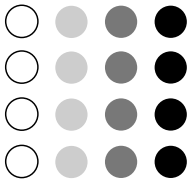


Defeating Prostate Cancer:
Crucial Directions for Research

Report of the Prostate Cancer Progress Review Group

August 1998

NATIONAL® CANCER INSTITUTE

FROM THE CHAIRMEN:

It is with great pleasure that we transmit the Report of the Prostate Cancer Progress Review Group to the Advisory Committee to the Director of the National Cancer Institute. This assessment of the Institute's progress in prostate cancer research was undertaken at the request of Dr. Richard Klausner, Director of the National Cancer Institute.

The overall goal of the Review Group was to develop a national plan consisting of a description of ongoing scientific activities and investigations relevant to prostate cancer and to provide to the Institute a list, in priority order, of scientific opportunities that should be pursued.

As co-chairs, we were pleased to serve with a committee of prominent members of the scientific, medical, industrial, and advocacy communities. Our colleagues represented the full spectrum of expertise needed to develop the comprehensive recommendations you will find in this report. We believe the hard work of this Review Group, which began its work in April 1997, has resulted in recommendations that, if pursued, will do much to eradicate morbidity and mortality due to prostate cancer, the leading site of new cancer cases and the second leading cause of cancer deaths in men in the United States.

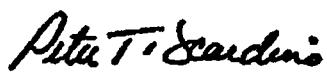
Our comprehensive assessment of the status of prostate cancer research, the depth and breadth of the Institute's investment in this research has provided us with a wealth of new scientific opportunities. We believe that this was, indeed, an opportune time to reassess the Institute's prostate cancer research portfolio and plan a research agenda for prostate cancer that will guide the prostate cancer research field into the next decade. We look forward to following the progress of the many recommendations made in this report and would be pleased to discuss our findings with the leadership of the National Cancer Institute.

Respectfully,

Donald Tindall, Ph.D.
Co-Chairman
Prostate Cancer
Progress Review Group

Peter Scardino, M.D.
Co-Chairman
Prostate Cancer
Progress Review Group

We the undersigned members of the Prostate Cancer Progress Review Group concur with the enclosed report.



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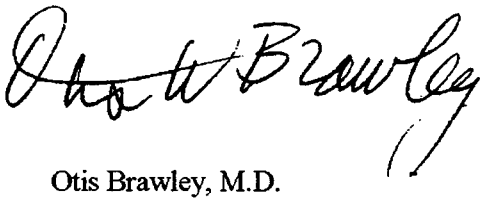

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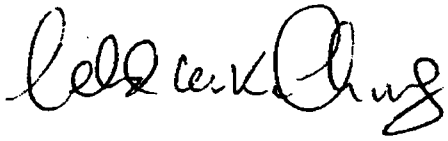

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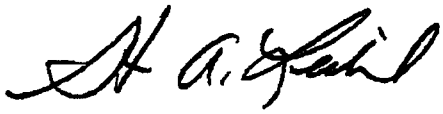

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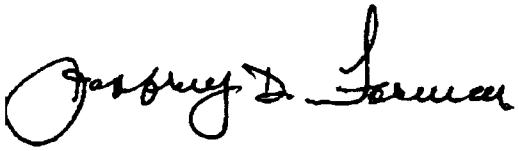

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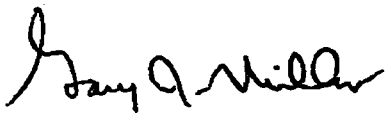

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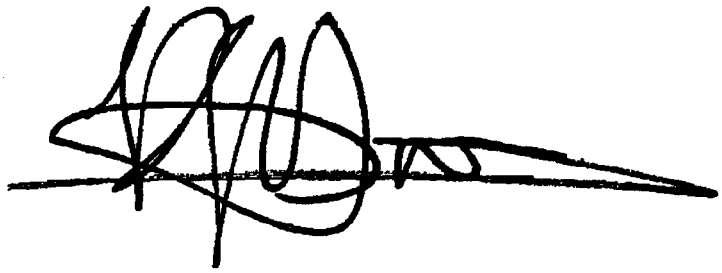

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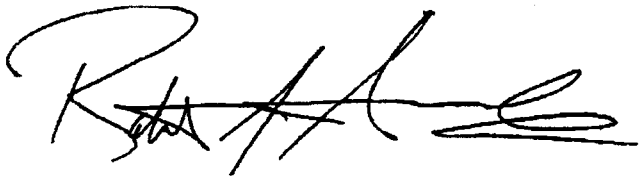

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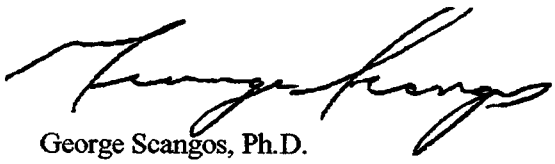

