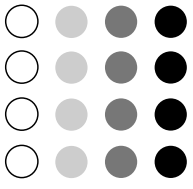


Progress
Review
Groups

Report of the Kidney/Bladder Cancers Progress Review Group

August 2002

NATIONAL® CANCER INSTITUTE

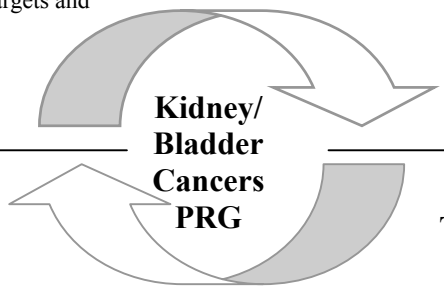
The 13 Priority Recommendations of the Kidney/Bladder Cancers Progress Review Group

Discovery

- Understand the biological mechanisms underlying the risk factors for kidney and bladder cancer phenotypes.
- Identify global genetic, epigenetic, RNA expression, and proteomic alterations in tumors, to detect such alterations in the urine and blood and to place them in specific biological pathways that are essential to the development, progression, response to therapy, and maintenance of subtypes of bladder and renal cancers.
- Understand the role of stroma and intercellular signaling in organogenesis, tumor development, and maintenance of malignant phenotypes in bladder and kidney cancers.
- Generate and characterize transgenic models, including conditional knockout and knockin strategies and orthotopic models, of bladder and kidney cancers, focusing on the use of tissue-specific promoters and targeting human disease-related genetic events. These models will allow identification and validation of prognostic, preventive, and therapeutic targets and their inhibiting agents.

Translation

- Examine blood, urine, premalignant tissue, and tumor tissue before prevention and therapy trials to identify and quantify disease and identify targets for therapy and predictors and mechanisms of response, resistance, progression, and relapse.
- Facilitate the development and utilization of noninvasive or minimally invasive techniques to image and assess the biological and clinical effects of targeted therapeutics.
- Identify and prioritize agents—alone or in combination—that target known cancer growth and progression pathways.



Cancer Control

- Describe the impact of kidney and bladder cancers and their treatment on the quality of life of individuals and their families throughout the cancer continuum and develop and assess interventions that will reduce morbidity and improve health-related quality-of-life outcomes.
- Identify, characterize, and validate molecular markers to determine the risk of disease, enhance early detection, and predict response to chemoprevention with new chemopreventive agents and strategies, employing new models as appropriate.
- Identify and explore the gaps between and barriers to standards of practice and care that currently result in disparate outcomes for patients with kidney or bladder cancer.

Treatment

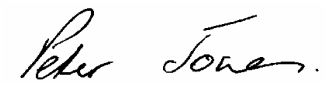
- Develop innovative therapeutic strategies that will eradicate disease, preserve organ function, and maintain quality of life, using mechanism-based agents that take into account known prognostic variables, molecular characteristics of tumors, assays of targeted effects, surrogate markers of efficacy, and novel delivery strategies.
- Develop and improve approaches to risk assessment of localized and advanced disease—which take into account known prognostic variables, including stage, histology, and novel molecular factors—to direct therapy.
- Develop evidence-based hypothesis-driven research efforts in palliative care for patients with advanced kidney or bladder cancer.

Report of the Kidney/Bladder Cancers Progress Review Group

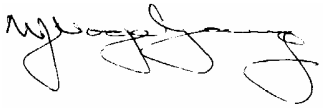
August 2002

From the Leadership

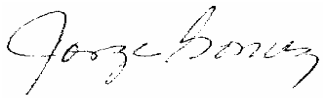
It is a great pleasure to submit this Report of the Kidney/Bladder Cancers Progress Review Group (PRG) to the Director and Advisory Committee to the Director of the National Cancer Institute. The PRG accepted the charge of Dr. Richard Klausner, who was then the Director of the National Cancer Institute, to develop a national plan for the next 5 years of kidney and bladder cancer research. This report represents the collaborative efforts of the scientists, clinicians, industry representatives, and patient advocates who participated in the PRG Roundtable Meeting. The priorities outlined in this report are a blueprint for progress toward preventing, diagnosing, and treating kidney and bladder cancers. We look forward to discussing these priorities and the plan for their implementation with the leadership of the National Cancer Institute.



Peter A. Jones, Ph.D.
University of Southern California
Norris Comprehensive Cancer Center
PRG Co-Chair



Nicholas J. Vogelzang, M.D.
University of Chicago
Cancer Research Center
PRG Co-Chair



Jorge Gomez, M.D., Ph.D.
National Cancer Institute
Organ Systems Branch
PRG Executive Director

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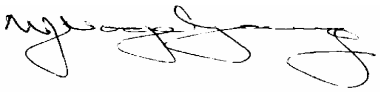
Peter A. Jones, Ph.D.
Co-Chair
University of Southern California
Norris Comprehensive Cancer Center



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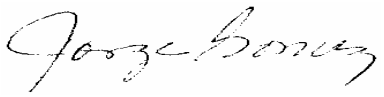
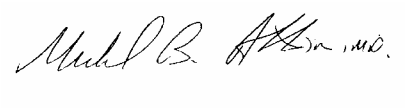
Co-Chair
University of Chicago
Cancer Research Center



Jorge Gomez, M.D., Ph.D.
Executive Director
National Cancer Institute
Organ Systems Branch

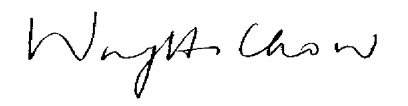


Michael B. Atkins, M.D.
Beth Israel Deaconess Medical Center

Arie Belldegrun, M.D.
School of Medicine, UCLA

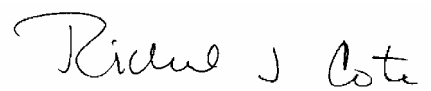
Donna Berry, Ph.D., R.N., A.O.C.N.
University of Washington

Ronald M. Bukowski, M.D.
Cleveland Clinic Taussig Cancer Center



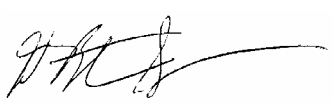
Wong-Ho Chow, Ph.D.
National Cancer Institute

Carlos Cordon-Cardo, M.D., Ph.D.
Memorial Sloan-Kettering Cancer Center

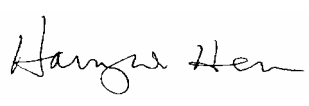


Richard J. Cote, M.D.
University of Southern California
Norris Comprehensive Cancer Center

Janice P. Dutcher, M.D.
New York Medical College
Our Lady of Mercy Cancer Center



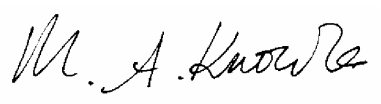
H. Barton Grossman, M.D.
University of Texas
M.D. Anderson Cancer Center



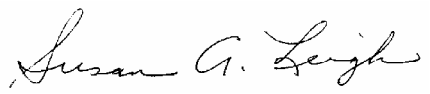
Harry W. Herr, M.D., F.A.C.S.
Cornell University Medical College
Memorial Sloan-Kettering Cancer Center

We the undersigned members of the Kidney/Bladder Cancers Progress Review Group concur with the enclosed report.

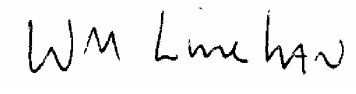
Othon Iliopoulos, M.D.
Massachusetts General Hospital
Harvard Medical School



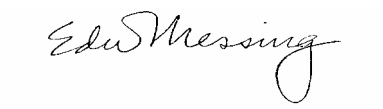
Margaret Knowles, Ph.D.
St. James's University Hospital
Imperial Cancer Research Fund
Clinical Centre at Leeds



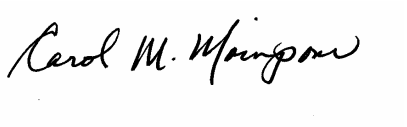
Susan Leigh, R.N.
National Coalition for Cancer Survivorship



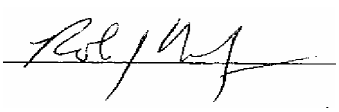
W. Marston Linehan, M.D.
National Cancer Institute



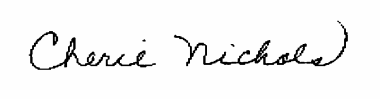
Edward M. Messing, M.D.
University of Rochester Medical Center



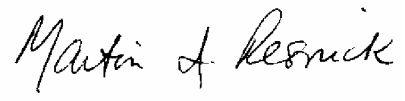
Carol Moinpour, Ph.D.
Fred Hutchinson Cancer Research Center



Robert J. Motzer, M.D.
Memorial Sloan-Kettering Cancer Center



Cherie Nichols, M.B.A.
National Cancer Institute

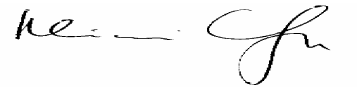


Martin I. Resnick, M.D.
Case Western Reserve University
University Hospitals of Cleveland

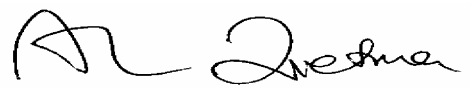
Raymond Ruddon, M.D., Ph.D.
Johnson & Johnson

Walter Stadler, M.D.
University of Chicago

Bin Tean Teh, M.D., Ph.D.
Van Andel Research Institute



Mimi Yu, Ph.D.
University of Southern California
Norris Comprehensive Cancer Center



Anthony L. Zietman, M.D., M.R.C.P., F.R.C.R.
Massachusetts General Hospital
Harvard Medical School

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This report is the product of months of intense work that drew on the combined expertise and efforts of many individuals. The Kidney/Bladder Cancers Progress Review Group (PRG) particularly acknowledges the contributions of:

- The many scientists, clinicians, and advocates from across the country who generously gave of their time and knowledge and without whose participation this report would not have been possible.

- The staff of the National Cancer Institute Office of Science Planning and Assessment, under the leadership of Cherie Nichols, who provided ongoing guidance and technical support to the PRG throughout the process of preparing this report—in particular, Deborah Duran, who coordinated the PRG, as well as Kevin Callahan, James Corrigan, and Annabelle Uy.

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Priorities of the Kidney/Bladder Cancers Progress Review Group

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OVERVIEW

Scope of the Problem

Each year kidney and bladder cancers account for approximately 88,300 cancer cases and 24,200 deaths in the United States, or nearly 7 percent of all cancer cases and more than 4 percent of all cancer deaths. These two cancers alone account for nearly 10 percent of all cancers in men and more than 4 percent of all cancers in women.

Significant gender and racial/ethnic disparities are evident in kidney and bladder cancer incidence and mortality. For example, although bladder cancer is three to four times more common in men than in women, women's survival rates lag 5 years behind those of men. The 5-year survival rate for women with bladder cancer is 78 percent, which is equivalent to the 10-year survival rate in men. The 10-year survival rate in women, 69 percent, is equivalent to the 15-year survival rate in men.

Compared with white men, black men have higher incidence and mortality rates for kidney cancer and higher mortality rates for bladder cancer. Although blacks are slightly more likely than whites to be diagnosed with kidney cancer in its early stages, 5-year survival rates for both localized and metastatic disease are lower in blacks than in whites. Bladder cancer is more likely to be diagnosed at a later stage in blacks than in whites. Among individuals diagnosed with metastatic bladder cancer, whites have a 5-year survival rate of 6.9 percent; the comparable rate in blacks is 3.8 percent (Surveillance, Epidemiology, and End Results Program [SEER] data, 1992–1997).

Kidney cancer incidence has been increasing at a rate of about 2 percent per year for the past 65 years; the reasons for this increase are unclear. Although most cases of kidney cancer occur in white males, rates of kidney cancer per 100,000 people are currently highest in blacks. Among women, the highest rates of kidney cancer are seen in blacks and American Indians. Whereas overall kidney cancer mortality has not increased in the past 20 to 30 years, certain groups, such as Asians and blacks, may be experiencing increases in mortality. On average, patients with kidney cancer die a decade earlier than those with bladder cancer, reflecting younger ages at diagnosis and lower survival rates. Overall 5-year survival rates in kidney cancer are 62 percent, compared with 81 percent in bladder cancer. Ten-year survival rates are 53 percent and 76 percent, respectively (SEER data, 1992–1997).

More than 40 percent of kidney cancer cases are not diagnosed until they have metastasized (SEER data, 1992–1997). The 5-year survival rate in patients with advanced kidney cancer is 9 percent; by contrast, close to 90 percent of patients with localized disease survive for 5 years. Therapy with interleukin-2 produces formidable toxicity but cures about 10 percent of patients with metastatic disease; however, use of this therapy has not increased the current median survival time of approximately 12 to 15 months.

In contrast to kidney cancer, incidence of bladder cancer is declining at just under 1 percent per year overall. Mortality from bladder cancer also has declined significantly, from 27 percent in 1974–1976

to 19 percent in 1989–1995. Approximately 75 percent of bladder cancers are present as noninvasive tumors; however, 20 years after resection, 80 percent of these cancers have recurred. Metastatic bladder cancer has a 5-year survival rate of 6 percent. Combination chemotherapy is the primary treatment modality for metastatic bladder cancer. Newer compounds such as gemcitabine and the taxanes appear to have reduced toxicity but have not improved the median survival time of 12 to 20 months.

It is clear that current diagnosis and treatment modalities for kidney and bladder cancers are extremely limited. Advances are sorely needed to reduce the burden of morbidity and mortality from these diseases. Adding to the challenge is the fact that both kidney and bladder cancers are families of heterogenous diseases, each with its own distinct molecular defects that require different treatment strategies. The term "kidney cancer" includes clear-cell carcinoma (about 75 percent of kidney cancer cases), papillary carcinoma (about 15 percent), and oncocytoma and other types (about 10 percent). The term "bladder cancer" includes transitional cell carcinoma (about 90 percent of all bladder cancer cases occurring in the United States), adenocarcinoma (about 7 percent), and squamous cell carcinoma (about 3 percent).

Premise for Planning

The Kidney/Bladder Cancers Progress Review Group (PRG) was charged with identifying and prioritizing research questions that will advance progress against these cancers during the next 5 years. The PRG used the "bench to bedside/bedside to bench" paradigm to structure its approach to this charge. To improve outcomes for kidney and bladder patients, **discoveries** at the laboratory bench of mechanisms or pathways specific to kidney or bladder cancer must be **translated** to **treatments** that can be applied at the patient's bedside as well as to strategies for preventing and **controlling** these diseases (Figure 1).

As a model, the PRG considered the von Hippel-Lindau (*VHL*) gene and its role in kidney cancer. The discovery of the central role of this gene in kidney cancer required both extensive laboratory effort and patient/DNA resources. The PRG posed the question: What steps are necessary to translate the *VHL* discovery into improved health outcomes for patients with kidney cancer?

The PRG hypothesized that with appropriate resources, molecules in the disordered VHL pathway could be used to monitor the cancer and could also serve as targets for kidney cancer-specific therapy (e.g., antibodies, small molecules, antisense therapies). Genes or proteins in the VHL pathway could be noninvasively imaged, measured in blood or urine, or used to predict prognosis. *VHL*-positive individuals could be considered for specific chemoprevention trials to prevent or retard the currently inevitable development of renal cell cancer.

The PRG considered the sequence of "bedside to bench" as an equivalent model. For example, without clinical identification of VHL families, *VHL* could never have been discovered in the laboratory. Thus the "bedside" must always be an equal partner in research activity with the "bench."

