified investigation. Particular attention was given to the importance of understanding the protein-protein interactions that determine the binding and transcriptional regulation occurring through the androgen receptor. Study of this topic has yielded a number of surprising new insights that may shed some light on the underlying mechanism of action of signal cross-talk between androgens and other growth factors that can lead to new approaches to therapeutic development. For example, a previously unsuspected interaction has been discovered between signaling through a molecule called transforming growth factor-beta (TGF-beta) and androgens. TGF-beta is a growth factor that has been found to have anti-proliferative effects, although its mechanism of action can be expressed through stimulatory and inhibitory effects at different times in different tissues. By inhibiting cell growth of normal cells it can serve to suppress tumor formation, but if it is active late in tumor development, it can further stimulate or facilitate metastasis. The mechanisms of these dual roles are being clarified; a protein called Smad3 seems to play a critical role in androgen action, resulting in stimulation of expression of prostate specific antigen. These findings open the possibility that interference with the TGF-beta/Smad pathway might block certain tumorigenic actions of androgens.

Cell Biology and Developmental Biology of the Prostate Gland: Another highly productive and innovative area of investigation has been in the application of systematic gene expression and proteomic methods to study of prostate biology. Several investigative teams have undertaken to

delineate the difference in patterns of gene expression using cDNA microarrays—also called gene chips—in specimens of benign prostatic hyperplasia and prostate cancer. Ultimately, the goal will be to clarify how protein expression patterns change with disease. These approaches are expected to delineate potential predictive markers for the development of cancer, and to allow identification of high-risk individuals. Substantial effort has been made to establish methods for high through-put definition of protein expression patterns, and further progress in this area is anticipated.

Definition and characterization of the cell types of the prostate is another area of intense investigation. There appear to be at least three important cell types in the prostate, all of which play a role in malignancies. Although most initial research on prostate cancer focused on the epithelial cell, the stromal or mesenchymal cell and neuroendocrine cells of the prostate also appear to play a role in prostate cancer. Recently, improved models for research on the stromal cell and the neuroendocrine cell lineage have been developed. In an important breakthrough, NIDDK investigators have established that cells of the neuroendocrine lineage in the prostate are capable of undergoing tumorigenesis.

Prostate Cancer-Related Initiatives Since 1998

To encourage innovative research in support of our prostate cancer programs, the NIDDK has issued or participated in a number of RFAs, Program Announcements, and RFPs since 1998:

- In January 1999, the NCI, NIDDK, and National Institute of Environmental Health Sciences (NIEHS) co-sponsored a Program Announcement entitled "Molecular Epidemiology of Prostate Carcinogenesis."
- In April 1999, the NCI, NIDDK, NIEHS, and the National Institute on Aging (NIA) co-sponsored a Program Announcement entitled "Biology, Development, and Progression of Malignant Prostate Disease."
- In January 2000, the NIDDK and the NIEHS co-sponsored an RFA entitled "Cell-Specific Delineation of Prostate and Genitourinary Development."
- In June 2000, the NIDDK issued a Request for Proposals (RFP) entitled "Urologic Diseases in America." This objective of this program is to compile a compendium delineating the changes in the epidemiology, health economic impact, and practice patterns for each of the diseases currently included within the scope of practice of the specialty of urology, and analyzed retrospectively over a ten-year period.
- In August 2000 an RFA entitled "Role of Hormones and Growth Factors in Prostate Cancer," was co-sponsored by the NIDDK, NCI, NIEHS, and NIA.
- To make comprehensive gene expression technologies widely available, the NIDDK issued an RFA in October, 2000 for "NIDDK Biotechnology Centers."
- In June 2001, the NIDDK and the NIA co-sponsored an RFA entitled "The Functional Atlas of Orphan Nuclear Receptors." This initiative will increase focus on the role(s) of orphan nuclear receptors and nuclear accessory proteins on obesity, diabetes, osteoporosis and prostate cancer.
- An RFA entitled "Progenitor Cell Genome Anatomy Projects" was issued in October 2001, and will be funded as a consortium of investigators who will serve as a resource to provide reagents and databases to the research community.
- Also in October 2001, the NIDDK and NCI co-sponsored a Program Announcement entitled

"Pilot and Feasibility Program in Urology."
- In December 2001, the NIDDK sponsored a Program Announcement entitled "NIDDK Small Grants for Underrepresented Investigators."
- In November 2001, an RFA co-sponsored by the NIDDK and NIA was issued, entitled "MTOPS Prostate Samples Analysis Consortium (MPSA)."
- In January 2002, an RFA co-sponsored by the NIDDK, the National Center for Complementary and Alternative Medicine, and the Office of Dietary Supplements was issued, entitled "Alternative Therapies for Benign Prostate Symptoms–Clinical Trials Consortium."
- In April 2002, an RFA co-sponsored by the NIDDK and NIA was issued, entitled "Androgen Receptor in Prostate Growth and Cancer."
- In April 2002, a Program Announcement co-sponsored by the NIDDK, NCI, NIA, and National Institute of Mental Health was issued, entitled "Complex Formation in Hormonal Regulation of Gene Expression."
- In May 2002, an RFA co-sponsored by the NCI and NIDDK was issued, entitled "Molecular Interactions Between Tumor Cells and Bone."