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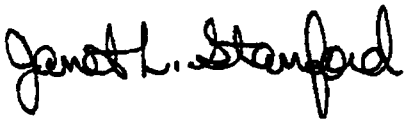

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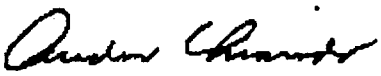

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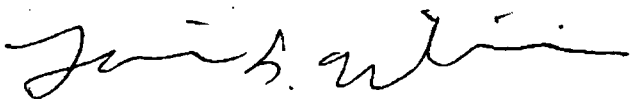

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ACKNOWLEDGEMENTS

Dr. Andrew Chiarodo served as Executive Director of the PRG and provided the crucial link between the members of the PRG and the members of the NCI Task Force. The work of the PRG would have been infinitely more difficult without Dr. Chiarodo's dedicated involvement.

The Progress Review Group benefited from the exceptional staff support and expertise of the Office of Science Policy (NCI), including Ms. Cherie Nichols, Chief, Office of Science Planning and Assessment; Dr. Susan Rossi, Senior Program Analyst; Ms. Kate Nagy, Program Analyst, Ms. Valerie Sasser, Program Analyst; Mr. John Tuskan, Program Analyst; Ms. Annabelle Uy, Secretary; and Ms. Marilyn Duncan, Program Assistant.

The members of the Task Force did an outstanding job with the large and complex task of reporting on the NCI research portfolio and the information they provided was central to deriving the estimates of funding support for the research topic areas of the PRG.

In addition, the PRG was fortunate to have the outstanding scientific writing expertise of Dr. Kathi Hanna and Dr. Miriam Davis. The United Information Systems (UIS) group provided excellent technical support to the prioritization effort and lastly, Ms. Sally Marshall provided gracious and helpful logistical support on behalf of the Cygnus Corporation.

TABLE OF CONTENTS **PAGE**

EXECUTIVE SUMMARY

technology to identify risk factors and how the environment modifies those predisposing risks. An understanding of the interaction of genetic and environmental risk factors that determine incidence in high risk (e.g., African American) and low-risk (e.g., Asian) populations is also important.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Prostate-specific antigen (PSA) testing has greatly facilitated the diagnosis of prostate cancer. But it has not been demonstrated that PSA screening actually reduces morbidity or mortality from this disease. One of the most perplexing aspects of prostate cancer is that more cancers develop in men over age 50 than ever become clinically apparent or prove lethal. Consequently, men face a serious dilemma: if their cancer goes undetected, they could develop a debilitating, potentially lethal disease; however, if their tumor would have remained quiescent for the rest of their natural life, detection could lead to the adverse consequences of unnecessary treatment. Fortunately, screening seldom detects the small, clinically unimportant tumors.

Progress in early detection requires that tests used for detection be refined to ensure that, whenever possible, the cancers detected are clinically important, that is, to detect only those cancers with the potential to kill their host if left untreated without missing any clinically important cancers. In addition, prognostic "markers" must be further refined to accurately measure the biologic potential of a cancer, allowing therapy to be tailored to the risk posed by the individual cancer.

NCI should place major emphasis on the development, validation and application of biologic markers or determinants that can provide reliable prognostic information. This effort will likely require the formation of a new, dedicated multidisciplinary prostate cancer marker consortium involving multiple institutions committed to translational research in prostate cancer. Since no single marker is likely to prove sufficiently predictive, panels of multiple markers will be required, and analyzed with the sophisticated tools of modern medical informatics.

At the same time, NCI should continue to support clinical trials to determine whether screening for prostate cancer reduces the risk of dying from this disease and should substantially expand studies of the effects of early detection on morbidity and quality of life.

LABORATORY AND CLINICAL MODELS

Laboratory and clinical models are critical for defining the mechanisms of prostate cancer progression and for testing preventive and therapeutic regimens. Yet only a few laboratory and clinical models have been developed, all of which are encumbered by insufficient biological knowledge of the human cancer they strive to simulate. Better understanding of the basic biology of human prostate cancer will accelerate and refine the process of model development.

A laboratory model ideally simulates all of the properties of prostate cancer in humans; however, such a model is difficult to achieve in practice. A constellation of models (xenograft, transgenic, reconstitution, animal, *in vitro*, and mathematical) must be

SECTION I.

BACKGROUND INFORMATION ON THE PROSTATE CANCER PROGRESS REVIEW GROUP

ABOUT THIS REPORT

Following this section, the Review Group presents a visionary statement of how best to move prostate cancer research efforts past current barriers and seize the opportunities that are emerging from past and ongoing research in prostate cancer. Section III contains detailed presentations of prioritized scientific questions and recommended actions
within the following eight categories of prostate cancer research.

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

SECTION II.