The PRG was also influenced by a recent unifying hypothesis in cancer biology that suggests mammalian tumorigenesis requires six essential pathways:

- Self-sufficiency of growth signals,

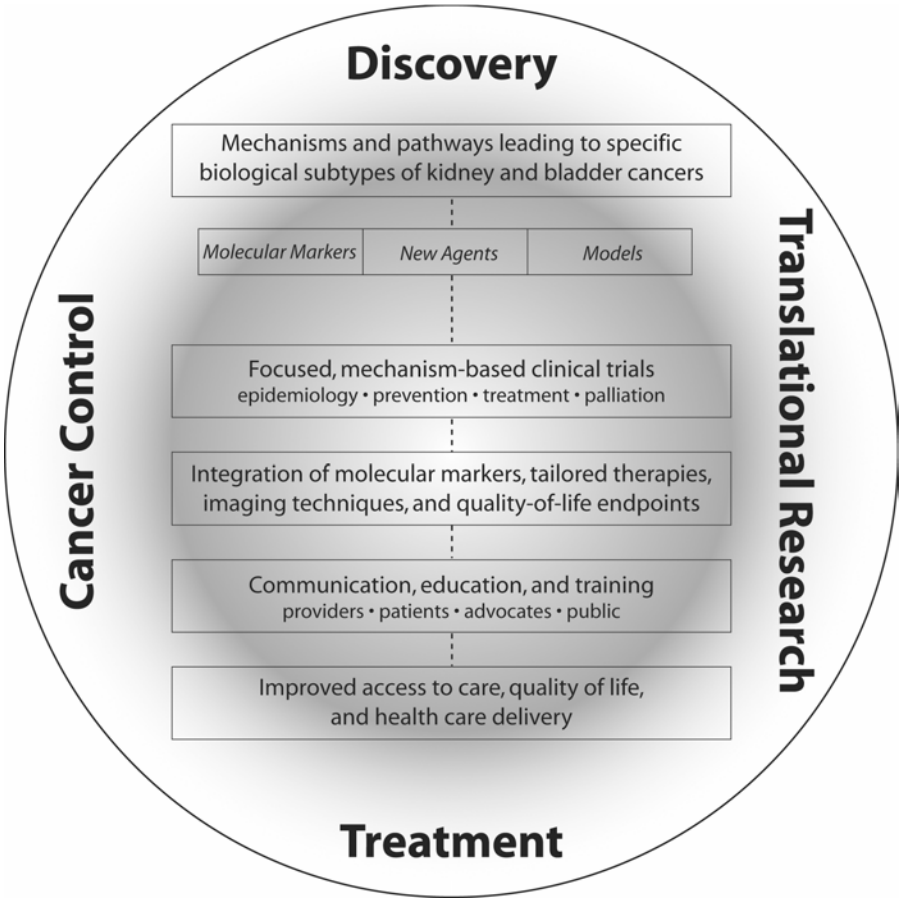

Figure 1: Schematic Diagram—Kidney/Bladder Cancers Progress Review Group conceptual organization and foundation for high-priority recommendations

- Insensitivity to anti-growth signals,
- Tissue invasion and metastasis,
- Limitless replicative potential,
- Sustained angiogenesis, and
- Evasion of apoptosis.

The existence of these six pathways and the commonality with which they are altered in human cancer provided a framework for the PRG's discussions. This unifying concept provided the glue to link the discussions of kidney and bladder cancers and also served as a mechanism to focus attention on the etiology, diagnosis, and treatment of these diseases.

Process

At a planning meeting on July 17, 2001, the PRG organized a Roundtable Meeting to

consider progress, identify gaps, and highlight research needs across the continuum of kidney and bladder cancer research. Four areas of discussion were identified that reflected the "bench to bedside/bedside to bench" paradigm: Discovery, Translational Research, Treatment, and Cancer Control. Each of these groups was subdivided into two or three subgroups (Table 1). Roundtable participants were identified with a particular emphasis in reaching out to the urologic community, including the American Urologic Association members. PRG members were assigned to serve as co-chairs for these breakout sessions.

The PRG Roundtable Meeting, which included approximately 120 participants, met November 28–30, 2001, in Chantilly, Virginia. Participants were assigned to one of the four overarching groups as well as to one of that group's component subgroups. Participants also were asked to choose a second subgroup to attend during a cross-talk session, in which subgroups solicited input from attendees assigned to other subgroups.

Each subgroup then identified top priorities for kidney and bladder cancer research over the next 5 years. Following this step, the subgroups reconvened in the four overarching groups. Each group reviewed the priorities of its subgroups and identified the three or four priorities it considered most crucial to advancing knowledge in the field. For each priority, the group's members provided a rationale and a list of the resources needed to overcome the limitations of previous research and capitalize on existing opportunities. These priorities were presented on the last day. After extensive discussion, consensus of the Roundtable participants resulted in 13 high-priority recommendations.

The documents written by the four overarching groups form the basis of this report. The 11 individual subgroup reports can be found in Appendix B.

GROUPS	SUBGROUPS
DISCOVERY	• Etiology and pathogenesis • Molecular profiling and pathways • Experimental model systems
TRANSLATIONAL RESEARCH	• Preparing for human studies • Correlative science • Clinical trials
TREATMENT	• Risk-directed treatment of localized disease • Treatment and palliation of advanced disease
CANCER CONTROL	• Screening and prevention • Quality of life • Health care delivery and communication

Table 1: Kidney/Bladder Cancers PRG Roundtable Groups and Subgroups

PRG Priority Recommendations

The PRG leadership used the 13 priority recommendations of the Roundtable consensus to develop the overview for research on kidney and bladder cancers. Each recommendation is described in detail in the corresponding group report (Discovery, Translational Research, Treatment, and Cancer Control) in the main section that follows.

The priorities have an important synergy in that progress in one area will bolster progress in others. Supporting priorities in only one or two areas will not be enough; to advance our knowledge and understanding of these cancers, we must make a commitment to research along the entire continuum.

The 13 priorities identified by the Kidney/Bladder Cancers PRG will stimulate multidisciplinary research that can significantly advance progress against kidney and bladder cancers. Addressing these priorities will ultimately lead to discoveries that will reduce the burden of these diseases in the United States and worldwide. The priorities, with a summary rationale for each, are as follows (see also Table 2).

Discovery

Priority 1: *Understand the biological mechanisms underlying the risk factors for kidney and bladder cancer phenotypes.*

Rationale

The etiological mechanisms of distinct phenotypes of kidney and bladder cancers are poorly understood. Novel prevention and treatment strategies may result from improved understanding of such mechanisms.

Priority 2: *Identify global genetic, epigenetic, RNA expression, and proteomic alterations in tumors, to detect such alterations in the urine and blood and to place them in specific biological pathways that are essential to the development, progression, response to therapy, and maintenance of subtypes of bladder and renal cancers.*

Rationale

Bladder and kidney tumors are heterogeneous in their histology and clinical behavior. Individual tumors show alterations in specific molecular pathways, potentially allowing customized clinical management for the individual patient. Understanding of the relevant growth and signaling pathways will allow the development of targeted therapies, including the use of small molecules produced through combinatorial chemistry.

Priority 3: *Understand the role of stroma and intercellular signaling in organogenesis, tumor development, and maintenance of malignant phenotypes in bladder and kidney cancers.*

Rationale

Stromal elements are known to influence epithelial differentiation in the bladder and kidney. The tissue microenvironment—including the extracellular matrix, stromal cell complement, inflammatory cells, and local immune response—may play a role in tumor development and growth. Most studies to date have examined only the characteristics of the tumor epithelial cells.

Priority 4: *Generate and characterize transgenic models, including conditional knockout and knockin strategies and orthotopic models, of bladder and kidney cancer, focusing on the use of tissue-specific promoters and targeting human disease-related genetic events. These models will allow identification and validation of prognostic, preventive, and therapeutic targets and their inhibiting agents.*

Rationale

Transgenic model systems will allow understanding of gene function, dissecting of molecular pathways, and generation of faithful models of human cancer and will also provide targets for drug discovery and chemoprevention. However, kidney and bladder cancers lag behind other organ systems in the development and utilization of these models.

Translational Research

Priority 5: *Examine blood, urine, premalignant tissue, and tumor tissue before prevention and therapy trials to identify and quantify disease and identify targets for therapy and predictors and mechanisms of response, resistance, progression, and relapse.*

Rationale

New anti-apoptotic and tumor-growth and inhibition molecular pathways have been identified that may influence the response to therapy in kidney and bladder cancers. The discovery of alterations in specific molecular pathways in these diseases should also facilitate the identification of molecular markers that would enable selection of appropriate patients for therapy, monitoring of the effectiveness of therapy in an individual patient, and testing of therapies in a patient population with a lower tumor burden.

Priority 6: *Facilitate the development and utilization of noninvasive or minimally invasive techniques to image and assess the biological and clinical effects of targeted therapeutics.*

Rationale

Because kidney and metastatic bladder tumors cannot easily be sampled during therapy, noninvasive and minimally invasive methods are needed to assess therapeutic effectiveness. It will also be important to identify surrogate markers of biological effectiveness in readily accessible tissues and to identify blood and urine markers of tumor burden that will enable better assessments of treatment efficacy.

Priority 7: *Identify and prioritize agents—alone or in combination—that target known cancer growth and progression pathways.*

Rationale

Recent studies in chronic myelogenous leukemia and gastrointestinal stromal tumors have provided proof of principle that strategies developed to target cancer gene pathways can have an effect in human tumors. Several targets are available from known cancer genes involved in the early development of several types of genitourinary cancer. Validation of the roles and therapeutic potential of agents that block these cancer gene pathways is urgently needed.

Treatment

Priority 8: *Develop innovative therapeutic strategies that will eradicate disease, preserve organ function, and maintain*

*quality of life, using **mechanism-based agents** that take into account known prognostic variables, molecular characteristics of tumors, assays of targeted effects surrogate markers of efficacy, and novel delivery strategies.*

Rationale

Few patients with kidney or bladder cancer can be cured by existing therapies. New agents targeting specific disease mechanisms are being identified in preclinical and correlative studies. Optimally, future clinical trials need to investigate both the clinical and biologic effects of these agents in clearly defined and selected patient populations.

***Priority 9:** Develop and improve approaches to risk assessment of localized and advanced disease—which take into account known prognostic variables, including stage, histology, and novel molecular factors—to direct therapy.*

Rationale

Kidney and bladder cancers are biologically heterogeneous diseases. It is clear that many patients with localized disease can be managed with less invasive therapy, whereas others need more aggressive therapy. Similarly, patients with advanced disease have disparate characteristics that affect therapeutic outcomes. Better predictors of behavior and response are needed to more appropriately guide treatment of the individual patient and predict prognosis.

***Priority 10:** Develop evidence-based, hypothesis-driven research efforts in palliative care for patients with advanced kidney or bladder cancer.*

Rationale

Therapy fails in 95 percent of patients with advanced kidney or bladder cancer. In both of these tumor types, the distribution of symptom clusters in advanced disease is relatively unknown and the prognostic significance and impacts on quality of life of these symptom clusters are not well studied. For example, it would be useful to evaluate different strategies for managing bone metastases and the effects of these different strategies on mobility, function, and pain.

Cancer Control

***Priority 11:** Describe the impact of kidney and bladder cancers and their treatment on the quality of life of individuals and their families throughout the cancer continuum, and develop and assess interventions that will reduce morbidity and improve health-related quality-of-life outcomes.*

Rationale

Although cure or increased life expectancy is a goal of medical treatment, patients and those who care for them agree that improving the quality of the patient's life is also a high priority. Understanding the factors that affect quality of life is a prerequisite for patient-oriented treatment decision-making.

***Priority 12:** Identify, characterize, and validate molecular markers to determine the risk of disease, enhance early detection, and predict response to chemoprevention with new chemopreventive agents and strategies, employing new models as appropriate.*

Rationale

Molecular markers can be used to select high-risk subjects for screening, resulting in more statistically powerful screening studies with smaller numbers of subjects than could be obtained by general population screening. Studies of unique populations—such as young adults with bladder cancer, patients with end-stage renal disease, and post-treatment cancer patients who continue to smoke—are likely to yield insights into risk factors for kidney and bladder cancers. Additionally, preclinical, mathematical, and other models are essential to the development and testing of successful, cost-effective screening and prevention strategies.

Priority 13: *Identify and explore the gaps between and barriers to standards of practice and care that currently result in disparate outcomes for patients with kidney or bladder cancer.*

Rationale

Delay in treatment appears to be correlated with a disproportionately higher death rate among women with bladder cancer, who are diagnosed 6 to 9 months later than men. Black men have a higher mortality rate for both bladder and kidney cancers than white men. Once the causes of these and other apparent disparities in health care delivery are understood, strategies can be devised to remedy them.

Resources

The PRG also identified resources that will be needed to achieve these priorities. These resources are summarized below and are also described in the corresponding overarching group report.

- Animal and cell-based models.
- Large, multifaceted studies (epidemiologic, treatment, chemoprevention) conducted with international collaboration. These studies should include quality-of-life endpoints, have standardized consent forms, and include comprehensive and longitudinal sampling of tumor, urine, and blood. Adequate infrastructure is necessary for these trials to be successful.
- Specimen banks (tumors, normal tissue, blood, urine, etc.) available to all investigators.
- Standardization of common data elements and assays, with clinical validation.
- Validated, high-quality, high-throughput technologies for the analysis of DNA, RNA, and protein in tumors.
- Bioinformatics and biostatistical approaches for clinical trial analysis.
- Resources, primarily through industry, to produce and screen small molecules to target tissue-specific growth and signaling pathways. (This effort will require close cooperation between academia and industry.)
- A patient advocacy group in bladder cancer, modeled after the kidney cancer advocacy group, which will help to establish research priorities at the national level and can advocate for scientific studies and clinical trials.
- Noninvasive imaging modalities to evaluate therapeutic efficacy *in vivo*.

- Suitable targets for testing in humans and agents capable of affecting those targets.

- Training of young investigators focused on kidney and bladder cancers.

- Centers and networks of disease-specific clinical research, which could include expanding the definition of the Specialized Programs of Research Excellence (SPORES) to encourage multi-institutional consortia.

- A centralized database management system for patients participating in clinical trials sponsored by the National Cancer Institute, cooperative groups, and the pharmaceutical industry, as well as for patients in investigator- or institution-initiated pilot trials.

- Training for physicians, nurses, and other providers in quality-of-life assessment and data utilization.

- Linking large databases such as SEER and Medicare to improve our understanding of practice patterns that may create gaps in and barriers to the care of patients with kidney or bladder cancer.

- Multimedia modalities and collaborative community outreach activities to enhance the provider-patient relationship.