Implementation Plans and New Initiatives to Address Targeted Areas of Scientific Emphasis.

The following topic areas, all traditionally areas of strength in NIDDK, present the opportunities for particular emphasis and expansion targeted in this five-year plan. Each of these research avenues is described more fully in sections that follow:

- Basic studies of the transition from benign to malignant prostate disease
- Cell and developmental biology of the normal prostate gland
- Androgen action, steroid hormone receptor interactions, and nuclear accessory proteins
- Epidemiology of prostate disease, particularly in minority populations
- Complications from surgery on the prostate

<u>Prospective Basic and Clinical Studies of the Transition between Benign Prostatic Hyperplasia and Prostate Cancer</u>

Goals:

- Define the effect of various strategies to treat benign prostatic hyperplasia on the incidence of prostate cancer
- Develop pathological criteria for sub-categorization of benign prostatic hyperplasia
- Examine correlations between molecular markers and pathological characteristics
- Establish the relative risk of prostate cancer associated with each sub-type
- Examine prospectively the prognosis of prostatic intraepithelial neoplasia (PIN)
- Elucidate further the detailed mechanisms of gonadotropin, androgen, and growth factor action on the prostate

Implementation:

The NIDDK supports an extensive investigative program on treatment of benign disease of the prostate, especially benign prostatic hyperplasia (BPH). A keystone of this program is an important clinical trial, the Medical Therapy of Prostate Symptoms (MTOPS) trial, which was completed in 2001. MTOPS assessed the effect of two different pharmacological agents—

finasteride and doxazosin—on the prevention of progression of symptomatic BPH in 3,047 men, and correlated those clinical effects with molecular and genetic actions on prostate biopsy tissue from participants in the study. The two drugs were found to be more effective in combination than alone to prevent progression of BPH. Together, finasteride and doxazosin reduced the risk of BPH progression by 67 percent. The risk of progression was reduced by 39 percent with doxazosin alone and by 34 percent with finasteride alone. The results of the MTOPS trial were presented at the annual meeting of the American Urological Association in May 2002, in Orlando, Florida. It is anticipated that the study results will have major implications for the treatment of BPH across the country.

While the MTOPS study was developed with the principal goal of prospective, randomized evaluation of medical therapy for prostate symptoms, it also has enormous potential for prospective evaluation of cancer risk. Patients were very carefully characterized and closely followed, with regular studies including stored plasma samples and, in a subset of 1,000 patients, repeat biopsies. All patients underwent regular ultra-sound imaging using state of the art quantitative techniques.

Over the next ten years, a substantial portion of these patients is expected to develop prostate cancer. This cohort provides an extraordinary and very cost effective opportunity for studies to address the goals enumerated previously.

An RFA entitled "MTOPS Prostate Samples Analysis Consortium" was issued in November 2001. Applications were received in March 2002, and grants will be funded in September 2002. This RFA is designed to develop a consortium of investigators who will utilize the prostate biopsy tissue obtained during the MTOPS trial to utilize the most current technology and science for research focusing on biomarkers that correlate the progression of benign prostate disease to either change in severity of symptoms or malignant disease.

<u>Cell Biology and Developmental Biology of the Prostate Gland</u>
Goals:

- Define the cellular characteristics of the epithelial cells, stromal cells, endothelial cells, neuroepithelial cells and inflammatory cells that make up the prostate
- Define the specific interactions between these cells
- Develop a complete characterization of the biological processes in the prostate during its development, maturation and transition from normal to hyperplastic to malignant states
- Encourage investigation that utilizes these insights to define new therapeutic targets

Implementation:
The NIDDK program in prostate biology and prostate growth provides a strong foundation for building expanded investigation in these areas. Our advisory groups consistently recommend strong investment in the basic biology of the prostate gland as the best long-term strategy to identify breakthroughs in therapy, prevention and diagnosis of prostate cancer. Most of the work on these topics is and will likely continue to be undertaken through investigator-initiated grants.

Mechanisms of Androgen Action, Steroid Hormone Receptor Interactions, and Nuclear Accessory Proteins

Goals:

- Define the potential roles of androgen and critical other steroid hormones in prostate growth, tissue interactions and development
- Define the structure of androgen nuclear receptors
- Define the interacting proteins and the ligand-metabolizing enzymes in the prostate

Implementation:

This important topic was identified as the number one priority in the *Report of the Prostate Cancer Review Group*, Subgroup A—Biology, Progression and Metastasis. It is widely recognized that the transition from androgen dependence to androgen independence is an absolutely critical event in the natural history of prostate cancer, and that this biological event often determines the patient prognosis. It is therefore critical that a precise understanding of the process of androgen regulation of gene transcription is developed.

As was recognized in the *Report*, this is an area traditionally supported by NIDDK, largely through investigator-initiated grants. Program initiatives over the next five years would undertake to encourage submissions in this area and to encourage investigators to examine these issues in prostate models. In addition to the RFA that was issued in April 2002, entitled "Androgen Receptor in Prostate Growth and Cancer," the Institute would explore targeted strategies to expand translational and industry investment in these areas.