VISIONARY STATEMENT

VISIONARY STATEMENT

Prostate cancer is the most frequently diagnosed cancer in American men and the second leading cause of cancer deaths.[1] In some Western countries, it has become the leading cause of cancer deaths. As our population ages, the impact of prostate cancer on American men will increase; no other cancer rises in incidence and mortality rate with increasing age as rapidly as does prostate cancer.[2] It has been estimated that over 1 million American men now alive and over age 50 will eventually die of prostate cancer unless new treatments are developed to control this disease.[3] Unfortunately, prostate cancer has a disproportionate impact on certain segments of our population. For example, African American men are more likely to develop prostate cancer and twice as likely to die from it than are other Americans.[4]

Over the past decade, the incidence of prostate cancer has increased sharply as PSA testing has become widely available. With widespread awareness about prostate cancer and a greater willingness to discuss this disease publicly, more than 50 percent of men over the age of 50 report that they have been tested for prostate cancer within the past two years. Much of the increased incidence, therefore, has been related to the identification through widespread screening of a large number of prevalent, but previously undetected, cases in the population. The gradual decline in the mortality rate seen in the past five years may be related, in part, to the remarkable sensitivity of PSA in detecting prostate cancer earlier, when it can be controlled with surgery or irradiation therapy.

In recent years, real progress has begun to be made against human cancer. The mortality rate for all cancers peaked early in this decade and has begun slowly to decline. But with over 39,000 deaths expected from prostate cancer alone this year much remains to be done. Prostate cancer presents some unique challenges. Cells that have the appearance of prostate cancer can be found in the prostate gland of nearly half of all men over the age of 50. Yet the lifetime risk of a man being diagnosed with clinically apparent prostate cancer is only 11 percent and the lifetime risk of dying of prostate cancer is only 3.6 percent. Thus, some 3 cancers develop for every one that will prove lethal. The ultimate strategy for defeating prostate cancer calls for developing ways to distinguish the harmless (indolent) cancers from the potentially lethal, and developing effective ways to prevent or treat the potentially lethal cancers.

The growth of scientific knowledge presents our nation with a unique opportunity to advance the attack on prostate cancer and to accelerate the pace of progress against this disease. Taking advantage of this opportunity,

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[1] Landis, S.H., Murray, T., Bolden, S., Wingo, P.A. Cancer statistics, 1998. *CA: A Cancer Journal for Clinicians* 1998;48:6-29.

[2] Carter H.B. and Coffey D.S. The prostate: an increasing medical problem. *The Prostate*, 1990; 16:39-48

[3] Scardino, P.T., Weaver, R., Hudson, M.A. Early detection of prostate cancer. *Human Pathology* 1992;23:211-222.

[4] Parker, S.L., Davis, K.J., Wingo, P.A., Ries, L.A.G., Heath, C.W. Jr. Cancer statistics by race and ethnicity. *CA: A Cancer Journal for Clinicians* 1998;48:31-48.

predisposition and exogenous exposures interact to determine prostate cancer susceptibility is needed for the design of effective preventive strategies. Moreover, dietary factors may provide both preventive and therapeutic benefits.

Special attention to the biology of the normal and malignant prostate cell will open new, unexpected opportunities for improving the diagnosis and treatment of prostate cancer. It is especially important to understand the prostatic stem cell in its relation to the development of cancer. Many other malignancies exhibit a close relationship between the growth control mechanisms employed by stem and progenitor cell populations for a given lineage. These relationships should be explored thoroughly in prostate cancer as well.

A fundamental and universal feature of every prostate cancer that proves lethal is the development of androgen independence, yet the mechanisms of androgen resistance or independence at the cellular level are poorly understood. There has been an appropriate intensive molecular analysis of the androgen receptor in prostate cancer, but the complexity of the phenotype of androgen resistance needs far more attention in order to develop better agents to suppress recurrence of cancers after initial hormonal therapy fails.

Prostate cancer cell surface and internal antigens can provide a suitable target for imaging these cancers and for the development of new diagnostic agents and novel therapeutic interventions. Immunological strategies are proving successful with other tumors and offer enormous promise in prostate cancer as well.

With the developments in biology have come exciting new drugs that act through a variety of novel mechanisms– drugs like angiogenesis inhibitors, and those that block signal transduction mechanisms. Moreover, the field of experimental therapeutics is growing rapidly. Testing these and other novel therapies against human prostate cancer will require a much more extensive infrastructure to support translational research. Regardless of the effects in tissue culture or animal models, new diagnostic agents or therapeutic interventions must be tested in humans. Clinical trials are the essential bridge between science and medicine.