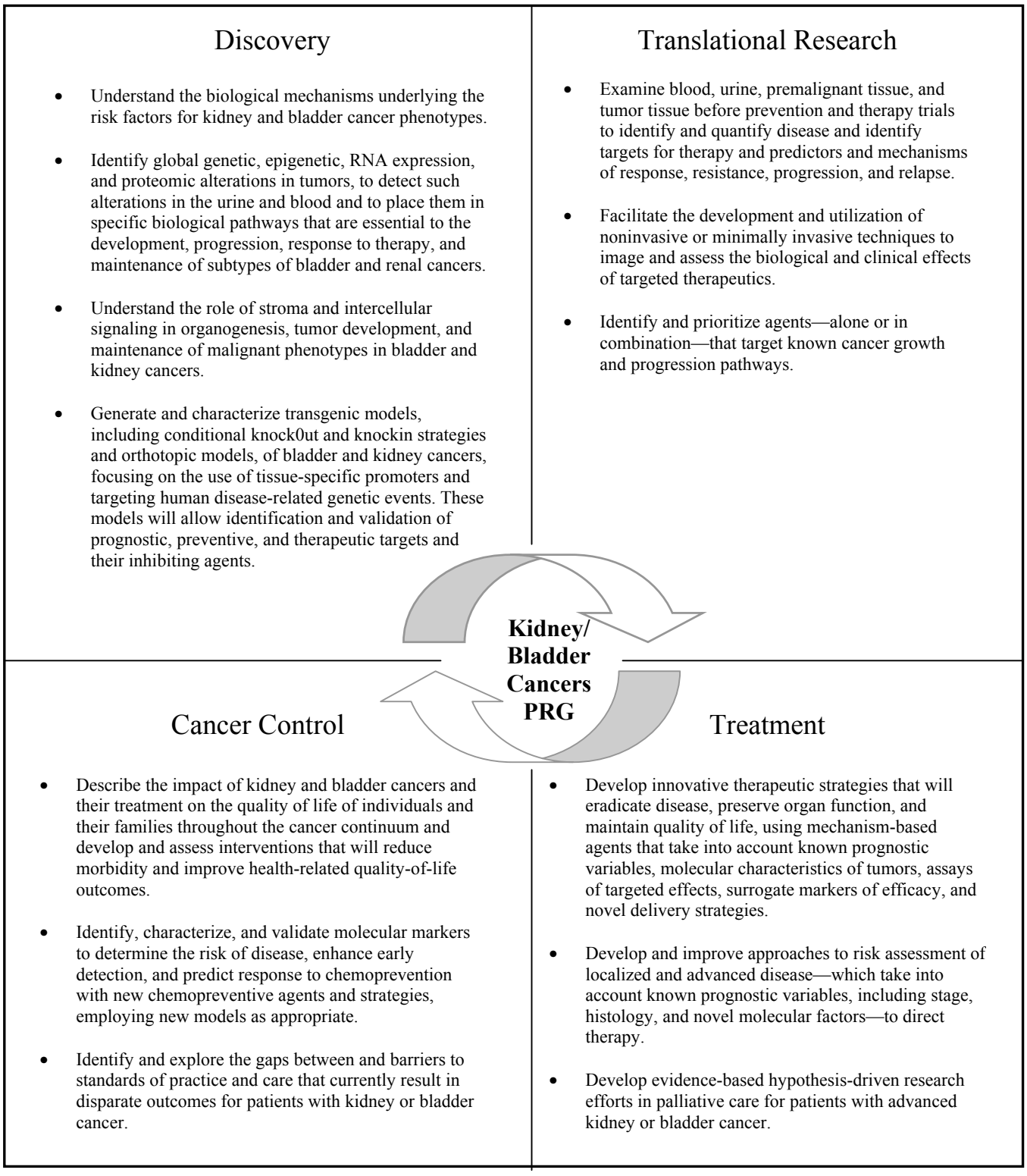

Table 2: The 13 Priority Recommendations of the Kidney/Bladder Cancers Progress Review Group

INTRODUCTION

Although research has shed some light on the environmental and genetic origins of kidney and bladder cancers, this knowledge has yet to be translated into significant reductions in the burden of these diseases. At present, mortality from kidney and bladder cancers is high and survival is low. Techniques for early diagnosis of these cancers are extremely limited and treatment fails in 95 percent of patients with advanced disease. Only greatly intensified research efforts across the disease continuum will change the currently bleak outlook for most individuals afflicted with these cancers.

The first known cause of human bladder cancer was occupational exposure to certain members of a class of chemical compounds known as the arylamines, which include 2-naphthylamine, 4-aminobiphenyl, and benzidine. Another well-established risk factor is cigarette smoking, which accounts for an estimated 50 percent of all bladder cancers diagnosed in the United States today. The length of time between carcinogen exposure and development of bladder cancer can be 20 years or more.

Experimental data also point to the involvement of the enzyme cyclooxygenase-2 in bladder cancer development. A recent U.S. study reports a statistically significant reduction in the risk of bladder cancer among regular, long-term users of nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit the expression of cyclooxygenase-2. Further research is needed to validate this finding and delineate its clinical significance.

Considerable experimental and epidemiologic data have established *Schistosoma haematobium* (schistosomiasis) as a causal agent of human bladder cancer, specifically squamous cell cancer. Schistosomiasis is hyperendemic in Egypt and parts of the Middle East, where bladder cancer is among the top three most frequently diagnosed cancers.

Finally, epidemiologic studies have suggested a 20 to 100 percent increase in bladder cancer risk among subjects in the highest category of long-term exposure to chlorinated surface water compared with those with no such exposure. Water consumption appears to exert a protective effect: a 1999 study found that men drinking six or more 8-oz cups of water per day halved their risk of bladder cancer compared with men who drank less than one cup of water per day.

For both renal cell carcinoma and cancer of the renal pelvis, cigarette smoking is a well-established risk factor. Phenacetin, a major ingredient of analgesics until about two decades ago when it was banned from all drugs manufactured in the United States, is a recognized causal factor for cancer of the renal pelvis. For renal cell carcinoma, several recent large-scale epidemiologic studies have confirmed obesity and hypertension as two independent, major risk factors. Some data suggest that trichloroethylene exposure is a risk factor for renal cell carcinoma. People with end-stage renal disease also are at increased risk for kidney cancer. In spite of significant numbers of studies, however, the etiology of most kidney cancer cases is unclear.

Overall, the etiological mechanisms of kidney and bladder cancers remain poorly understood. Better elucidation of these mechanisms may lead to much-needed new treatments, diagnostic methods, and prevention strategies for these diseases.

In the United States, bladder cancer mortality varies by region and is highest in the Northeast. Most bladder cancers in the United States are transitional cell carcinomas; this tumor type was the focus of the Progress Review Group's deliberations. Outside the United States, patterns of bladder cancer incidence, pathology, and mortality are different; squamous cell carcinoma is the prominent histological type. Although kidney cancer has a less geographically distinct fingerprint than bladder cancer, risk does seem to be associated with higher socioeconomic status and higher mortality rates are seen in many areas of the midwestern United States.

Renal cell carcinoma accounts for 80 to 85 percent of all kidney cancers in the United States. The remaining kidney cancers are mostly cancers of the renal pelvis (including the ureter). Kidney cancer is most commonly sporadic, but it can also be hereditary. Six clinically distinct types of inherited kidney cancer have been identified thus far, von Hippel-Lindau (VHL) syndrome being the best characterized. VHL—an autosomal dominant syndrome in which kidney cancer arises from multiple benign renal cysts— occurs in 1 of every 36,000 live births, and kidney cancer occurs in 28 to 45 percent of VHL-affected individuals. Benign cystic VHL-associated tumors can also develop in the spine, brain, eye, pancreas, inner ear, and adrenal gland. Certain VHL kindreds also develop pheochromocytomas.

Research on the pathobiology of *VHL* mutations is expanding our knowledge of kidney cancer, although much work remains to be done. It is known that clear-cell carcinoma has a high degree of vascularity and that *VHL* mutations occur in 70 percent of sporadic cases of kidney cancer. The wild-type VHL protein normally forms a complex that causes the degradation of hypoxia-inducible factor-alpha (HIFα), a transcription factor that regulates a number of genes involved in angiogenesis and cell growth. Mutations in the *VHL* gene variably affect the ability of the protein to form the repressive complex, resulting in an overproduction of vascular endothelial growth factor (VEGF), Glut-1, and platelet-derived growth factor. However, links have not been established between these various molecular changes and clinical behavior. This is one of many promising areas of discovery research in which additional efforts may lead to significant advances.

Approximately 30 percent of kidney cancers are incidentally detected because of widespread and increasing use of computed tomography (CT) for other medical indications. Advances in imaging—such as CT, magnetic resonance imaging, and positron-emission tomography—are allowing diagnosis of malignancy at earlier stages. However, no population-based kidney cancer screening studies using CT have been conducted, nor have correlations of imaging patterns with molecular and clinical behavior been performed.

Unlike kidney cancer, bladder cancer does not have a substantial number of hereditary forms. However, the ready accessibility of the bladder to repeated cystoscopic examinations and biopsies has improved our understanding of bladder cancer biology. Alterations in the genes coding for p53, p14, p16, Rb, and cyclin D—among others—have been noted, and many bladder cancers are missing arms of chromosomes 9 and 17. Overexpression of the epidermal growth factor family of receptors is common. The patterns of gene alterations in low-grade papillary tumors are markedly different from

those in more aggressive disease. Correlations between molecular and clinical phenotypes have been inconsistently and infrequently performed, suggesting that future research will bring major opportunities to improve the management of bladder cancer.

The primary treatment modalities for localized bladder cancer are transurethral resection and cystectomy; other options include intravesical chemotherapy and immunotherapy. Adjuvant chemotherapy for poor-risk localized disease has a controversial history but now appears to improve survival. In localized kidney cancer, radical nephrectomy remains the standard of care, but minimally invasive and nephron-sparing surgical techniques are becoming widely used. Early successes with radiofrequency and cryosurgical ablation of small kidney cancer are being reported.

Treatment options for metastatic bladder and kidney cancers are few and largely ineffective. Although newer compounds such as gemcitabine and the taxanes seem to lessen toxicity in the treatment of metastatic bladder cancer, they have not improved median survival. Highly toxic interleukin-2, the only approved treatment for metastatic kidney cancer, likewise has not improved median survival. Many other therapies are being studied, including anti-vascular endothelial growth factor, anti-endothelial growth factor receptor, vaccines, cytokines, and activated T cells, but none has yet had a major impact on the natural history of these diseases. New prognostic molecular markers are needed that may eventually allow individually targeted therapy.

The recurrence rate for bladder cancer is 80 percent; it is estimated that nearly 400,000 individuals in the United States are at risk for recurrence. Chemoprevention trials in this population are sorely needed; the recent data on a possible protective effect of NSAIDs on bladder cancer incidence should provide an impetus for additional research in this area. There is some evidence that earlier detection leads to better outcomes in kidney cancer, although few screening studies have been conducted. More research is needed to apply new knowledge about the molecular origins of kidney cancer to the identification of biomarkers for this disease.

Despite the severe limitations of existing therapies for kidney and bladder cancers, the number of survivors of these diseases is increasing. Factors influencing quality of life in these people are largely uninvestigated. Furthermore, disparities in incidence and mortality suggest that state-of-the-art care, with all its limitations, is out of reach for many individuals with kidney or bladder cancer. As we endeavor to develop new therapies that will extend patients' lives and lessen the burden of these diseases, it is equally important to conduct research aimed at strengthening health care delivery and improving quality of life.

Discovery

Discovery—the acquisition of new knowledge about the processes, mechanisms, and pathways of disease—drives the development of new approaches to detecting, diagnosing, treating, preventing, and controlling disease. In turn, insights gained in the clinical application of new knowledge often raise new questions that can only be answered through further laboratory investigation. The Discovery Group considered the challenges and knowledge gaps that exist in the biology, genetics, and epidemiology of kidney and bladder cancers.

Background—State of the Science

Bladder Cancer

The earliest cytogenetic studies in bladder cancer showed evidence of alterations in chromosome arms 9p, 9q, 11p, and 17p, the most common defects being allelic losses, loss of heterozygosity, and microsatellite alterations. Subsequent studies from a number of groups have led to the description of a detailed and sophisticated model of important molecular events in bladder cancer. These studies have demonstrated that lesions long recognized as morphologically and biologically distinct (e.g., papillary tumors versus flat and invasive tumors) are characterized by distinct molecular alterations.

It is also becoming increasingly clear that the important regulatory events in bladder cancer pathogenesis are linked through specific pathways. Attention has focused on tumor suppressor genes (in particular, *TP53* and *RB*) and their proteins, which play an important role in cell cycle regulation by inhibiting cellular proliferation at the G1/S transition. Several studies have now shown that *TP53* alteration is an important predictor of bladder cancer progression. This association was most pronounced in patients with organ-confined tumors.

Alteration in *RB* expression is a relatively frequent event in bladder cancer and has been shown to be a significant predictor of outcome. The evaluation of bladder tumors for both *TP53* and *RB* alterations may be useful, particularly for determining the risk of progression for patients with superficial papillary tumors. There is now evidence that the status of other cell cycle regulatory genes and proteins, such as p21 (*WAF1/CIP1*) and the INK_{4A} locus, may also be important predictors of bladder cancer progression.

Epigenetic and post-translational mechanisms are implicated in the functional inactivation of tumor suppressor genes. Promoter methylation appears to be a general mechanism for loss of gene expression and may play an important role in bladder cancer. It now also appears that the constitutive phosphorylation of pRb (which results from defects in the Rb pathway, including the loss of p16 expression, upregulation of cyclin D1, or both) may be an important mechanism of inactivation.

Several oncogenes have been identified in bladder cancer, including h-*ras*, c-*myc*, *FGFR3*, and *mdm2*. The epidermal growth factor-1 and its receptor (EGFR) are found in a substantial proportion of bladder cancers. The proto-oncogene *ERB-B2* (also known as *HER-2/NEU*, a member of the EGF family) has been shown to be important in several tumors and may be a prognostic factor in bladder cancer as well, although results to date have been mixed. Other molecular factors that may have relevance in the invasion, metastasis, and progression of bladder cancer include peptide growth factors and cellular adhesion molecules such as E-cadherin and integrins.

In normal tissues the ability to induce new blood vessel growth is a tightly regulated process. Dysregulation of this process is a key feature of tumors. The prognostic significance of tumor angiogenesis has been investigated in a variety of tumor systems, including bladder cancer. p53 has been shown to be an important regulator of angiogenesis in bladder cancer through its regulation of thrombospondin-1. The expression of factors that regulate

angiogenesis, including vascular endothelial growth factor (VEGF), may be important prognostically and therapeutically.

Other molecular features of bladder tumors may have important prognostic or therapeutic value. The examination of antigens associated with normal and malignant urothelium using mouse monoclonal antibody technology has led to the identification of a series of determinants that appears to be associated with urothelial transformation and progression. Microsatellite analysis has been used, with promising results, to detect tumors in urine and bladder wash specimens.

Increased understanding of molecular pathways is leading to the development of new therapeutic strategies. Attention has focused on a number of pathways, including angiogenesis, cell cycle regulation, oncogenes, and growth factor receptors. Important areas of study in bladder cancer include EGFR inhibitors and the role of *TP53* alterations in the development of resistance and response to standard chemotherapeutic agents.

Several studies have demonstrated the requirement for appropriate epithelial-mesenchymal interactions during bladder organogenesis. The role of tissue microenvironment (including extracellular matrix, angiogenic molecules, growth factors, and proteases) in tumor development is under explored. Host immune response, another component of tumor microenvironment, has a documented role in restricting the progression of superficial bladder tumors.

Kidney Cancer

Studies of families with inherited kidney cancer have provided new information about the genes that predispose to this disease. To date, six clinically distinct types of inherited kidney cancer have been identified: von Hippel-Lindau (VHL) disease, hereditary papillary renal carcinoma, familial renal oncocytoma/Birt-Hogg-Dube syndrome, hereditary leiomyomatosis renal cell carcinoma, familial renal carcinoma, and renal carcinoma associated with a constitutional chromosome 3 translocation. Major advances in our understanding of the biology of renal cell cancer during the past decade were made possible primarily by the identification and cloning of tumor suppressor genes and oncogenes responsible for familial renal carcinoma syndromes.

Germline mutations in the *VHL* gene predispose affected individuals to the development of clear-cell renal carcinoma. The *VHL* gene is inactivated (by mutation or hypermethylation) in up to 70 percent of sporadic clear-cell renal carcinomas. The VHL protein is an ubiquitin ligase receptor targeting specific substrates for ubiquitin-mediated degradation. Hypoxia-inducible factor 1-alpha (HIF-1α) and HIF-2α, the known substrates of VHL, are potent inducers of angiogenesis. Under conditions of normoxia, VHL binds directly to HIF-1α and HIF-2α and promotes its degradation. Up-regulation of HIFα activity in $VHL^{-/-}$ renal carcinoma cells may explain the angiogenic nature of renal cell neoplasms and may significantly contribute to renal epithelial tumorigenesis. Other upstream regulatory elements of the hypoxia-HIF-VHL pathway, as well as critical downstream targets, are unknown.