Epidemiology of Prostate Disease

Goals:

- Define which segments of the U.S. population have enhanced or reduced susceptibility to benign prostatic hypertrophy and prostatitis, and the relationship between altered risk of benign disease and altered risk of prostate cancer
- Identify genetic and environmental factors associated with enhanced or reduced cancer risk, particularly in minority men

Implementation:

Studies of prostate cancer have established that African American men are at increased risk, and suggest reduced risk in Americans with Asian backgrounds. There is less data on the relative risk for these populations of benign disease, or on the association between benign disease and cancer risk. The Institute has expanded its urology epidemiology program. The NIDDK's epidemiology support contract has doubled in size. Through a Request for Proposals issued in 2000, the Institute currently is funding a contract with University of California at Los Angeles and the RAND Corporation to develop a national compendium focusing on the health care burden of urological disease in the United States. The NIDDK will be collaborating with and utilizing existing National Cancer Institute data on prostate cancer and incorporating these data into the compendium. This will provide valuable information on trends of prostate disease, trends in treatment, and overall costs for all ethnic groups. It also will provide a resource for epidemiological data to evaluate correlations between benign and malignant prostate disease. Another resource for evaluating the development of prostate cancer in minority populations will be the data and biopsy tissue from the MTOPS study. The data and tissue will be analyzed by

the MTOPS Prostate Sample Analysis Consortium (MPSA), which will be developed and funded in FY 2002 as the result of a recently issued RFA.

Complications of Surgery on the Prostate
Goals:

- Define strategies to reduce the incidence of urinary incontinence and impotence after surgery
- Develop new therapies and investigate efficacy of established therapies for these two surgical complications.

Implementation:
Better strategies are urgently needed to prevent the two feared complications of surgery on the prostate—urinary incontinence and impotence. Although new surgical approaches for both benign prostatic hypertrophy and prostate cancer have reduced the rate of these complications, further research is needed. Clinical and basic investigation in these two areas is a traditional strength of the programs supported by NIDDK. Creation of a clinical trials consortium to evaluate surgical outcome prospectively and rigorously, and to test new therapies would be encouraged in this area. The NIDDK has now established a Urinary Incontinence Treatment Network (UITN), a consortium of investigators focusing on developing and conducting clinical trials and data collection on persons with urinary incontinence. During the first phase of the UITN, the investigators will be focusing their studies on female incontinence; subsequent phases will address male incontinence, both primary and secondary to treatment for prostate cancer.

Research Training and Manpower Issues
Our advisory groups consistently identify a shortage of trained, experienced investigators in urology as an impediment to development of strong research in this area. The NIDDK will substantially strengthening its strong program of support for training and career development in urology.

Programs would be developed to target the following needs**:**

- Training of investigators with expertise in both clinical urology and in the design and implementation of clinical trials;
- Recruitment of Ph.D. investigators from a variety of basic science disciplines to study of prostate cancer;
- Development of careers of Ph.D. investigators.

Existing NIH training mechanisms, including the recently initiated awards for training of clinical investigators and mid-career investigators (K23 and K24), provide valuable approaches to these problems. The NIDDK has also in the past utilized mechanisms of co-funding with non-profit foundations. The NIH-American Foundation for Urological Disease fellowships, is one example of training programs that would continue.

George M. O'Brien Urology Research Centers
The NIDDK currently supports five George M. O'Brien Urology Research Centers. Some prostate cancer related work is performed in all of these centers; three have a particular focus on the biology of the prostate**.**

Centers with a particular focus on prostate are as follows:

- The Center at the University of Washington focuses on prostate cancer. This includes how prostate cancer spreads to tissues beyond the prostate gland, the mechanisms that control the expression of prostate-specific antigen (PSA), development of research methods for gene therapy of prostate cancer, and interference with tumor progression, which may lead to treatments for prostate cancer.

- The Center at the Cleveland Clinic is investigating regulatory mechanisms of prostate tumor progression, specifically the cellular changes that are associated with the progression of disease from normal to premalignant conditions.

- The Center at The University of Texas Southwestern Medical School is examining several aspects of benign and malignant prostate growth, including the genetic alterations involved in prostate cancer, and the expression of male hormones in benign and malignant prostates.

In the current funding year, supplementary pilot and feasibility funds are being made available to these centers to develop new directions for work related to prostate cancer. Expansion of support for these centers in future fiscal years would be anticipated.

The current cycle of funding for these Research Centers will end in FY 2003. Consequently, the Institute will be issuing an RFA for recompetition of the George M. O'Brien Urology Research Centers. It is anticipated that this RFA will be funded in FY 2003. The RFA will invite both renewal and new applications that will continue the current focus on basic investigation, but potentially also will include translational and pilot clinical research studies. The RFA will emphasize collaboration between clinical and basic science investigators addressing some of the areas for investigation listed above, and also will emphasize the importance of training new investigators in urological research with special emphasis on diseases of the prostate. The Institute will enlist the participation of the NCI and other relevant institutes in both the development as well as co-sponsorship of this RFA.