Many features of prostate cancer make the disease a good target for gene therapy. Among these features are its slow growth, enabling long-term control even if the cancer is not eradicated, the discrete and accessible nature of the prostate gland, and the fact that the response to therapy can be monitored throughout the course of the disease through PSA, biopsies, and scans. Prostate cancer, among the solid tumors, seems to be particularly suitable for gene therapy, since the organ is expendable, the primary tumor is accessible for applying treatment and monitoring the response, and a circulating marker of response is readily available. Gene therapy has thus far been associated with low morbidity and could be applied repeatedly to palliate these slow growing cancers long enough for patients to live out their natural lives even if the cancer is not completely eradicated. In addition, limited, occult micrometastases—the major cause of treatment failure—may be particularly susceptible to gene therapy strategies, which augment the immunogenecity of

SECTION III.

PRIORITIES AND RECOMMENDATIONS

contained within the prostatic parenchyma to a systemic disease involving the seminal vesicles, lymph nodes, skeleton, and other distant organs involves fundamental changes dictated by genetic as well as epigenetic (environmental, behavioral, and dietary) influences. Supporting this contention are clinical and laboratory studies that demonstrate putative roles for hereditary factors, tumor characteristics (including DNA repair, cell cycle progression, and apoptotic potential), and host factors (comprising stromal-epithelial interactions, angiogenic influences, and host immune surveillance) in prostate cancer progression and metastasis.

Unfortunately, our understanding of the underlying mechanisms that dictate prostate development, carcinogenesis, tumor progression, and metastatic dissemination is still very rudimentary. The biochemical and molecular mechanisms that control cellular interaction during prostate organogenesis, morphogenesis, and functional differentiation remain undetermined. The differentiative and proliferative potentials of prostatic stem cells have not been defined. The inter- and intra-cellular signaling pathways that govern androgen receptor-mediated gene transcription and also communicate with other signal transduction pathways remain uncharacterized. Moreover, the specific target genes and gene products that are directly controlled by key signaling molecules during the various stages of prostate cancer development and progression have not been identified. Further research is needed into cellular signaling, cell surface receptor activity, and the interactions of prostate cancer cells with soluble and matrix-associated molecules that regulate prostate cancer growth, progression, and dissemination.

Tumor-host interactions are pivotal to the mechanisms of cancer cell invasion, migration, and metastasis. Such interactions are reciprocal, and reflect both the endocrine and immunologic status of the host, which can either foster or reject the survival of the neoplastic cells. The importance of understanding prostate cancer-skeletal interactions, in particular, is underscored by the strong propensity of prostate cancer to metastasize to the bone and the subsequent unique osteoblastic response observed in patients with metastatic disease. Hence, it will be necessary to identify the molecular and biochemical features of bone physiology and pathophysiology that influence interaction between prostate tumor and bone cells, and the subsequent characteristic osteoblastic reactions that are induced when tumor cells metastasize to the skeleton.

Recently, new technologies such as microdissection, microarray, and comparative genomic hybridization have been utilized to evaluate clinical specimens, enabling the identification, cloning, and characterization of prostate cancer progression-associated molecular markers that might someday be used to define and characterize the malignant potential of prostate cancer in individual patients. Despite the identification of these novel prostate cancer progression-associated biomarkers, validation of these findings, as well as discoveries of the molecular basis of cell communication and intra- and intercellular signaling, has not been performed with respect to progressively tumorigenic and metastatic clinical prostate cancer specimens. An intensified pursuit is needed to delineate the relevant and basic biological parameters discovered thus far and relate

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

This important topic receives exceedingly low levels of NCI funding. The lack of funding could be misleading, however, because other NIH institutes, such as NIDDK and NIEHS may fund this general area of research.

Despite numerous research projects being performed by academic institutions and industry on the subject of nuclear receptors and drugs that may block receptor-ligand interaction, affect steroid metabolism, and interfere with prostate development, a lack of communication between academic and industrial centers on this topic has impaired development of this important research concern.

In addition, although many studies have been performed at the cellular and molecular levels to delineate steroid receptor action and any subsequent role in carcinogenesis, relationships between steroid hormone-induced gene transcription, growth, differentiation, and senescence at the organistic levels remain rudimentary.

The following are barriers to progress in this area: 1) lack of consensus on the most appropriate models and targets that should be pursued and validated; and 2) inadequacy of extrapolating data obtained from culture cells or cell-free systems to that of the prostate gland *in situ*.

Recommended Actions:

To understand the structure and activity of the well-defined molecules such as nuclear receptors and steroid-metabolizing enzymes, it is critical to obtain crystallography data on the molecules of concern. In addition, increasing efforts need to be devoted to identifying and characterizing partners of nuclear receptors that may function together either alone or crosstalk with other cell signaling pathways to control proliferative and differentiative signals in cells.

1. Expedite structural and pharmacological studies of important nuclear receptors and steroid-metabolizing enzymes.

2. Expedite human genome-based studies and the identification, cloning, and characterization of proteins relevant to normal and cancerous prostate cells. Such information may be valuable in assisting further progress in this area of research.