Besides the *VHL* gene, germline mutations of the c-*met* proto-oncogene also are responsible for a genetic predisposition to certain papillary renal tumors. Although some information is known about the c-met signaling pathway, the critical elements leading to tissue-specific tumorigenesis (such as in the case of renal carcinoma) are not known. The germline mutations responsible for other familial renal carcinoma syndromes also are unknown.

There is scant information regarding the status of the pathways that regulate cell cycle progression, DNA damage response, and telomere shortening. Although these pathways have been extensively investigated in other solid tumors, there are few references to mutational analysis of these pathways in renal carcinoma cell lines or renal tumor samples. We also have no stepwise progression model of kidney cancer as we do for colon and bladder cancers. This may be due in part to tumor detection at a late stage and to the inaccessibility of the kidney to screening instrumentation.

Immune response has a documented role in eliminating a small but finite subset of kidney tumors, but the antigens eliciting such a response are unknown. Also, immunologic abnormalities are frequently detected in patients with kidney cancer. Reliable markers of a patient's immune status—predicting tumor response to immunologic manipulations—and strategies to overcome tumor-associated immunologic deregulation are currently unavailable. As in bladder cancer, the role of tissue microenvironment in kidney cancer is under explored.

In contrast to breast, ovarian, lung, and colon cancers, no single chemotherapeutic agent or combination of agents produces a significant clinical response in kidney cancer. The molecular nature of this chemoresistance remains elusive.

Clinical advances in both bladder and kidney cancers will be facilitated by novel animal models that parallel the human disease. The location of bladder tumors makes bladder cancer a particularly attractive model for testing new-targeted interventions that can be delivered intravesicularly. In this regard, there is a particular need to develop appropriate orthotopic animal models for kidney and bladder cancers. The use of high-throughput genomic and proteomic assays linked to comprehensive tissue banks and databases and coupled with robust bioinformatics will be a key element in elucidating the components of regulatory and signaling pathways involved in kidney and bladder tumorigenesis and progression.

Priority 1: *Understand the biological mechanisms underlying the risk factors for kidney and bladder cancer phenotypes.*

- Elucidate the biological mechanisms underlying the following long-established risk factors for kidney and bladder cancers:
  - Obesity and hypertension, which increase risk for kidney cancer,
  - Cigarette smoking, which increases risk for both bladder and kidney cancers, and
  - Gender-specific differences in overall risk for kidney and bladder cancers and among individuals with comparable risk-factor profiles.

- Elucidate the etiologic profiles responsible for specific histologically or molecularly defined phenotypes of kidney and bladder cancers. Well-designed molecular epidemiological studies should include molecular markers of exposures, genetic susceptibility, and effect (including tumor markers).

Rationale

The etiologic mechanisms of distinct phenotypes of kidney and bladder cancers are poorly understood. Novel prevention and treatment strategies may result from improved understanding of such mechanisms.

Barriers to Progress

- Lack of communication and collaboration among epidemiologists, molecular biologists, endocrinologists, nutritionists, toxicologists, and members of other disciplines.
- Recent federal legislation and interpretation of that legislation, which is hindering the procurement of clinical data and specimens.
- High cost of genetic and pathologic analysis in large studies.

Resources for Priority 1

- Development of appropriate animal and cell-based models.
- Large, multifaceted epidemiologic studies.
- A nationally standardized human consent form.

Priority 2: *Identify global genetic, epigenetic, RNA expression, and proteomic alterations in tumors, to detect such alterations in the urine and blood and to place them in specific biological pathways that are essential to the development, progression, response to therapy, and maintenance of subtypes of bladder and renal cancers.*

Rationale

Individual bladder and kidney tumors show alterations in specific molecular pathways, potentially allowing customized clinical management for the individual patient. High-throughput technologies allow global characterization of the tumor genome (DNA copy number, methylation status, etc.), transcriptome, and proteome. Applications of these profiles include:

- Classifying tumors on a molecular basis,
- Identifying and validating targets for therapy, and
- Defining the molecular signatures of response to therapy according to therapeutic target, tumor type, and subtype.

In bladder tumors, profiles can be used to define alterations associated with recurrence of pTa tumors, progression of pTa and pTis tumors, and metastasis of invasive cancer. Profiles of kidney cancer cases can be used to better define differences among different histologic subtypes. In VHL-associated tumors, profiles may enable the identification of events during transformation, from early neoplastic growths to acquisition of the tumor phenotype.

Understanding the relevant growth and signaling pathways will enable the development of targeted therapies, including the use of small molecules produced through combinatorial chemistry. This will require close cooperation between academia and industry.

Priority 3: *Understand the role of stroma and intercellular signaling in organogenesis, tumor development, and maintenance of malignant phenotypes in bladder and kidney cancers.*

Rationale

Stromal elements are known to influence epithelial differentiation in the bladder and kidney. For example, in 1936 Charles Huggins showed that bladder epithelium developed into bone when transplanted to muscle. Most studies to date have examined only the characteristics of tumor epithelial cells and not the extracellular matrix, stromal cell complement, inflammatory cells, or local immune response.

Specific research goals include:

- Examining the cell types in the tumor microenvironment and their activation status,
- Defining interactions between tumor cells and the extracellular matrix,
- Identifying factors regulating angiogenesis in the tumor microenvironment,
- Defining the role of inflammation during tumorigenesis, and
- Understanding the role of the host immune response during tumorigenesis and therapy.

Resources for Priorities 2 and 3

- Comprehensive tissue collections with associated clinicopathologic information.
- Longitudinal series of tumor samples, including samples from each presentation of tumor in a patient over time.
- Samples from clinical trials, both fresh frozen and archival.
- Larger numbers of samples from international collaborations.
- Blood and urine banks for validation of candidate markers.
- Data dictionaries for common data elements.
- Resolution of patient consent issues for prospective and retrospective studies to facilitate the efficient use of clinical material.
- High-throughput technologies for the analysis of DNA, RNA, and especially protein in tumors, as well as for access to, validation of, and quality control of high-throughput assays.
- Bioinformatics and biostatistical approaches for the analysis of data from high-throughput assays.
- Resources, primarily through industry, to produce and screen small molecules to target tissue-specific growth and signaling pathways. (This effort will require close cooperation between academia and industry.)

- A patient advocacy group in bladder cancer, modeled after the kidney cancer advocacy group, which will help to establish research priorities at the national level and can advocate for scientific studies and clinical trials.

Priority 4: *Generate and characterize transgenic models, including conditional knockout and knockin strategies and orthotopic models, of bladder and kidney cancer, focusing on the use of tissue-specific promoters and targeting human disease–related genetic events. These models will allow identification and validation of prognostic, preventive, and therapeutic targets and their inhibiting agents.*

Rationale

The advent of transgenic technologies has enabled the specific targeting of well-defined genetic alterations in the tissue of interest. Such systems will enable understanding of gene function, dissecting of molecular pathways, and generation of faithful models of human cancer. This knowledge will also provide targets for drug discovery and chemoprevention. However, kidney and bladder cancers lag behind other organ systems in the development and use of these models. Kidney tubular cells are among the most difficult epithelial cell types to cultivate *in vitro*. Access to these normal cells will enable understanding of the mechanisms of malignant transformation.

Similarly, the further development of early- and late-stage bladder and kidney cancer cell lines will have a major impact on elucidating multistep tumor progression. High-throughput cell-based and *in vivo* assays are needed to validate novel targets of potential clinical relevance in human kidney and bladder cancers. These efforts should be paralleled by the development of surrogate biological markers to correlate with *in vivo* tumor response.

Resources for Priority 4

- Low-throughput technologies (e.g., histopathology, immunohistochemistry).
- High-throughput technologies.
- Noninvasive imaging to evaluate therapeutic efficacy *in vivo*.
- Biostatistics, bioinformatics, and computational genomics.

Conclusion

Enormous potential opportunities exist for new research in kidney and bladder cancers at the discovery level and for the application to patient management of new knowledge about basic molecular defects. By further defining the biology of bladder and kidney cancer progression, we can better understand risk based on specific molecular criteria. This will enable development of management strategies such as molecular and pathologic staging schemes that are based on patient-specific risk assessment, treatment response, and the presence of therapeutic targets.

Translational Research

Advances in discovery—defining the mechanisms and pathways involved in the pathogenesis of kidney and bladder cancers—will provide a wealth of new information. Through translational research, new information can lead to the development of:

- Molecular markers for diagnosis, prognosis, and treatment,

- New agents for treatment and chemoprevention,
- Valid preclinical experimental models, and
- Multidisciplinary clinical trials that integrate molecular markers, imaging, tailored therapy, and quality-of-life endpoints.

The Translational Research Group considered strategies to facilitate the translation of new discoveries about kidney and bladder cancers for the optimal benefit of patients with these diseases.

Background—State of the Science

Effective therapies for patients with bladder or kidney cancer—especially for those with advanced disease—are currently limited. High-dose interleukin-2 (IL-2) therapy can produce high-quality durable responses in a subset of patients with previously untreated kidney cancer. Nonmyeloablative allogeneic transplantation also appears promising, producing responses in up to 50 percent of patients with refractory disease. However, these treatments are highly toxic, costly, and available only to a small proportion of Stage IV patients. New immunotherapeutic agents have been tested either alone or in combination with IL-2, but none has been shown to be superior to high-dose IL-2 alone. Novel approaches—including dendritic cell vaccines and antiangiogenic and adjuvant therapies—have intriguing rationales and some glimmers of efficacy in kidney cancer but have yet to establish a therapeutic foothold.

Although cytotoxic chemotherapy can produce responses in a substantial percentage of patients with Stage IV transitional cell cancer of the urothelium, toxicity can be quite extensive and few patients achieve durable benefit. Neoadjuvant and adjuvant chemotherapy may improve survival in some patients, but the fraction of patients benefiting is small. In addition, intravesical therapy with cytotoxic and immune agents has shown promise in superficial bladder cancer, but these observations must be further developed, refined, and optimized.

Clearly, advances are needed in the treatment of both kidney and bladder cancers. As with any cancer, translational research studies will be required to rationally develop future treatment strategies and to tailor those therapies to the patients most likely to benefit.

Until recently, the most significant difficulty in developing new therapies for these diseases was the lack of potential targets and agents. However, many of the molecular pathways in bladder and kidney cancer pathogenesis have recently been elucidated. Maturation of high-throughput genetic and epigenetic analyses will likely further refine this knowledge.

Two likely consequences of these efforts will be the definition of multiple molecular subtypes of each cancer and multiple putative therapeutic targets. Continued improvements in the sophistication of chemical and biochemical assay systems will likely provide agents that specifically inhibit these identified targets, which will pave the way for clinical investigations.

In addition, increasing knowledge about the mechanisms underlying tumor angiogenesis and tumor resistance to immunotherapy is also likely to suggest novel immuno-therapeutic and antiangiogenic approaches

for these diseases. The potential for combining agents directed against unique targets with each other or with novel immunotherapeutic or antiangiogenic approaches is both exciting and daunting. We need informed and reasoned methods for identifying, selecting, and prioritizing the chemical and biological agents (alone and in combination) that should be clinically investigated and the patient populations and tumor subtypes in which they should be tested.

Kidney and bladder cancers provide unique opportunities for conducting translational studies. For example, in superficial bladder cancer, tumor and normal tissue can be studied and sampled before, during, and after therapy. The growing acceptance of the clinical utility of debulking nephrectomy in patients with metastatic kidney cancer also provides a rationale for obtaining neoplastic and perhaps normal renal tissue during the peritherapy time period. In addition, the development of less-morbid surgical techniques, such as laparoscopic nephrectomy and partial nephrectomy, facilitates the tissue acquisition process and potentially reduces delays in the initiation of therapy.

The application of sophisticated molecular techniques to urine analysis provides an opportunity to study cells and macromolecules from the bladder and kidney that may reflect the status of alterations in certain cancer-specific pathways as well as the biological effects of therapy. Finally, recent advances in imaging techniques have great potential for facilitating clinical investigation by providing a method for targeting biopsies to areas of specific interest, monitoring the specific effects of therapy, and identifying noninvasive markers of treatment effects.

Opportunities for targeted intervention are also available, including VHL, HIF-1, VEGF, and C-MET in kidney cancer and p53, Rb, HER-2/NEU, H-RAS, C-MYC, and MDM2 in bladder cancer. These targets are discussed in detail in the Discovery report.

Although opportunities for translational research in kidney and bladder cancers are abundant, a number of logistical obstacles exist. These include the lack of:

- Centralized tissue and specimen banks,
- Access to promising agents, either alone or in combination,
- Standardized and validated assays and imaging techniques,
- Centers and networks capable of performing these complex investigations,
- A sufficient number of adequately trained investigators interested in these diseases, and
- Patient and physician willingness to participate in translational research efforts.

To take advantage of these opportunities and improve the care of patients with bladder and kidney cancer, three research priorities and six necessary resources for supporting these efforts are recommended.

Priority 5: *Examine blood, urine, premalignant tissue, and tumor tissue before prevention and therapy trials to identify and quantify disease and identify targets for therapy and predictors and mechanisms of response, resistance, progression, and relapse.*

Such targets and mechanisms might include:

- Markers of occult disease and disease behavior,
- Assays of immunologic competence (T cells and dendritic cells),
- Tumor-based mechanisms of resistance, such as lack of susceptibility to apoptosis or altered signaling pathways,
- Histopathologic features,
- Angiogenesis markers, and
- Molecular profiles (gene mutation analysis, gene expression studies, and proteomics).

Rationale

Because available therapies benefit only a small proportion of patients, it is critical to identify the patient populations most likely to benefit. Additionally, mechanisms of resistance must be identified to facilitate the development of alternative approaches for patients who are unlikely to respond. Because many of these resistance mechanisms may be directly related to tumor burden, the ability to identify patients with radiologically occult or biologically aggressive disease for therapeutic and prevention strategies will also be extremely important.

Defects in immune function have been found in patients with advanced kidney cancer and have been tentatively linked to disease progression. Some patients with advanced kidney cancer exhibit elevated serum vascular endothelial growth factor (VEGF) levels; in other cancers, such as head and neck cancer, elevated VEGF levels have been associated with defects in dendritic cell maturation. Assessing the prevalence and functional significance of these defects may enable the prescribing of these often-toxic therapies only for those patients most likely to respond. Such an approach may also highlight obstacles to be overcome in the development of new immunologic strategies.

Because many but not all cases of superficial bladder cancer respond to intravesical immunotherapy, investigation of immune competence in urine and blood may also enable the identification of predictors of response in this patient population.

Angiogenesis appears to be critical to the initiation and progression of clear-cell (von Hippel-Lindau–related) renal carcinoma and anti-angiogenic strategies, such as anti-VEGF antibody and thalidomide, have shown modest benefit. Although the role of angiogenesis in bladder cancer has been less well characterized, this process may be critical to metastasis development. However, there are no pre-therapy markers capable of predicting response to antiangiogenic approaches. Although bladder cancer is sensitive to a variety of cytotoxic chemotherapies, a significant proportion of patients do not respond or respond only transiently. Only rarely does a patient with kidney cancer benefit from such treatment. The identification of tissue-based (tumor and stromal) correlates of response will enable antiangiogenic and cytotoxic chemotherapy approaches to be focused on the patients most likely to benefit.

New techniques, such as tissue microarrays and gene and protein expression analyses, can be powerful tools for identifying novel tumor factors associated with resistance. Only limited investigations have been

performed to determine the presence and relevance of these factors to treatment resistance in bladder and kidney cancers. Fortunately, pretreatment bladder and renal tissue is often accessible via cystoscopy or cystectomy in patients with invasive or superficial bladder cancer or via debulking nephrectomy in patients with Stage IV kidney cancer. Identification of molecular- and protein-based mechanisms of resistance will help tailor therapies to appropriate patients as well as aid in the development of new therapies to overcome these mechanisms.