National Human Genome Research Institute

Progress in Pursuit of Our Goal

The intramural research program of the NHGRI continues to focus significant effort on the identification of genes important in hereditary susceptibility to prostate cancer as well as genes involved in sporadic cases and disease progression. In the past, genetic contributions to most common diseases were virtually impossible to sort out. NHGRI intramural studies of prostate cancer provide a compelling example of how research tools developed by the Human Genome Project are bringing clarity to such scientifically murky health problems. Because prostate cancer clusters in some families, especially when the onset is early, researchers have suspected the disorder has a strong genetic component. That suspicion was borne out in 1996 when an international team of researchers, led by scientists at the NHGRI and Johns Hopkins Medical Institute, studied 91 high-risk prostate cancer families and mapped the first hereditary susceptibility to prostate cancer to a region on chromosome 1 that they called the Hereditary

Prostate Cancer 1 Region (HPC1). This was the first proof that prostate cancer risk is controlled by specific genes. Since then, these and other research teams have mapped prostate cancer susceptibility genes to two other parts of chromosome 1, as well as to chromosomes 17, 20, and X.

Recently, researchers from a consortium of 14 institutions including NHGRI, Johns Hopkins Medical Institute, and the Cleveland Clinic have reported for the first time in the February 2002 issue of *Nature Genetics* that they have identified a specific gene, ribonucleases L (RNASEL) in the HPC1 region that contains mutations associated with prostate cancer in some families with a history of the disease. Scientists have found mutations that inactivate the RNASEL gene. Previous studies have shown that RNASEL plays a role in defending cells from viruses and assists in normal cell turnover or programmed cell death. Inactivating this cellular self-destruct mechanism through genetic mutation may explain why some prostate cells become cancerous.

These new discoveries help prove that hereditary factors play a major role in prostate cancer risk. Because researchers know that mutations in this one gene do not explain all forms of inherited prostate cancer, and that mutations in a number of genes can lead to the development of prostate cancer, NHGRI investigators continue to aim at identifying all of the common contributing genes to hereditary susceptibility

In this way, Human Genome Project tools are allowing scientists to develop a comprehensive understanding of the causes of prostate cancer. Improved understanding of the molecular causes of prostate cancer will lead to better abilities to predict which men are at highest risk, which can allow them to be carefully watched for early signs of prostate cancer. In the longer term, better understanding of this disease will expand potential areas for new therapies and provide a fundamentally new paradigm for sorting out the hereditary, environmental, and socio-economic bases of human illness.

<u>African American Hereditary Prostate Cancer (AAHPC) Study Network</u>
During the past several years, the National Center for Minority Health and Health Disparities (formerly the Office of Research on Minority Health) and NHGRI have supported innovative research collaborations between investigators from Howard University and scientists in the NHGRI intramural research program. The collaboration involves support for projects involving African Americans affected with diabetes and in 1997, NHGRI added hereditary prostate cancer within this core of collaborative projects. The African American Hereditary Prostate Cancer (AAHPC) Study Network was established.

African American prostate cancer families are almost completely missing from other pedigree collections, despite the higher incidence and higher lethality of prostate cancer in African American men. Through a competitive review, the AAHPC Study Network has funded seven centers around the country. For most of these, the Principal Investigator is an African American urologist. Community acceptance and participation has been good and over 50 families have been identified with at least four affected males. DNA from these families is being studied to see if linkage can be confirmed to the known hereditary prostate cancer location on chromosome 1, as well as whether other linkages exist.

Barbados Prostate and Breast Cancer Study

In a cooperative effort with the State University of New York at Stony Brook, and the University of the West Indies the NHGRI intramural program is participating in a population-based study of the island of Barbados. Barbados represents an ideal resource for genetic-based studies of diseases prevalent in populations of West African ancestry. Prostate and breast cancer are the most common cancers in Barbados, which has among the highest incidence rates of both diseases of any country on earth. Prostate cancer is substantially more common in African-American (and particularly Afro-Caribbean men) than in Caucasian or Asian men.

In collaboration with the Health Ministry of Barbados, and Stoneybrook University in New York, NHGRI intramural investigators propose to complete a national population-based care-controlled epidemiological study of all prostate and breast cancer cases with age/gender matched population controls over a four-year period. The study will examine a broad range of risk factors plus known and novel gene loci with state-of-the-art analytical tools resulting in a comprehensive approach to the study of prostate and breast cancer. The overall goals will be to identify specific factors involved in genetic susceptibility of these cancers in Barbados, which can then be used to increase the overall understanding of disease in this and other populations.

Genetic Changes – Prostate Cancer Cells

While hereditary factors are heavy contributors to the development of prostate cancer for some men, most prostate cancer results from changes in the genetic material of individual cells that occur throughout life. Using the techniques of modern genomics, NHGRI investigators are seeking to define the genetic changes in cells that lead to the initiation and progression of prostate cancer.

Several developing technologies now are being used to gain insight into the human cell and to transform the study of human genetics. Much of it is borrowed from the computer chip industry and the devices are often called "DNA chips." In most experiments in the past investigators have looked at one gene at a time. Yet humans are thought to have tens of thousands of genes, and they work in concert or committees (scientists call these pathways) to get things accomplished. Ultimately, to really understand the behavior of the human organism, and what goes wrong when a disease occurs, what we would really like to be able to do is look at the behavior of all the genes in a single experiment. That might finally provide a true picture of what's going on inside the body.

DNA chips are now being used to look at the changes in gene expression that occur as prostate tissue progresses from normal epithelium, to a pre-malignant state called “pin,” to a low grade malignancy, to a higher grade malignancy, to a malignancy which is no longer hormonally responsive. In each state of progression, certain genes are turned on and off in a particular tumor, representing the pathways of control of cell growth that are contributing to the malignant state. Each of these changes represents a crucial clue to the pathogenesis of prostate cancer, and can suggest new ways of treating or preventing the disease.

Of course not every prostate cancer follows the same set of steps; when a pattern of abnormal gene expression is observed in a particular tumor, it is critical to determine whether this is a common or rare event. To explore this question, NHGRI investigators have developed the

"Tissue Chip" -- hundreds of different tissue samples, derived from normal or malignant tissue, are arrayed on to a microscope slide using robotic technology. Using this chip, the over expression of a particular candidate prostate cancer gene can be assessed in one experiment in a very large number of tumors, and an analysis which would have taken many months in the past can be done in one day. In this way one can identify the major culprits in prostate cancer, and focus new interventions on these common themes. Work in this area was again recently published in a collaborative effort between NHGRI's intramural research program, and investigators at the Johns Hopkins University.

Future Directions – NHGRI Prostate Cancer Research

Although researchers are convinced of a relationship between the RNASEL gene and prostate cancer, much more work is needed to show how commonly it causes or modifies the clinical course of the disease. A larger number of men need to be studied to see how often mutations in the gene are associated with the disease and to find out how often mutations occur in men without the disease. It is hoped that this will help physicians know how good a predictor this gene may be for prostate cancer. The AAHPC Study Network will play a key role in enlarging the pool of families. NHGRI investigators continue to aim at identifying all of the common contributing genes to hereditary susceptibility. As the precise genes are identified, clinical studies would be undertaken to offer genetic testing to men from high risk families, to identify those at greatest risk for life-threatening disease and design a program of surveillance to identify their cancers early enough to achieve cure. In addition, using the chip technology, the common changes in gene expression that contribute to various steps in malignant transformation would be cataloged, and used to derive new hypotheses about the molecular steps involved in prostate cancer. These would in turn suggest new and more powerful ways to treat or prevent the disease.

National Center for Research Resources

The National Center for Research Resources (NCRR) serves as a "catalyst for discovery" by creating and providing critical research technologies and shared resources. NCRR supports primary research to create and develop these critical resources, models and technologies; promotes resource sharing and collaborations within and across scientific disciplines; enhances research competitiveness through institutional development; increases student and public understanding of the health sciences; and provides career development for biomedical investigators. NCRR programs are concentrated in four divisions: Biomedical Technology, Clinical Research, Comparative Medicine, and Research Infrastructure. As such, the multidisciplinary research supported by NCRR spans the seven strategic NCI areas.

Biology, Progression, and Metastasis: NCRR-supported investigators at the Case Western Reserve University are studying the genetic basis of prostate cancer to determine susceptibility to disease and are determining whether certain genes are associated with more aggressive forms of prostate cancer. Researchers at the University of Utah General Clinical Research Center (GCRC) are identifying genetic markers and determining the molecular mechanisms of prostate cancer.

Etiology and Prevention: Researchers at Research Centers in Minority Institutions (RCMI), are studying the antiproliferative effects of luteinizing hormone releasing hormone (LHRH) on the

human, androgen-independent prostate cell line and deriving recombinant monoclonal antibodies against prostate cancer antigens, which may lead to targeted treatment for prostate cancer. Investigators from Dartmouth College are focusing on active specific immunotherapy as an alternative treatment to surgery and hormonal intervention. GCRC researchers are studying the safety and efficacy of finasteride to prevent prostate cancer, the ability for dietary soy and other nutritional factors to reduce prostate cancer progression, and the molecular epidemiology of prostate cancer. Researchers at the University of Arkansas GCRC are examining factors that may explain the higher incidence rates of prostate cancer among African Americans and the role certain chemicals in tobacco smoke and meats cooked at high temperature play in the etiology of prostate cancer.

Early Detection Diagnosis and Prognosis: The GCRC at University of Colorado Health Sciences Center, the University of Pittsburgh, and the University of Utah are all taking part in a Prostate, Lung, Colon and Ovarian Cancer Screening Trial. The trial is designed to determine if screening for prostate cancer with serum prostate specific antigen and digital rectal exam will reduce cancer-specific mortality. Also, researchers at the University of Washington GCRC are determining if a newly identified factor called human-cachexia associated protein (HCAP) has a role in prostate cancer.

Treatment: Investigators at GCRCs are testing various therapies, such as LY335979, CPT-11, Estramustine, histrelin, Atragen, EB-1089, arsenic trioxide and monoclonal antibodies, to treat hormone refractory prostate cancer. At Oregon Health & Science University, GCRC researchers are trying to determine if calcitrol will lower prostate specific antigen levels and stop or slow tumor growth. GCRCs are determining if drugs currently used to treat osteoporosis in women are can effectively prevent osteoporosis in men with prostate cancer. Several GCRCs are trying to determine if dendritic cell-based vaccines are effective therapeutic options for patients with advanced or metastatic prostate cancer while other GCRCs are studying the therapeutic effects of recombinant vaccines.