Currently, no markers identify occult bladder or kidney cancer. The discovery of alterations in specific molecular pathways in these diseases should facilitate the identification of molecular markers of occult disease and, conceivably, aggressive behavior. Identification of such markers would greatly facilitate the development of adjuvant therapeutic strategies for these diseases by allowing selection of appropriate patients for therapy and enabling monitoring of the effectiveness of therapy in an individual patient. Consequently, smaller, more targeted studies could be performed.

Identification of molecular markers will enable testing of therapies in a patient population with a lower tumor burden and, thus, lessen the likelihood of tumor-related immune dysfunction or nascent resistance. Finally, it is likely that the identification of markers of minimal residual disease and disease behavior as well as tumor-related resistance factors may enable the identification of patients with precursor lesions who might benefit from prevention strategies.

Priority 6: *Facilitate the development and utilization of noninvasive or minimally invasive techniques to image and assess the biological and clinical effects of targeted therapeutics.*

Examples of techniques to be investigated include:

- Functional imaging of the tumor and tumor-host vasculature,
- Minimally invasive biopsies,
- Better use of biopsy material,
- Neoadjuvant systemic therapy, coordinated with subsequent surgical treatment strategies,
- Urine and serum markers for tumor burden and assessment of tumor behavior, and
- Surrogate markers of clinical effects (i.e., target inhibition in blood, urine, tumor, skin, or other tissue that can be easily and repetitively sampled).

Rationale

The ability to serially sample patients during therapy will allow us to:

- Determine the optimal biological dose of a particular therapy,
- Demonstrate biological efficacy before formal assessments of clinical efficacy,
- Identify biological and imaging correlates of clinical efficacy, and
- Discriminate between failure to inhibit the putative target and clinical failure that occurs because the inhibited pathway is not biologically critical.

Because kidney and metastatic bladder tumors cannot easily be sampled during therapy, noninvasive and minimally invasive methods are needed to assess therapeutic effectiveness.

To expand our knowledge of current therapies and to develop new ones, we will need to obtain and analyze tissues to determine whether the putative therapeutic targets have been affected. This will require:

- Minimally invasive surgical and nonsurgical techniques for obtaining tumor tissue serially,
- Methods for the optimal use and evaluation of small amounts of fresh, frozen, and paraffin-fixed tissues samples (e.g., RNA- and DNA-based assays) obtained in the course of therapy, and
- Improved imaging techniques (positron-emission tomography and magnetic resonance imaging techniques augmented with labeled specific probes) that will provide functional (antiangiogenesis, immune-mediated mechanisms) and molecular (apoptosis, inhibition of specific signaling pathways) data sufficient to determine the effect of the particular therapy on its putative target (tumor, vasculature, or other) and guide minimally invasive biopsies to the regions of maximal interest.

New trial designs, such as neoadjuvant therapy followed by cystectomy, cystoscopic biopsy, or nephrectomy, may be necessary to provide sufficient tumor and adjacent normal tissue for more complex assays. Such approaches can likely be justified on clinical grounds but still require the cooperation of multidisciplinary teams, coordination with laboratory investigators, and patient acceptance.

It will be critically important to validate these imaging procedures and surrogate marker assays in animal models and against specific tissue-based assays. The development of standards for these tests and the identification of appropriate situations for their application will also facilitate the translation of this work from the laboratory to clinical trials and, ultimately, to the clinic.

Priority 7: *Identify and prioritize agents—alone or in combination—that target known cancer growth and progression pathways.*

- Develop and evaluate therapies in physiologically relevant models broad enough to accommodate new therapeutic modalities for early and advanced cancers.
- Identify markers of disease progression and response to therapy in these models.
- Develop appropriate models for evaluation of novel delivery strategies.

Rationale

High-throughput genomic and proteomic technologies have allowed the identification of a large number of new cancer genes as well as other potential biomolecular targets. These cancer genes provide targets that form the components of tumor growth and progression pathways for these cancers.

Recent studies in chronic myelogenous leukemia and gastrointestinal stromal tumors have provided proof of the principle that strategies developed to target cancer gene pathways can have an effect in human tumors. Several targets are available from known cancer genes involved in the early

development of several types of genitourinary cancer. These targets provide an unusual opportunity for molecular therapeutics based on rational rather than empiric approaches. Validation of the roles and therapeutic potential of agents that block these cancer gene pathways is urgently needed.

To capitalize on current and future opportunities to investigate targeting strategies in bladder and kidney cancers, appropriate *in vivo* and *in vitro* models must be developed to screen and validate relevant pathways and monitor the effects of purported small-molecule inhibitory compounds. A series of tissue banks—including tumor, urine, and serum banks linked to complete clinical data—is a vital tool for identifying new therapeutic options. Such tissue banks will also require bioinformatics products to analyze a wealth of data. A system to facilitate communication and information sharing among scientists with expertise in various fields will also need to be developed.

Resources for Priorities 5, 6, and 7

Translational research is difficult to perform. It requires the coincident availability of a variety of resources, including:

- Suitable targets for testing in humans,
- Agents capable of affecting those targets,
- A trial design that is acceptable to patients and suitable for testing the proposed strategy,
- A group of investigators with the capability and funding to perform the study and take optimal advantage of the limited material available for correlative studies, and
- A patient population willing to participate in the research study.

To accomplish the priorities described above, a variety of resources must be created or enhanced and made more accessible to the bladder and kidney cancer research community. These resources include:

- A specimen bank: The bank must include tumor tissue, blood, urine, and normal tissue from patients with bladder or kidney cancer. Both pretreatment and posttreatment samples are needed to achieve many of the objectives mentioned above. For example, there is a critical need to create tumor tissue arrays to screen new therapeutic agents. It would be best if this material was centralized and made widely available to researchers. This would require the determination of optimal methods of procurement, preservation, and analysis; the development of a prioritized distribution process; and the design of flexible consent forms that maximize tissue availability and assure an ethically sound link to a clinical database.
- A drug bank: Obtaining access to new agents with specific mechanisms of action to conduct clinical trials is often extremely time consuming for patients and physicians. Although agents may exist, the kidney or bladder cancer populations might not be seen as sufficiently attractive study targets. In addition, commercial property, patent, and competition issues may inhibit the Phase I and II disease-specific study of promising combinations of agents (e.g., combinations of anti-VEGF and anti-epidermal growth factor receptor

agents). To overcome these obstacles, it may be necessary to establish a drug bank of new agents emerging from academic and industrial laboratories. Basic and clinical researchers would have access to the bank for proof-of-principle studies.

- Assay standardization and clinical validation: The effective application of new noninvasive or minimally invasive methods for monitoring therapy will require extensive efforts to standardize and validate these approaches. These efforts should include:
  - Workshops to discuss the relative merits of particular assays and develop guidelines for appropriate assay use,
  - Central laboratories for standardization of current and new monitoring approaches,
  - Quality-control mechanisms to assess assay sensitivity, specificity, precision, reliability, and other characteristics,
  - Publication requirements for the inclusion of assay methods and specifications, and
  - Animal and tissue studies to validate assay techniques.
- Training of young investigators focused on kidney and bladder cancers: There is a unique need in the fields of kidney cancer and bladder cancer to develop trained physician-scientists to collaborate with basic and other scientists in studying patients and transferring promising strategies, such as image-based therapies and molecular therapeutics to clinical use. In addition, physician-scientists must be prepared to help patients understand the clinical trial process. This critical deficit needs to be supported at the level of residency training or a generation of opportunities will be lost. This issue is particularly acute in training programs for urologic surgeons; recent budgetary constraints have forced most programs to abandon the sixth optional research year in favor of a 5-year clinical residency. A National Cancer Institute funding mechanism (potentially in partnership with the National Institutes of Health) could help certain departments to support a year of basic or clinical research training as a critical adjunct to residency review committee–approved residency programs. In addition, career development awards and training grants specific to kidney and bladder cancers at the young investigator level will encourage talented individuals to focus on these diseases.
- Centers and networks of disease-specific clinical research: Accomplishing the translational objectives described above will require the establishment of multidisciplinary teams that include urologists, medical oncologists, pathologists, radiologists, and scientists.
- Specialized Programs of Research Excellence grants would be particularly useful in this regard. However, as the population of patients with kidney or bladder cancer is less abundant than is the case in some other cancers, multi-institutional involvement in translational research studies—via the formation or expansion of cooperative group networks focused on these diseases—will facilitate rapid completion of Phase

II and III trials. Such networks or centers should be geographically dispersed to optimize patient access to novel therapies and translational research.

- Overcoming barriers to patient participation in translational research: Barriers to patient participation in translational research are substantial. These studies often involve unproven agents with the potential for severe toxicity. This research also will likely require frequent study visits, phlebotomy, imaging, and potentially more invasive procedures. Extensive travel to and from treatment facilities may be necessary. These obstacles often make such studies less attractive to patients than standard therapies, even standard therapies that have been proven ineffective.

Overcoming these barriers will require a concerted effort to educate primary care physicians and oncologists about the merits of translational research. The provision of incentives to doctors for referring patients to translational studies should be considered. It will also be important to educate patients about the value of translational research in developing the treatments of the future. The latter effort can be greatly facilitated by establishing and maintaining open communication between researchers and patient advocacy groups.

Conclusion

Successful translational research in kidney and bladder cancers will lead to improved treatments for these diseases in the future. Ideally, patients will be diagnosed earlier through the use of molecular markers and imaging techniques and each patient's therapy will be tailored according to the genetic characteristics of that individual's cancer.

Treatment

Successes in discovery and translational research will lead to advances in treatment. Advances in treatment can also direct studies in discovery, translational research, and cancer control. The Treatment Group considered strategies for enhancing therapies for kidney and bladder cancers, thereby reducing morbidity and mortality from these diseases.

Background—State of the Science

Experience indicates that either local or distant disease will recur in 30 to 70 percent of patients who present with localized kidney or bladder cancer. A variety of treatment approaches are used, ranging from organ-sparing to extirpative therapy. Limited information is available to determine which therapy is most appropriate for a given patient. Unfortunately, few clinical trials are addressing this very important issue, reflecting the relatively limited number of patients with these cancers.

For kidney cancer, the standard of care over the last 50 years has been the radical nephrectomy. Since the 1980s, however, nephron-sparing techniques have been developed. Though these techniques were originally intended for patients with one kidney, chronic renal disease, or bilateral tumors, their use has been extended to patients with a normal contralateral kidney. This trend has been encouraged by the refinement of appropriate surgical techniques and by an increase in the number of patients with small tumors identified through modern imaging techniques. Most recently, minimally invasive ablative

techniques have shown promise. Cryosurgery and radiofrequency ablation have been used either laparoscopically or percutaneously under radiographic imaging guidance. However, the exact role of each of these techniques remains undefined.

At the other end of the spectrum, there exists a group of patients with kidney cancer who are at high risk for recurrence after local therapy. Conventional surgical pathological criteria are able to identify only some of these individuals. There is a clear need not only to identify all those at risk for recurrence but also to develop more effective adjuvant therapies.

Bladder cancer encompasses a very broad spectrum, from early superficial tumors to metastatic disease. Patterns of relapse after treatment of superficial disease are characterized by local recurrence and phenotypic progression. Randomized trials of local immunotherapy and topical chemotherapy have shown that though recurrence may be delayed, invasion is not necessarily reduced. Once patients have progressed to muscle-invasive disease, the standard therapy is radical cystectomy, with its many quality-of-life implications. Though there have been attempts at organ conservation using limited surgical techniques, either alone or in combination with chemotherapy or radiation, the role of organ-conserving approaches in the management of patients with bladder cancer has not been established. Better markers are required to define those subpopulations that will do well with more limited therapy.

In many patients with advanced bladder cancer, failure occurs distantly rather than locally. Metastases ultimately develop in as many as 50 percent of patients with muscle-invading tumors. As with kidney cancer, adjuvant trials involving these patients are necessary but have been difficult to perform because of limited patient numbers and physician bias.

Currently, immunotherapy is used for metastatic kidney cancer and chemotherapy and radiation therapy are used for metastatic bladder cancer. Nevertheless, less than 10 percent of treated patients with advanced disease survive long term (more than 5 years).

However, subsets of patients with advanced kidney or bladder cancer have complete responses and long-term disease-free survival. At present, clinical criteria are the only way to prospectively identify patients with the potential for long-term survival. The current staging systems and prognostic factors have recently been combined, which enables improved prediction of disease recurrence and outcomes for individual patients.

Recently, awareness has developed that each of these diseases is heterogeneous in its pathology and molecular characteristics. These new insights may lead to individualized therapeutic approaches. For example, in clear-cell renal cancer, 70 percent of sporadic tumors contain alterations of the von Hippel-Lindau gene (*VHL*) or deletions of chromosome arm 3p, indicating loss of tumor-suppressor function and activation of growth-stimulating pathways. In some cases, there is evidence for silencing of the *VHL* gene by promoter hypermethylation, which is potentially reversible with appropriate drug treatment. These findings suggest that specific defects cause clear-cell renal cancer and may lead to the identification of specific targets for new therapeutic approaches. In bladder malignancies, although no such specific early molecular target has been identified to date, *TP53* mutations can occur in early

dysplastic lesions; *TP53* status is currently being tested as a means to direct treatment and predict prognosis.

Ninety-five percent of patients with advanced kidney or bladder cancer develop progressive disease despite initial therapy. Up to 30 percent of patients with metastatic kidney cancer develop symptomatic bone metastases that require specific therapies. Evidence-based approaches to and guidelines for the management of symptom clusters of advanced disease (e.g., anemia, anorexia, fatigue) are lacking.

Barriers to progress in curing these two diseases include:

- Underfunding of laboratory and clinical research in kidney and bladder cancers,
- Insufficient training and educational opportunities in these diseases,
- Limited access to novel agents for these diseases,
- Limited systematic collection of tumor tissue and other specimens associated with appropriate clinical information, and
- Lack of adequate populations in which to study novel agents.

Priority 8: *Develop innovative therapeutic strategies that will eradicate disease, preserve organ function, and maintain quality of life, using mechanism-based agents that take into account known prognostic variables, molecular characteristics of tumors, assays of targeted effects, surrogate markers of efficacy, and novel delivery strategies.*

- Investigate the role of *VHL* mutations and their associated pathways that may identify molecular proximal targets for novel therapeutic interventions. This is an extraordinary opportunity to develop molecular targeted therapy.
- Identify and validate innovative therapies and targets for treatment in bladder and kidney cancers and, where appropriate, integrate these agents into existing therapy.
- Support innovative trial design such as window of opportunity trials for rapid evaluation of new treatment options using surrogate markers.
- Identify and target mediators of paraneoplastic syndromes.

Rationale

- Few patients can be cured by existing therapies. New agents targeting specific disease mechanisms are being identified in preclinical and correlative studies. Future clinical trials need to optimally investigate both the clinical and biologic effects of these agents in clearly defined and selected patient populations.
- *VHL* mutations are associated with 70 percent of clear-cell renal cancer cases, which represent 60 percent of all kidney cancer. Targeting this pathway represents a unique opportunity to develop specific therapy for a causative mutation.
- Current systemic therapy is inadequate. Identification of molecular targets may lead to improved therapy. Such targets (e.g., epidermal growth factor receptor, vascular endothelial growth factor, and

m-Tor) have not been well explored in kidney and bladder cancers.

- The current system of clinical studies is inadequate to assess the large numbers of novel therapies currently being developed. Many organ-conserving strategies currently exist and are used empirically, and many new technologies are in development. Support must be provided for rapid assessment of the efficacy, safety, cost, and impact on quality of life of these approaches to localized and advanced disease. One suggested approach for localized disease is neoadjuvant treatment with surgical, radiographic, and biologic monitoring of response. The response would determine whether organ preservation is feasible. A second suggested approach is earlier use of novel agents in untreated patients with advanced disease (window of opportunity therapy).