Cancer Control Survivorship and Outcomes: Clinical trial results, from Harbor-UCLA Research and Education Institute GCRC, indicate that prostate cancer androgen ablation therapy is associated with a major increase in non-prostatic cancer mortality. Researchers are determining whether exercise along with androgen ablation therapy significantly increases risk factors for co-morbid conditions, such as coronary heart disease, diabetes and fracture risk, which negatively influence survival. The Johns Hopkins GCRC is determining the effects of adrogen-deprivation treatment (ADT) on lean body mass, muscle strength, sexual functioning, and quality of life in medically castrated men with prostate cancer. Howard University RCMI has created an African American hereditary prostate cancer study network.

Resource and Capacity Building: NCRR has provided funds to construct a research laboratory for prostate cancer research at the University of Missouri Kansas City.

National Institute of Environmental Health Sciences

Prostate cancer is a disease of enormous public health importance; it is the most frequently diagnosed cancer in American men. However, little is understood about its pathogenesis. Effective prevention will depend on research into how genetic predisposition and environmental exposures the risk of prostate cancer. The National Institute of Environmental Health Sciences (NIEHS) is spearheading this approach to understanding gene-environment interactions in prostate cancer development, with the help of several key initiatives.

Environmental Genome Project: The tools of molecular genetics provide new opportunities to understand the genetic basis for individual differences in susceptibility to environmental exposure. The NIEHS is expanding its research program on genetic susceptibility to environmentally-associated diseases through its Environmental Genome Project. The purpose of this Project is to systematically identify the allelic variants of disease susceptibility genes in the U.S. population, develop a central database of known polymorphisms for these genes, and foster population-based studies of gene-environment interaction in disease etiology. By identifying those genes and allelic variants that affect individual response to environmental toxins, we can better predict health risks and develop environmental policies to protect the most vulnerable subgroups of the population from diseases such as prostate cancer.

The NIEHS Environmental Genome Project is a broad, multi-center effort to identify systematically the alleles of environmental disease susceptibility genes. Susceptibility genes to be studied include, but are not limited to, five broad gene classes: genes controlling the distribution and metabolism of toxicants; genes for the DNA repair pathways; genes for the cell cycle control system; cell death/differentiation genes; and genes for signal transduction systems controlling expression of the genes in the other classes. This effort would result in the systematic identification of the polymorphisms of these genes found in the U.S. population. A central database of the polymorphisms would be made available. This database will support both functional studies of alleles and population-based studies of disease risk.

Toxicogenomics and Prostate Cancer: Toxicogenomics is a new scientific field that examines how the entire genome is involved in biological responses of organisms exposed to environmental toxicants/stressors. Toxicogenomics combines information from studies of genomic-scale mRNA profiling (by microarray analysis), cell-wide or tissue-wide protein profiling (proteomics), genetic susceptibility, and computational models to understand the roles of gene-environment interactions in disease. The National Center for Toxicogenomics (NCT) is a coordinated, multi-disciplinary research program of the National Institute of Environmental NIEHS, National Institutes of Health (NIH).

cDNA microarrays are tools that can be used to analyze changes in genome-wide patterns of gene expression. This technology is revolutionizing the way toxicological problems are investigated. Given that exposures to different classes of toxicant result in distinct patterns of altered gene expression, microarray technology can be used to categorize and classify these effects through the direct comparison of gene expression patterns in control versus treated samples on the same cDNA microarray. In defined model systems, treatment with known agents, dioxin-like compounds, or estrogenic chemicals may provide a gene expression

"signature" on a microarray which represents the cellular response to these agents. These same systems can then be treated with unknown, suspect agents to determine if one or more of these standard signatures is elicited. This approach will also help elucidate an agent's mechanism of action and may also be used to detect changes in exposed human populations. It is also likely that new molecular targets of toxicant action will be identified, and that these new targets may be good candidates for analysis in the Environmental Genome Project.

The NIEHS is in the process of establishing cDNA microarray technology in a collaborative research effort with the National Human Genome Research Institute. Custom cDNA arrays or "chips" are being developed that comprise human cDNA clone subarrays oriented toward detection of the expression of genes involved in responses to toxic insult. The goals of the project are to use gene expression methodologies to: 1) identify toxicants on the basis of tissue specific patterns of gene expression (molecular signature); 2) elucidate mechanisms of action of environmental agents through the identification of gene expression networks; 3) use toxicant-induced gene expression as a biomarker to assess human exposure; 4) extrapolate effects of toxicants from one species to another; 5) study the interactions of mixtures of chemicals; and 6) examine the effects of low dose exposures versus high dose exposures. In addition, gene expression profiles are likely to be excellent surrogate markers of safety and efficacy for use in clinical trials, which face a similar "bottleneck" effect to that identified for toxicology studies. Future resources in the area of prostate cancer could be applied, in part, to the NIEHS effort to develop cDNA microarray technology for the elucidation of prostate-specific patterns of gene expression resulting of exposure to low level environmental toxicants either singly or in mixtures. Funds would also be targeted to identify gene expression networks that may lead to the induction and/or progression of prostate cancer.

New Models for Prostate Cancer Research: There is a lack of appropriate animal models for prostate cancer. NIEHS researchers are working with a new mouse model called TRAMP (Transgenic Adenocarcinoma of the Mouse Prostate). These mice develop prostate cancer by six months of age. A colony has been established, and the first study will be to characterize the pathogenesis of lesion development and related parameters in target tissues. Researchers are also interested in the dietary modulation of IGF-I and in determining how this affects the pathogenesis and development of the prostate cancer in the TRAMP model. Tissues from the prostate lobes of the TRAMP mouse are being prepared for microarray studies to identify genes that might explain the response of the different lobes to development of prostate cancer. Other studies in the TRAMP model include examining strategies for chemoprevention using dietary genistein.

Genetic Susceptibility and the Environment in Prostate Cancer Risk: The research on genetic susceptibility tests the hypothesis that commonly inherited allelic variants of certain genes, in conjunction with environmental exposures, affect a person's risk of developing disease. The primary focus of this work has been on bladder cancer, although recently we have expanded to include studies of prostate. NIEHS researchers have obtained DNA samples with linked epidemiologic information with which to extend earlier findings of an association between a polymorphism in the 3'UTR of the vitamin D receptor gene and prostate cancer risk. Genotyping has been completed and data analysis is to begin. In addition, researchers have genotyped prostate cancer cases and controls for a polymorphism in CYP17, a gene involved in androgen

metabolism, and are starting data analysis. Opportunities exist to accelerate this project as well as enable the NIEHS to extend it using results from the Environmental Genome Project.

Environmental Agents and Prostate Cancer: Among the studies supported by the NIEHS on prostate cancer are many focusing on effects of different environmental agents that act on the prostate through many different pathways. One study is examining whether exposure to environmental doses of cadmium increases the risk of prostate cancer, in part, due to this metal's ability to activate the androgen receptor. Other studies are focusing on effects of dioxin and the arylhydrocarbon receptor on androgen regulation and prostate development and disease.

National Institute on Aging

NIA-Sponsored Initiatives in Prostate Cancer Research
Aging, Race, and Ethnicity in Prostate Cancer is the title of the NIA RFA-AG-02-003 released August 29, 2001. The application receipt date was December 12, 2001. After review of the applications in early spring, five to seven meritorious awards will be made in July 2002.

The NIA extramural research plan is to have a consolidated group of studies on human prostate cancer through this integrated aging/cancer research initiative. The NIA issued the RFA solicitation with set-aside funds to expand the knowledge base on aging- and age-related aspects of prostate cancer. Conceptually initiated by the NIA Geriatrics Program and co-sponsored with the NIA Biology of Aging Program in 2000, research applications responding to this RFA were encouraged to address age- and aging relevant issues concerning genetic and environmental risk factors, pre-malignant changes, tumorigenesis, detection of localized and advanced disease, prognostic indicators, disease progression, and response to treatment.

NIA first singled out prostate cancer as one of the first extramural research initiatives in the Geriatrics Program Cancer Section (established in 1996). Prostate cancer is a disease of older men with 71 percent of incident tumors and 92 percent of prostate cancer mortality occurring in the age group 65 years and older. Prostate cancer has the highest incidence of any malignancy for white and black men 65 years and older, 932.2 and 1457.7 per 100,000 population, respectively. In addition, age-adjusted mortality rates are more than twice as high for African Americans as for white Americans. The highest rates of prostate cancer mortality per 100,000 population are in black males aged 80-84 (922.4) and 85+ (1323.8). For white males the highest rates are also in the same age groups 80-84 (403.6) and 85+ (732.8).

Guided earlier by these and other important prostate cancer statistics, NIA issued the Program Announcement, "Aging, Race, and Ethnicity in Prostate Cancer" (PA-97-019) in the NIH Guide to Grants and Contracts (Volume 25, Number 44). The PA, three years in duration, encouraged the extramural research community to take advantage of recently acquired scientific knowledge and expertise developed in biology, gerontology, oncology, urology, and other disciplines and professions, as well as to apply these resources to aging-relevant research questions on prostate cancer for aging males of different races and minority backgrounds. The clinical component of the PA encouraged studies on determinants of age- and race-associated differences in prostate cancer detection, treatment, and survival. Other major components of the PA solicited studies on

the etiology and risk factors that affect the rate of increase with age in prostate cancer and on developing new methods and testing improved methods to identify high risk older white and African American men and low risk men of different racial and ethnic origins. These features of the PA were incorporated in the recently issued NIA RFA.

NIA's Baltimore Longitudinal Study (BLSA) of Aging

The NIA's intramural program has used its unique resource, the Baltimore Longitudinal Study of Aging (BLSA), to investigate the longitudinal trends in prostate specific antigen (PSA) in relationship to developing prostate cancer. The goal is to prospectively identify men at high risk for the disease, and in determining the prognostic and diagnostic value of PSA. NIA investigators have also examined the linkage between longitudinal testosterone levels, insulin-like growth factors (IGF-I and IGF-II, and IGF binding protein-3), selenium and dietary intake on prostate cancer risk.

Research from the BLSA continues to study the time course for the development of prostate cancer and markers useful in early diagnosis. The goal is to define which groups of men should be tested, how long and how often they should be tested to maximize the identification of treatable prostate cancer while minimizing the costs of evaluation. Recent work has shown that 60 year old men with PSA levels less than 0.5 ng/ml and 65 year old men with PSA levels less than 1.0 ng/ml have a very low risk of developing prostate cancer by age 75 years. These data suggest that a decrease in intensity of screening among older men with low PSA levels may not lead to an increase in undetected cancers.