- Mediators of paraneoplastic events may influence disease outcome and management. Examples include anemia, fever, hypercalcemia, and anorexia/cachexia, all of which are mediated by endogenous factors. These may be appropriate targets to direct therapy that could improve patient well-being.

Priority 9: *Develop and improve approaches to risk assessment of localized and advanced disease—which take into account known prognostic variables, including stage, histology, and novel molecular factors—to direct therapy.*

- Develop molecular biomarkers and functional imaging techniques to improve our ability to select patients for appropriate therapy. These tools may be used to increase the accuracy of staging, predict tumor behavior, and predict an individual's response to therapy.

- Develop methodologies to refine existing and new prognostic classifications, to enable better evaluation of therapeutic outcomes and for use in clinical trials.

Rationale

Kidney and bladder cancers are biologically heterogeneous diseases. It is clear that many patients with localized disease can be managed with less invasive therapy whereas others need more aggressive therapy. Similarly, patients with advanced disease have disparate characteristics that affect therapeutic outcomes. Better predictors of behavior and response are needed to more appropriately guide treatment of the individual patient and predict prognosis.

Priority 10: *Develop evidence-based, hypothesis-driven research efforts in palliative care for patients with advanced kidney or bladder cancer.*

- Identify, characterize, and evaluate symptom clusters for both diseases and their impact on disease outcome and quality of life.

- Develop pharmacological, non-pharmacological, and complementary/ alternative strategies for targeted palliation through evidence-based approaches.

Rationale

Therapy fails in 95 percent of patients with advanced kidney or bladder cancer. In both of these tumor types, the distribution of symptom clusters in advanced disease is relatively unknown and the prognostic

significance and impact on quality of life of these clusters are not well studied. For example, it would be useful to evaluate different strategies for managing bone metastases and the effects of these different strategies on mobility, function, and pain.

Resources for Priorities 8, 9, and 10

- Expand the definition of the Specialized Programs of Research Excellence (SPOREs) to encourage multi-institutional consortia of centers of excellence in clinical research. We recommend a goal of three to five SPOREs in kidney and bladder cancers. This mechanism would enhance the performance of high-priority translational projects and facilitate investigations of targeted palliative-care approaches. It would also encourage the recruitment of scientists into kidney and bladder cancer research.

- Increase public awareness and education about kidney and bladder cancers to encourage patient and physician participation in clinical trials.

- Develop the K08 mechanism to support physician-scientist career development in kidney and bladder cancer research.

- Develop specimen repositories (including tumor and normal tissue, serum, and urine) to allow future correlations with clinical trial outcomes.

- Develop a centralized database management system for patients participating in clinical trials sponsored by the National Cancer Institute, cooperative groups, and the pharmaceutical industry, as well as in investigator- or institution-initiated pilot trials.

Conclusion

Advances in the treatment of kidney and bladder cancers will lead to improved outcomes and provide data on outcomes and risk that can inform cancer control research, as well as help direct and focus discovery and translational research.

Cancer Control

Cancer control encompasses many issues: screening, risk assessment, quality of life, and health care delivery and communication. Research in this area can have a dramatic impact on diagnosis and treatment and can also inform basic science. The Cancer Control Group considered strategies for improving screening for and prevention of kidney and bladder cancers as well as for enhancing patient quality of life, health care delivery, and health care communication.

Background—State of the Science

Bladder cancer—the fourth most common cancer in men and the eighth most common cancer in women in the United States—is uniquely suitable for screening because of its easy accessibility by means of cystoscopy and urinary markers. Metastases are almost invariably associated with concomitant or previous muscle-invading cancers. The vast majority of patients with muscle invasion have it at initial presentation; few have evidence of previous superficial tumors. Moreover, because autopsy series show no incidentally found bladder cancer, it is very likely that even early bladder cancer will cause symptoms to appear rapidly, leading to diagnosis and treatment. Because all tumors arise on the urothelial surface, there is a window of time (before muscle invasion occurs) during which they can be detected and treated with strategies that are highly

successful and relatively nonmorbid. Because bladder cancers grow quite rapidly (otherwise, many more would be detected incidentally at autopsy), studies to enhance early detection are imperative to improve outcomes. Screening aimed at early detection in people without a history of prior bladder tumors holds great promise for reducing mortality from bladder cancer.

Although few screening studies have been conducted in kidney cancer, evidence suggests that earlier detection and treatment will result in improved outcomes. The evolution of less-invasive treatment modalities for small tumors makes this an especially opportune time to pursue screening studies. Recent advances in understanding the molecular bases of kidney cancers provide exciting potential new biomarkers for early detection and prognosis.

Preclinical and limited clinical data demonstrate that bladder cancer is responsive to primary and secondary preventive efforts; few similar data exist for kidney cancer. Although improved understanding of the pathways of both bladder and kidney carcinogenesis presents new targets for prevention, the lack of identifiable high-risk populations (particularly for sporadic kidney cancer) and surrogate endpoint biomarkers (for both malignancies) limits our ability to implement prevention studies.

Barriers to patient enrollment in clinical trials and specimen acquisition are significant impediments to progress. To move prevention of both these diseases forward, sample sizes that allow for sufficient statistical power and access to specimens with appropriate clinical follow-up are essential.

The United States now has half a million survivors of kidney and bladder cancers. The National Cancer Institute's scientific portfolio supports few, if any, projects that address the quality of life of these survivors. Numerous gaps exist in the science of quality of life in kidney and bladder cancers. Available quality-of-life instruments do not include measures specific to either early- or later-stage bladder or kidney cancer.

Because of the chronic nature of both diseases, it is essential to assess quality of life prospectively over the survival continuum and to address variables that may be related to quality of life (e.g., treatment decision-making and roles of caregivers and family). Improving quality-of-life outcomes for patients with kidney or bladder cancer must also include careful assessment of treatment side effects and distress associated with invasive surveillance procedures.

There is a dearth of studies on the relationship between quality of life and adherence to treatment. Anecdotal information suggests that a number of patients withdraw from potentially curative treatments because of unacceptable side effects. There is also a shortage of randomized, controlled trials or long-term cohort studies that test the effectiveness of interventions to improve quality of life and ameliorate symptoms. All kidney and bladder cancer studies should assess the effects of socioeconomic status, ethnicity, language, age, gender, and culture on quality of life.

Health care delivery and communication are important yet often neglected issues in the study of bladder and kidney cancers. Lack of communication with and suboptimal quality of care delivered to specific populations appear to result in disparate outcomes.

Examples of such disparities include differences in the incidence of kidney and bladder cancers in different geographic locations and differences in mortality rates by gender and race. Mortality from both bladder and kidney cancer is higher in black men than in white men. Although overall death rates for bladder cancer are declining, mortality among white women has not declined. Coincidentally, smoking is increasing only in this population subgroup. Research that addresses these disparities in terms of health care delivery and communication ultimately is likely to improve quality of life and patient-oriented outcomes.

Public understanding of the risk factors for kidney and bladder cancers is low. Few patients recognize that bladder and kidney cancers are linked to smoking and that kidney cancer is linked to obesity. Patients often do not know that blood in the urine is a sign of bladder cancer.

Particularly in women, hematuria is often attributed to benign conditions, leading to clinically important delays in diagnosis of an underlying malignancy. Earlier evaluation of hematuria in all populations may lead to earlier diagnosis of bladder and kidney cancers at a stage when they are easily treated and have a low probability of being lethal. Variable access to specialty care is a barrier to appropriate care because of lack of information and knowledge deficits among non-cancer specialists, care providers, and patients.

In other diseases, the activities of advocacy groups have helped reduce gaps and barriers between standards of practice and care received. However, a strong patient advocacy group for bladder cancer does not exist. Support services within the kidney advocacy community need to be enhanced. Advocates should be involved as decision-making participants in advisory groups, councils, and research teams.

Although the three priorities below are numbered for reader convenience, the numbers do not reflect rank or importance. The Cancer Control Group considered all three priorities to be of equal weight.

Priority 11: *Describe the impact of kidney and bladder cancers and their treatment on the quality of life of individuals and their families throughout the cancer continuum, and develop and assess interventions that will reduce morbidity and improve health-related quality of life outcomes.*

Research would include:

- Descriptive studies to characterize the symptoms and side effects particular to kidney and bladder cancers, identifying relationships between symptom clusters and other relevant factors,

- Evidence-based interventions to address disease- or treatment-related side effects, notably fatigue, sexual dysfunction, urinary dysfunction, pain, depression, fear, and anxiety,

- Studies of smoking cessation and relapse prevention in patients who continue to smoke or have recently quit after diagnosis,

- Development of criteria for clinically significant change in quality-of-life measures, and

- Assessment of patient satisfaction with treatment outcomes.

Predictor and Outcome Variables

- Symptoms, symptom management, morbidity, and mortality.
- Treatment, surveillance, and adherence.
- Socioeconomic status, ethnicity, age, and gender.
- Co-morbidities.
- Stage of disease.
- Access to care and patterns of care.
- Patient and provider attitudes to care decisions.
- Health behaviors (e.g., smoking).
- Neuroendocrine and immune function.
- Adherence to treatment and surveillance procedures.
- Patient satisfaction with care.

Types of Studies

- Prospective, longitudinal trials.
- Cross-sectional studies.

Rationale

Quality of life is a highly valued component of care for persons with kidney or bladder cancer. Although cure or increased life expectancy is a goal of medical treatment, patients and those who care for them agree that improving the quality of that life is also a high priority. Although early diagnosis can increase life expectancy, it may also be associated with long-term treatment-related side effects or continued surveillance, which can negatively affect quality of life. Common distressing problems include sexual and urinary dysfunction and invasive follow-up procedures. Adjuvant therapies can create serious side effects that often limit many aspects of functioning and well-being.

Because current treatment options in advanced kidney and bladder cancers do little to prolong life, maintaining or improving quality of life becomes a primary goal of treatment and care. Patients increasingly expect that their quality of life will be considered in their plan of care, and this expectation affects their satisfaction with care. Understanding the factors that affect quality of life is a prerequisite for patient-oriented treatment decision-making.

Initial quality of life is a predictor of later quality of life and survival, making it critical to continuously monitor quality of life. Compromised quality of life—mediated by such variables as adherence to treatment, surveillance, immune function, and smoking—may have an impact on treatment and disease outcomes. Pilot data suggest that quality-of-life interventions can lengthen survival.

Resources for Priority 11

- Develop new instruments or refine existing instruments to include kidney and bladder disease- and treatment-specific measures of health-related quality of life for use in the collection of prospective data across the continuum of care.
- Develop gender-specific questions concerning urinary and sexual function.

- Encourage the use of common, standardized instruments across studies, testing validity and reliability in the populations of interest.

- Include quality of life as a primary endpoint in clinical trials.

- Establish or enhance multi-institutional, interdisciplinary collaborations.

- Develop and incorporate new technologies to facilitate data collection.

- Enhance the support offered by kidney cancer advocacy groups and provide infrastructure for the development of bladder cancer advocacy groups; these groups could encourage participation in cancer clinical trials.

- Train physicians, nurses, and other providers in quality-of-life assessment and data utilization.

- Establish and support multi-institutional, inter-disciplinary collaborations.

Priority 12: *Identify, characterize, and validate molecular markers to determine the risk of disease, enhance early detection, and predict response to chemoprevention with new chemopreventive agents and strategies, employing new models as appropriate.*

Rationale

Molecular markers can be used to select high-risk subjects for screening, resulting in more statistically powerful screening studies with smaller numbers of subjects than could be obtained by general population screening. Unique populations have contributed dramatically to our understanding of the genetic and molecular bases of kidney cancers (von Hippel-Lindau syndrome, hereditary papillary renal cancer, Wilms tumor, etc.). This knowledge has also revolutionized our understanding of the far more common sporadic forms of the disease. Other unique populations—such as young adults with bladder cancer, patients with end-stage renal disease, and post-treatment cancer patients who continue to smoke—offer the potential to provide new models that may generate similarly valuable knowledge with broad applicability. Studies of such populations are likely to yield insights into risk factors for kidney and bladder cancers. Additionally, preclinical, mathematical, and other models are essential to the development and testing of successful and cost-effective screening and prevention strategies.

New markers are available and others are being developed that have high sensitivity and specificity. Bladder cancer is ideally suited to secondary prevention. Validated surrogate endpoints will facilitate the evaluation of novel chemopreventive agents and strategies.

Bladder cancer is an attractive target for prevention efforts because renal excretion of oral agents enables prolonged exposure to high concentrations of drugs. Additionally, the urothelium is easily evaluated and monitored with strategies that are highly successful and relatively noninvasive. The frequent recurrence of superficial bladder cancer with low occurrence of muscle-invasive disease permits the safe and efficient assessment of strategies to prevent secondary bladder cancers with a modest number of patients and short follow-up. New and more effective preventive agents, combinations, and strategies are urgently needed because even the most effective intravesical agent (bacillus

Calmette-Guerin) has local toxicity and a high rate of long-term failure.

Early excision of small renal cell carcinomas cures almost all patients. Identification of novel markers could enhance the detection of small tumors (less than 2 cm) and enable ablation of these lesions, with relatively low morbidity, with newly developed, minimally invasive treatments. Molecular markers can also be used to identify patient subgroups according to their risk of progression and determine targets for emerging therapies.

With improved understanding of molecular oncology, patients with hereditary kidney cancer syndromes and lesions provide excellent opportunities for chemoprevention strategies. Advances in this arena will translate immediately, improving clinical outcomes and quality of life in patients with the more common sporadic renal cancer.

Resources for Priority 12

Previously identified molecular markers lack the sensitivity and specificity to be useful as tools for early detection and screening. Promising new markers are now available and in development, and their clinical utility for screening needs to be validated.

Because screening trials require large populations followed over long periods, adequate infrastructure is required to facilitate recruitment and retention of participants; design of this infrastructure can profit from input from patient advocates. The increasing availability of multiple markers requires rigorous and innovative statistical analysis. Novel, economical trials will require statistical tools capable of analyzing multiple variables assessed in a small data set.

Few resources are being directed toward new agents for prevention of kidney and bladder cancers, reflecting the relatively small numbers of patients at risk and the likelihood of poor economic returns on such investments. Chemopreventive agents are often tested as single agents; however, data suggest that such drugs exert greater impact when directed in combination to target different pathways. Furthermore, novel intervention strategies directed at blocking the proximate carcinogen may prevent the disease. Epidemiologic studies imply that natural products, such as vitamins and herbal compounds, may provide preventive benefit in both diseases, but these agents are not being studied because they cannot easily be patented and are available over the counter in unregulated formulations. These natural products can have unknown interactions that confound clinical trial data.

The National Cancer Institute and the Food and Drug Administration must jointly develop mechanisms to encourage research in the above areas. In addition, mechanisms must be developed to encourage studies of combination drug strategies. This may require increased collaboration between governmental agencies and industry. Finally, it should be brought to the attention of industry that bladder cancer, in particular, is a highly prevalent disease that should be economically attractive as a subject of study.

In both kidney and bladder cancers, the relative rarity of many unique subgroups limits the capacity of a single institution to conduct studies with meaningful statistical power. Multi-institutional collaboration and specimen banks with associated clinical longitudinal data focused on these unique populations would address this barrier.

Priority 13: *Identify and explore the gaps between and barriers to standards of practice and care that currently result in disparate outcomes for patients with kidney or bladder cancer.*

Rationale

Bladder and kidney cancers are chronic diseases in an aging healthy population. Delay in treatment appears to be correlated with a disproportionately higher death rate among women with bladder cancer, who are diagnosed 6 to 9 months later than men. Black men have a higher mortality rate for both bladder and kidney cancers than white men, despite lower incidence of both diseases. These apparent disparities in health care delivery can be addressed by evaluating:

- Hematuria screening practices,
- Time from symptom onset to diagnosis and therapy,
- Access to and enrollment in clinical trials,
- Age-related treatment bias,
- The relationship between smoking and bladder and kidney cancers, especially among women, and
- Differences in mortality by gender, race, ethnicity, and geographic location.

Once the causes of these disparities are understood, strategies can be devised to remedy them.

Resources for Priority 13

When large databases such as SEER (Surveillance, Epidemiology, and End Results) and Medicare are linked, data can be assessed to improve understanding of practice patterns that may create gaps in and barriers to the care of patients with kidney and bladder cancer. A provider-patient partnership can be enhanced through the use of multimedia modalities and collaborative community outreach activities, especially using centers of clinical research that specialize in kidney and bladder cancers. Regulatory barriers that impede the identification of patients at risk and their health conditions, including those related to the protection of human subjects, should be reduced. Studies of populations with disparate outcomes should be targeted to determine why barriers to appropriate care exist and to develop strategies to eliminate them.

Conclusion

Cancer control research has enormous potential to decrease morbidity and mortality from kidney and bladder cancers by enhancing strategies for screening and prevention and identifying approaches that can maximize patient quality of life and overcome barriers to health care delivery.

Kidney/Bladder Cancers PRG Conclusion

These four overarching areas—discovery, translational research, treatment, and cancer control—combine to produce a continuum of cancer research and care. All four areas must be addressed if research on kidney and bladder cancers is to be fruitful. Cancer research is its own ecosystem, with each "species" of research dependent on all the others. If one aspect is ignored, others will suffer. By contrast, if one aspect is strengthened, the effect will spread.

The Kidney/Bladder Cancers Progress Review Group (PRG) considers implementation of the 13 priorities presented in this report to be essential if significant progress is to be achieved in reducing morbidity and mortality from kidney and bladder cancers. Each year there are approximately 24,200 deaths (70 per day) from these two diseases in the United States. This should compel scientists, physicians, and public health advocates to take action. We encourage readers to peruse the 11 subgroup reports in Appendix B, which expand further on the priorities ultimately chosen for this report and offer additional direction for the research community. The material in these reports represents the careful consideration of all participants in the Kidney/Bladder Cancers PRG Roundtable Meeting.

Appendix A

About the National Cancer Institute's
Progress Review Groups

About the National Cancer Institute's Progress Review Groups

The National Cancer Institute (NCI) supports basic, clinical, and population-based research to elucidate the biology, etiology, early detection, prevention, and treatment of cancers of various organ sites. These research efforts have produced a substantial base of knowledge that, while providing a wealth of new scientific opportunities that can further advance our knowledge and progress against these diseases, also requires that the Institute determine the best uses for its resources.

To help ensure the wise use of resources, NCI has established Progress Review Groups (PRGs) to assist in assessing the state of knowledge, reviewing the Institute's research portfolio, and identifying scientific priorities and needs for its large, site-specific research programs.

CHARGE TO THE PRGS

Each PRG is charged to:

- Identify and prioritize scientific research opportunities and needs to advance medical progress against the cancer(s) under review.
- Define the scientific resources needed to address these opportunities and needs.
- Compare and contrast these priorities with the current NCI research portfolio.
- Prepare a written report that describes findings and recommendations.
- Discuss a plan of action with NCI leaders to ensure that the priority areas are addressed.

The following section details the process used to execute these charges.

THE PRG PROCESS

PRG members are selected from among prominent members of the scientific, medical, and advocacy communities and from industry to represent the full spectrum of scientific expertise required to make comprehensive recommendations for the NCI's cancer research agenda. The membership is also selected for its ability to take a broad view in identifying and prioritizing scientific needs and opportunities that are critical to advancing the field of cancer research.

The leadership of each PRG finalizes an agenda and process for a PRG Planning Meeting. At the Planning Meeting, participants are identified to take part in a subsequent Roundtable meeting. Topics are identified for Roundtable breakout sessions to which participants will be assigned and for which the PRG members will serve as co-chairs.

A PRG Roundtable brings together in an open forum approximately 100–180 leading members of the relevant cancer research, medical, industry, and advocacy communities to formulate key scientific questions and priorities for the next 5–10 years of research on specific cancers. As part of the process, the NCI provides the PRG Roundtable with an analysis of its portfolio of cancer research in the relevant organ site. This analysis is intended to enable the Roundtable to compare and contrast identified scientific priorities with the research currently being done under the Institute's auspices. Input from the Roundtable is used by the PRG in

delineating and prioritizing recommendations for research, related scientific questions, and resource and infrastructure needs. At its discretion, the PRG may solicit additional input from the research and advocacy communities through workshops, ad hoc groups, or by other means. The PRG also may consider the deliberations of previously convened expert groups that have provided relevant cancer research information.

THE PRG REPORT

After the Roundtable, the PRG's recommendations are documented in a draft report, multiple iterations of which are reviewed by the PRG leadership and PRG members. The final draft report is then submitted for deliberation and acceptance by the NCI Advisory Committee to the Director. After the report is accepted, the PRG meets with the NCI Director to discuss the Institute's response to the report, which is widely disseminated and integrated into the Institute's planning activities. At this meeting, the PRG and the NCI identify the research priorities that ongoing NCI initiatives and projects do not address. Then the PRG and NCI discuss a plan for implementing the highest research priorities of the PRG. This plan becomes a blueprint for tracking and hastening progress against the relevant cancer.

PRG reports on breast cancer; prostate cancer; colorectal cancer; pancreatic cancer; lung cancer; brain tumors; leukemia, lymphoma, and myeloma; and gynecologic cancers, in addition to this PRG report on kidney/bladder cancers, are available online at http://planning.cancer.gov. Currently, a report on stomach and esophageal cancers is planned.

Appendix B

Kidney/Bladder Cancers PRG
Roundtable Breakout Groups

Discovery Subgroup 1A—Etiology and Pathogenesis

Co-Chairs: *Mimi Yu, Ph.D., Wong-Ho Chow, Ph.D., David Hein, Ph.D., Carl Dixon, J.D.*

Participants:

Paul Cairns	Ronald Ross
Andrew Freedman	Debra Silverman
Karl Kelsey	Paul Skipper
Jonathan Li	Berton Zbar

BACKGROUND—STATE OF THE SCIENCE

Although there are common etiologic factors in kidney and bladder cancers (such as cigarette smoking), the working models of etiology and pathogenesis for these two urinary tract cancers are sufficiently diverse to warrant separate discussion of their current research status.

Current Status of Etiologic Research in Kidney Cancer

Renal cell carcinoma accounts for 80 to 85 percent of all cases of kidney cancer that occur in the United States. The remaining 15 to 20 percent consists mostly of cancer of the renal pelvis, which is anatomically and histologically distinct from renal cell carcinoma and generally demonstrate different risk factor patterns. Even for shared risk factors, dose-risk relationships can differ between renal cell carcinoma and cancer of the renal pelvis. Thus disease associations for renal cell carcinoma and renal pelvis cancer are discussed separately below.

Cigarette smoking is an established cause of both renal cell carcinoma and renal pelvis cancer. Cigarette smoke contains volatile nitrosamines, which are renal carcinogens in animals. The increased risk for renal cell carcinoma associated with a given level of cigarette smoking, however, is less than for renal pelvis cancer. The transitional cell urothelium of the renal pelvis is exposed to the same potential carcinogens in urine as are the renal tubular cells that give rise to renal cell carcinoma. Thus either the tubular cells are less sensitive to tobacco carcinogens or the exposure level of the target cells to these compounds is higher for the renal pelvis. There is little evidence that use of other tobacco products increases kidney cancer risk.

Phenacetin, a major ingredient of analgesics until about two decades ago, is a recognized causal factor for renal pelvis cancer. Fewer data are available on the phenacetin-renal cell carcinoma link, and human results have been inconsistent.

Other common analgesics include acetaminophen (a major metabolite of phenacetin in humans) and non-steroidal anti-inflammatory agents (NSAIDs), including aspirin. Although some experimental evidence supports a link between both acetaminophen and NSAIDs and kidney cancer, human data have been less than conclusive.

Recent large-scale epidemiologic studies have confirmed obesity and hypertension as independent risk factors for renal cell carcinoma, but the mechanisms by which obesity and hypertension lead to the development of cancer are unclear. Not surprisingly, the use of diuretics and other antihypertensives shows a consistent, positive association with renal cell carcinoma risk. Data are inconclusive with respect to the drugs' direct role in the development of renal cell carcinoma, independent of the hypertension for which the drugs are prescribed. Limited evidence suggests the use of amphetamines (a common ingredient in diet pills) as a direct risk factor for renal cell carcinoma. There is no evidence that obesity or hypertension is related to renal pelvis cancer.

Few epidemiologic studies have examined the role of diet in kidney cancer development. Although nitrosamines are renal carcinogens in animals, there is little evidence that cured meat consumption (a major source of nitrosamine/precursor exposure in humans) relates to kidney cancer risk. Limited data link increased intake of green or cruciferous vegetables and carotenoids to a reduced risk of renal cell carcinoma. Limited data also associate high intake of meat, protein, and fats with increased risk of renal cell cancer, but information is scarce on dietary factors and renal pelvis cancer risk.

A history of hysterectomy is a consistent risk factor for renal cell carcinoma, but data are sparse on whether oophorectomy in conjunction with hysterectomy affects subsequent risk for renal cell carcinoma. Animal experiments suggesting that estrogen may protect against kidney cancer provide a plausible biological explanation for the increase in risk of renal cell carcinoma following hysterectomy, which is typically accompanied by bilateral oophorectomy. However, limited epidemiologic data on use of oral contraceptives, use of replacement estrogens, and parity fail to support estrogen as a chemopreventive agent of renal cell carcinoma.

Renal cell cancer is generally not considered an occupation-related cancer, but reports have related increased risk to several occupational exposures, including petroleum, asbestos, lead, and cadmium. A specific mutational hot spot in the von Hippel-Lindau (*VHL*) gene in renal cell cancer was reported among patients with high cumulative exposure to trichloroethylene but not among unexposed patients. Information linking occupational exposures with renal pelvis cancer is sparse.

Studies of families with inherited kidney cancer have provided new information on the genes that predispose to kidney cancer. Several clinically distinct types of inherited kidney cancer have been identified: VHL syndrome, hereditary papillary renal carcinoma, familial renal oncocytoma/ Birt-Hogg-Dube syndrome, hereditary leiomyomatosis renal cell carcinoma, familial renal carcinoma, and renal carcinoma associated with a constitutional chromosome 3 translocation. The *VHL* gene is known to be inactivated by mutation or hypermethylation in 60 to 70 percent of sporadic clear-cell renal carcinomas.

Current Status of Etiologic Research in Bladder Cancer

The first known cause of human bladder cancer was occupational exposure to certain chemical compounds known as the arylamines, which include 2-naphthylamine,

4-aminobiphenyl, and benzidine. These industrial dyes have been under strict federal regulation for more than 40 years; thus it is believed that occupational exposure to these compounds contributes minimally to the present burden of bladder cancer in the United States.

Another well-established risk factor for bladder cancer is cigarette smoking, which is estimated to account for 50 percent of all cases diagnosed in the United States today. Arylamines are present in cigarette smoke and are leading candidates as the etiologic agents for smoking-related bladder cancer. Pipe smoking is associated with a modest increase in bladder cancer risk, but there is little evidence that the use of other tobacco products is related to the risk of bladder cancer.

Arylamines require metabolic activation to become fully carcinogenic agents. Research during the past decade implicates arylamine-metabolizing genes in bladder cancer risk. The evidence is strongest for two polymorphic detoxification genes, N-acetyltransferase 2 (*nat2*) and glutathione S-transferase M1 (*gstm1*). Bladder cancer risk is increased in slow versus rapid *nat2* acetylators and *gstm1*-null individuals (those lacking both copies of the gene) show an increased risk of bladder cancer relative to those with at least one copy of the gene.

A recent U.S. study reported that female smokers incurred a higher risk of bladder cancer than male smokers of comparable intensity and duration of use. Consistent with this gender differential, female smokers exhibited higher levels of arylamine-hemoglobin adducts compared with male smokers of similar intensity. However, this gender effect was absent from many earlier studies, including the large-scale National Bladder Cancer Study. Several recent studies of lung cancer provide limited evidence that, when smoking habits are comparable, women experience a higher risk for lung cancer than men do.

Hair dyes represent another potentially substantial source of arylamine exposure in humans. Many oxidative-type (or permanent) hair dyes are mutagenic in the Ames assay, but no current ingredients of commercial hair dyes are known animal carcinogens. Individuals with occupational exposure to hair dyes experience an increased risk of bladder cancer, although other lifestyle aspects of this population may be responsible for their elevated risk. Results of several epidemiologic studies examining personal use of hair dyes show no material increase in bladder cancer risk among users. Most of these earlier studies did not differentiate between the three major types of dyes—permanent, semi-permanent, or temporary rinse. A recent U.S. study that examined personal hair dye use according to type of dye shows a statistically significant, frequency- and duration-dependent increase in bladder cancer risk with use of permanent dyes. Consistent with our biochemical understanding of arylamine metabolism, risk was principally confined to individuals possessing the NAT2 slow acetylation phenotype.

N-Nitrosamines are bladder carcinogens in rodents. Human exposure to nitrosamines or their precursors occurs via tobacco smoke or ingestion of cured meats. Nitrosamines can be formed from ingested nitrates and secondary amines by nitrate-reducing bacteria in the human bladder; vitamin C can block this nitrosamine formation. Epidemiologic studies of dietary nitrosamines and vitamin C have been inconclusive.

In rodents, vitamin A analogues can prevent the induction of bladder cancer by chemical carcinogens, including *N*-nitrosamines, leading to the hypothesis that vitamin A or its precursors (beta-carotene and other carotenoids) protect against human bladder cancer. Epidemiologic studies to date have been inconclusive.

Arsenic is a naturally occurring element; inorganic arsenic compounds have been shown to cause lung and skin cancers in humans. Much of the epidemiologic evidence linking arsenic exposure to bladder cancer development was derived from studies conducted in an area of Taiwan in which residents are exposed to high levels of inorganic arsenic via well water. These findings have been confirmed in other high-arsenic areas such as Chile and Argentina. The effect of low-level arsenic exposure from drinking water in the United States has not been carefully investigated.

Chlorine is currently added to roughly 75 percent of the drinking water in the United States as a means of water purification. The presence of chlorine and organic contaminants in water can lead to the formation of halogenated organic compounds that are rodent carcinogens. The concentration of these chlorination byproducts is one to two orders of magnitude higher in treated surface water than in treated groundwater. Epidemiologic studies have suggested a 20 to 100 percent increase in bladder cancer risk among subjects in the highest category of long-term exposure to chlorinated surface water compared with those with no such exposure. Water consumption appears to exert a protective effect: a 1999 study found that men drinking six or more 8-oz cups of water per day halved their risk of bladder cancer compared with men who drank less than one cup of water per day.

Total fluid consumption in relation to bladder cancer risk has been examined in several studies. The hypothesis is that increased fluid intake leads to increased frequency of urination, thereby reducing contact time between carcinogens and the urothelium and thus leading to reduced risk of bladder cancer. Results have been inconclusive; the observed intake-disease associations range from negative to null to positive.

Phenacetin-based analgesics are known to cause cancer of the renal pelvis (transitional cell carcinomas) in humans and to be carcinogenic to the bladder as well. Acetaminophen has served as a substitute since the ban of phenacetin, but acetaminophen is a major metabolite of phenacetin in humans. There is no evidence that acetaminophen use is associated with bladder cancer.