Another approach to the use of PSA is to examine how it changes over time. In previous work from the BLSA a rate of change in PSA exceeding 0.75 ng/ml per year was associated with an increased risk for the diagnosis of prostate cancer. These data have now been confirmed in large prospective screening trials. Investigators have also shown that a PSA screening frequency of two years is not likely to miss a curable prostate cancer when the initial PSA level is less than two ng/ml, thus reducing the required frequency for PSA screening in many men. Recent analyses, has examined another group at increased risk, men with PSA in the 2 to 4 ng/ml range who are frequently evaluated and may be biopsied. BLSA data were used to demonstrate the impact of PSA velocity on cancer diagnosis in men with PSA values between 2 and 4 ng/ml. Velocities above .1 ng/ml/year were associated with a 6.5 fold increased risk than a lower velocity for the subsequent diagnosis of prostate cancer.

PSA may have a role as a long term risk assessment for prostate cancer. In 40-50 year old and 50-60 year old men a PSA level above the median value (0.6 ng/ml for 40-50 year olds, and .7 ng/ml for 50-60 year olds) is associated with a 3-4 fold increased risk of being diagnosed with prostate cancer over the subsequent 20-30 years. The men at increased risk may benefit from more frequent screening and are likely to be the most responsive to preventive measures as they are identified for prostate cancer.

Recently, free/total PSA ratio has become available for clinical use. Low ratios have been shown to be associated with prostate cancers. Studies of men in the BLSA have shown that the free/total PSA ratio is abnormally low 10 years prior to diagnosis in the cohort of subjects who ultimately were diagnosed with prostate cancer. Therefore, by using the PSA free/total ratio it is

possible to identify men at risk even when total PSA values are within normal limits as was the case in the BLSA cohort. Further correlations of these data show that the percentage of free prostate-specific antigen in sera predicts aggressiveness of prostate cancer before diagnosis. These findings can improve the ability to screen men for this disease and make it possible to identify men who are at higher risk of developing an aggressive cancer. By knowing early that a cancer is present, and by knowing its aggressiveness, men and their physicians can better plan appropriate therapeutic strategies.

BLSA data has been used to examine other factors that may be associated with increased prostate cancer risk. NIA and Johns Hopkins University School of Medicine investigators have used the BLSA cohort to examine the role of hormones in promoting prostate cancer as well as the potential use of hormone measurements as potential markers of prostate cancer risk. These studies have employed a "retro-prospective" study design, using stored samples from the BLSA collection taken as much as 15 years before men developed clinical evidence of prostate cancer and comparing them with samples from age-matched men followed for similar periods of time with no diagnosis of prostate cancer. To date, these studies have provided evidence that serum testosterone levels, whether measured as total or biologically available fraction, do not predict subsequent development of prostate cancer.

Previous studies evaluating the roles of circulating insulin-like growth factors (IGF-I and IGF-II) and their major plasma binding protein, IGF binding protein-3 (IGFBP-3), have suggested that lower than average levels of IGF-I and high levels of IGF-II may each be independently associated with a reduced risk of prostate cancer, while the apparent protective effect of IGFBP-3 was not statistically significant. In contrast, recent NIA intramural studies have shown that once levels of PSA are known, determinations of IGF-I, IGF-II, and/or IGFBP-3 add no useful predictive information for identifying patients at high risk for prostate disease in groups of longitudinally-followed middle aged and older men. Serum selenium levels were examined in relationship to later development of prostate cancer using a case control design. The risk of prostate cancer was lower in men with serum selenium levels above the lowest quartile with odds ratios of .29,.34, and .48 for subsequent quartiles (p=0.049). Age of the patients at diagnosis did not affect the protective effect observed for higher selenium values. The findings are consistent with other reports that higher serum selenium levels may be associated with a decreased risk of prostate cancer. At this point, we cannot address whether supplemental selenium may reduce the risk of prostate cancer.

National Institute of Nursing Research

Care of Men with Prostate Cancer:

NINR has identified opportunities for expanding its biobehavioral and psychosocial research on prostate cancer to include:

- managing symptoms following treatment (e.g., urinary incontinence and pain);
- nursing interventions to improve quality of life, including sexual role and function;
- decision–making associated with treatment options (e.g. watchful waiting vs. surgery);
- decision–making associated with screening for prostate cancer, especially in minority populations.

These studies would provide important knowledge to improve decision-making, management of symptoms, and quality of life for men with prostate cancer.

National Institute of Mental Health

NIMH supports research on the interactions of stress and emotions with life-threatening illnesses such as cancer. A primary focus of NIMH-supported research related to prostate cancer is characterization of the stress of having prostate cancer and undergoing a radical prostatectomy. This research examines psychological, physiological, and quality-of-life changes associated with the surgery and short- and long-term recovery; it also examines dispositional and environmental factors that might serve to predict response to surgery and long-term recovery. An objective of this research is to develop a pre-surgical stress management approach that will reduce the negative impact of prostatectomy on patients. Other NIMH research explores the genetic basis of familial prostate cancer.