NSAIDs, including aspirin, are recognized chemopreventive agents for colon cancer, presumably via their inhibition of the expression of cyclooxygenase-2, an inducible enzyme linked to many aspects of colon carcinogenesis. Experimental data also point to the involvement of cyclooxygenase-2 in bladder cancer development. A recent U.S. study reports a significantly reduced risk of bladder cancer among regular, long-term users of NSAIDs.

Individuals who have first-degree relatives with bladder cancer are twice as likely to develop the disease as those without such a family history, suggesting involvement of hereditary factors in bladder cancer development.

Priority 1: *Elucidate the biological mechanisms underlying the following long-established risk factors for kidney and bladder cancers.*

- Obesity or hypertension, which increase kidney cancer risk,
- Cigarette smoking, which increases both bladder and kidney cancer risk, and
- Gender-specific differences in risk of kidney and bladder cancers overall and among those with comparable risk-factor profiles.

Rationale

The etiologic mechanisms of kidney and bladder cancer development are still poorly understood despite more than a decade of consistent epidemiologic evidence for these risk factors. An understanding of the biological mechanisms underlying these frequent risk factors may suggest novel prevention and treatment strategies. For example, cancer risk factors may be linked to up-regulation or down-regulation of genes that control key junctions in carcinogenesis pathways. Identification of these links between risk factors and pathways can lead to molecularly targeted therapies designed to restore the normal functions of these genes.

Barriers to Progress

- Lack of communication between epidemiologists and laboratory-based scientists.
- Recent federal legislation and interpretation of that legislation hindering the procurement of clinical data and specimens.

Resources

- Appropriate animal and cell-based models.
- A nationally standardized human consent form.

Priority 2: *Elucidate the etiologic profiles responsible for specific histologically or molecularly defined phenotypes of kidney and bladder cancers. Well-designed molecular epidemiologic studies should include molecular markers of exposures, genetic susceptibility, and effect (including tumor markers).*

Rationale

Kidney and bladder cancers are heterogeneous. This heterogeneity, manifested pathologically, genetically, and clinically, implies that both kidney and bladder cancers are multiple diseases. Only a few epidemiologic risk factors responsible for each distinct form of kidney and bladder cancers are known—for example, schistosomiasis for squamous cell cancer and chronic renal failure for papillary renal cell cancer.

Barriers to Progress

- Lack of communication and collaboration among epidemiologists, molecular biologists, endocrinologists, nutritionists, toxicologists, etc.
- Recent federal legislation and interpretation of that legislation hindering the procurement of clinical data and specimens.

- High cost of genetic and pathologic analysis in large studies.

Resources

- Large, multifaceted epidemiologic studies.

- A nationally standardized human consent form.

Discovery Subgroup 1B—Molecular Profiling and Pathways

Co-Chairs: *Margaret Knowles, Ph.D., Othon Iliopoulos, M.D., Frederic Waldman, M.D., Ph.D.*

Participants:

Bernard Bochner
Richard Cote
Joyce Graff
Mary Ellen Haisfield-Wolfe
Adrian Harris
James Herman
Perry Nisen
Mark Schoenberg

BACKGROUND—STATE OF THE SCIENCE

Major advances in our understanding of renal and bladder cancer biology have occurred during the past decade. These include the identification and cloning of tumor suppressor genes and oncogenes responsible for familial renal carcinoma syndromes and sporadic bladder cancer. Germline mutations in the von Hippel-Lindau (*VHL*) gene predispose affected individuals to development of clear-cell renal carcinoma. In addition to familial tumors, biallelic inactivation of this gene is an early event in the development of the majority of clear-cell sporadic renal cancers. Similarly, activating germ line mutations of the c-*met* proto-oncogene lead to certain papillary renal tumors.

The VHL protein is a ubiquitin ligase receptor that targets specific substrates for ubiquitin-mediated degradation. Hypoxia-inducible factors HIF-1α and HIF-2α are substrates of the VHL protein and potent inducers of angiogenic and growth factor peptides. At normal oxygen levels, the protein binds directly to HIF-1α and HIF-2α and promotes their degradation. Constitutive up-regulation of HIFα activity in $VHL^{-/-}$ renal carcinoma cells may explain the hypervascular nature of renal cell neoplasms and it may significantly contribute to renal epithelial tumorigenesis. Other upstream regulatory elements of the hypoxia-HIF-VHL pathway as well as critical downstream targets are currently not known.

Although a fair amount is known about the c-met signaling pathway, the critical elements that lead to tissue-specific tumorigenesis, such as in renal carcinoma, are not known.

No familial bladder cancer syndromes exist, but many genetic alterations have been identified in sporadic bladder tumors, including mutations of *TP53*, *RB*, *CDKN2A/ARF*, *FGFR3*, and H-*RAS* and non-random deletions and amplifications of several specific chromosomal regions, some of which show a clear association with a more aggressive tumor phenotype. In addition, genes relevant to both bladder and kidney cancer are frequently silenced by *de novo* promoter methylation.

Histologically distinct types of both kidney and bladder cancers exist. For kidney cancer these include clear-cell (conventional), papillary, chromophobe, and oncocytoma; for bladder cancer these include transitional cell, squamous cell, and adenocarcinoma. Specific kidney cancer cytogenetic abnormalities correlate with histologic

subtypes, indicating that specific signaling pathways are deregulated. The development of transitional cell carcinoma of the bladder, the most common form of the disease in Western countries, appears to occur via at least two pathways. This gives rise to two major groups of tumors, the more common superficial papillary tumors (about 80 percent) with good prognosis and the less common (about 20 percent) solid invasive tumors with poor prognosis. Many molecular alterations have been found in invasive tumors but few, apart from deletions of chromosome 9 and mutation of the FGF receptor 3, have been found in superficial tumors. Heterogeneity exists within these histologic groups such that tumors with similar morphology often show dramatically different clinical behavior.

Additional genes mutated in kidney and bladder cancers remain to be identified. For example, germline mutations responsible for familial renal carcinoma syndromes—other than *VHL*- and c-*met*–related tumors—are still unknown. The presence of modifier genes and gene polymorphisms responsible for disease severity and risk factor impact is clinically suspected but still unconfirmed. In both kidney and bladder cancers, a multitude of common deletions and amplifications have been catalogued but target genes are not yet identified.

Several studies have demonstrated the requirement for appropriate epithelial-mesenchymal interactions during kidney and bladder organogenesis. The role of tissue microenvironment (including extracellular matrix, angiogenic molecules, growth factors, and proteases) in tumor development is under explored. Squamous or adenomatous metaplasia of the bladder epithelium may represent examples of deregulated epithelial differentiation that are influenced by these factors. Host immune response, another component of the tumor microenvironment, has a documented role in eliminating a small but finite subset of renal tumors and restricting progression of superficial bladder tumors.

Kidney cancer remains one of the most chemoresistant human tumors; no single agent or combination of chemotherapeutic agents produces a significant clinical response in patients with kidney cancer. The molecular nature of this chemoresistance remains elusive, although over-expression of transporter proteins has been suggested.

The availability of the near-complete sequence of the human and murine genomes and the development of powerful technologies for tumor profiling at the genomic, RNA, and protein expression levels provide tools that will enable detailed dissection of complex biological processes and phenotypes. This approach has potential for defining mechanisms of normal tissue development, tissue remodeling, wound healing, and the development of diverse tumor types. Already, studies in other tumor types have demonstrated that molecular classification can provide additional diagnostic information; it is anticipated that prognostic information and the identification of novel therapeutic targets will follow. Clear possibilities exist for better molecular characterization of kidney and bladder tumors; however, to date, these approaches have not been extensively applied.

Priority 1: *Identify global genetic, epigenetic, RNA expression, and proteomic alterations in tumors, to detect such alterations in the urine and blood and to place them in specific biological pathways that are essential to the development, progression, and maintenance of subtypes of bladder and renal cancers.*

Rationale

Bladder and kidney tumors are heterogeneous in their histology and clinical behavior. Individual tumors show alterations in specific molecular pathways, potentially enabling customized clinical management for the individual patient. High-throughput technologies enable global characterization of the tumor genome (DNA copy number, methylation status, etc.), transcriptome, and proteome. Applications of these profiles include:

- Classifying tumors on a molecular basis, which will complement histopathology and other standard prognostic parameters,
- Identifying patterns of alterations representing preneoplasia,
- Identifying and validating targets for therapy, and
- Defining the molecular signatures of response to both standard and molecularly targeted therapies, according to therapeutic target, tumor type, and subtype.

Tissue selection for study will be different for bladder and kidney tumors, which usually present differently. For bladder tumors, profiles will be used to define alterations associated with recurrence of pTa tumors, progression of pTa, progression of pTis, and metastasis of invasive cancer. Profiles of kidney cancers will be used to better define differences among histologic subtypes and among metastatic and non-metastatic phenotypes. In VHL-associated tumors, profiles may enable identification of events during transformation from early neoplastic growths to acquisition of the tumor phenotype. In both bladder and kidney cancers, molecular profiling and its correlation with clinical data may facilitate identification of genes and pathways that modify disease severity.

Studies should emphasize careful choice of tissues for evaluation to maximize the potential for identifying key differences between subgroups. The availability of methods for tissue microdissection and for the amplification of small quantities of DNA and RNA will enable analysis of small populations of epithelial cells that are potential precursors of cancer.

Tumor profiling data could be informative for and complementary to the dissection of pathways already known to be deregulated in kidney and bladder cancers. To this end, the identification and cloning of genes responsible for familial renal carcinoma syndromes will provide additional insights into pathways deregulated in this disease.

Priority 2: *Understand the role of stroma and intercellular signaling in organogenesis and tumor development in the kidney and bladder.*

Rationale

Stromal elements are known to influence epithelial differentiation in the bladder and kidney. The tissue microenvironment—including the extracellular matrix, stromal cell complement, inflammatory cells, angiogenic response, and the local immune response—may play a role in tumor development, growth, and progression. Most studies to date have examined only the characteristics of tumor epithelial cells. In addition to direct analyses of human tissues, these studies will involve tissue culture models and animal models. Studies at the

single-cell level will be facilitated by the recent development of robust methods for microdissection, amplification, and quantitation of DNA and RNA targets from single cells and by methods of cell tagging for experiments with live cells.

Specific goals include:

- Examining the tumor microenvironment in terms of cell types and their activation status,
- Defining interactions between tumor cells and the extracellular matrix,
- Identifying factors regulating angiogenesis in the tumor microenvironment,
- Defining the role of inflammation during tumorigenesis, and
- Understanding the role of the host local immune response during tumorigenesis and therapy.

Priority 3: *Identify and validate candidate tumor markers for early detection, diagnosis, prognosis, imaging, and disease monitoring and as surrogate endpoints for therapeutic response.*

Rationale

New technologies enable sensitive analysis of clinically relevant molecular markers in circulating and secretory compartments. Tumor molecular profiles will identify tumor-specific and biologically relevant markers. Markers must be validated by using large collections of clinical samples and associated clinicopathologic information.

Resources

- Comprehensive tissue collections with associated clinicopathologic information.
  - Longitudinal collections of tumor samples, including samples from each presentation of tumor in an individual patient over time.
  - Samples (both fresh-frozen and archival) from clinical trials.
  - Large numbers of samples from international collaborations.
  - Blood and urine banks for validation of candidate markers.
  - Data dictionaries for common data elements.
  - Resolution of patient consent issues to ensure no barriers to the efficient use of clinical material for prospective and retrospective studies.
  - Especially in bladder cancer, patient advocate groups to facilitate the design of and entry into clinical trials.
- High-throughput technologies.
  - Continued development of technologies for analysis of small amounts of DNA, RNA, and especially protein from tissue samples.
  - Continued support for access, validation, and quality control of high-throughput assays (e.g., tissue microarrays).

- Continued development of bioinformatics and biostatistical approaches for analyzing data from high-throughput assays.

- Cell-line and animal models for testing hypotheses.

- Molecularly targeted therapeutics.

Discovery Subgroup 1C—Experimental Model Systems

***Co-Chairs**: Carlos Cordon-Cardo, M.D., Ph.D., Raymond Ruddon, M.D, Ph.D., Xue-Ru Wu, M.D., Ph.D.*

Participants:

Natasha Aziz
Susan Borghoff
Barry Gold
John Lazo
Judith Mietz
Frank Solano
Zhong Zhong

BACKGROUND—STATE OF THE SCIENCE

Cancer results from the perturbation or aberrant function of molecular pathways that control fundamental biological processes such as cell proliferation, survival, differentiation, and genomic integrity. Thus the analysis of these molecular processes in cell-based and animal models—mainly those aimed at recapitulating alterations found in human primary bladder and renal tumors—is expected to facilitate our understanding of cancer etiopathogenesis and tumor progression.

Few cell lines are available for *in vitro* model systems, and those that exist are mainly for the study of bladder cancer. It is important to expand such a collection, primarily by establishing and characterizing cell lines from precursor lesions and early-stage bladder and kidney cancer from human tissues and animal models. There also is a critical need to culture murine and human lines of normal uroepithelial and proximal tubular epithelial cells as well as cells derived from other tubular epithelial segments of the nephron (Henle's loop). To avoid contamination artifacts and the heterogeneity produced by multiple passages, it will be important to determine the genotype and phenotype of all available bladder and renal cell lines by using state-of-the-art low- and high-throughput technologies. Similarly, generating co-culture systems of stroma–tumor cell populations for bladder and kidney cancers will enable a further understanding of the signaling pathways maintained by cell-cell and cell-matrix interactions. Finally, it is important to launch an initiative on uroepithelial and renal stem cell analyses, focusing on mammalian stem cell sources.

The development of new methods for manipulating the mouse genome has revolutionized our ability to characterize gene function *in vivo* and to generate mouse models of human cancer. The mouse is an ideal model system because mice are physiologically similar to humans and a large number of mouse mutants are already available. This, combined with the development of high-resolution and physical-linkage maps of the mouse genome, enables the identification of genes associated with cancer susceptibility. Furthermore, many molecular lesions that have been associated with a specific human cancer cause a similar disease when introduced to the mouse genome and expressed in the appropriate cellular

compartment. It is also evident that modeling cancer in the mouse goes beyond simple mimicry of the human pathological condition, providing insights into the mechanisms underlying etiopathogenic processes.

Over the past two decades, important technological developments in mouse genetics have made it possible to add normal and mutated genes to the mouse genome (transgenic approach); to replace normal genes with mutated genes (knockin approach); and to delete or disrupt genes (gene targeting or knockout approach). These methodologies have furthered understanding of gene function and enabled the dissection of biological pathways *in vivo*. The National Cancer Institute has recognized the key role of this area of investigation by instituting the Mouse Model of Human Cancer Consortium.

Tissue-specific promoters that drive the expression of activated oncogenes in bladder uroepithelium, such as uroplakin promoters, have been used to generate models of superficial papillary and flat carcinoma *in situ* lesions. Similar promoters are being identified for distinct tubular epithelial cells along the nephron. The use of such tools in the context of transgenic systems could promote the generation of faithful models of kidney cancer.

Available xenograft models, such as orthotopic implantation models, should also be used to address preclinical issues of clinical relevance (response to therapy and mechanisms of resistance). Implanting tumor cell lines, and even primary tumor samples, into the subcapsular kidney region is proving efficient in generating needed models of kidney cancer. This also represents an important area for further investigation. Capitalizing on available models derived from chemical carcinogenesis is another important theme because well-characterized models are already available for bladder and kidney cancer. These models are particularly important in addressing critical issues related to risk factors, including polymorphisms and genetic modifiers and chemoprevention strategies. Another area of special interest represents the development of syngeneic models to determine immune response and immunotherapy approaches of bladder and kidney cancers.

The further development and use of non-mammalian *in vivo* models is of crucial relevance. Models of renal tumorigenesis have been developed in a *Drosophila* sp model, and zebrafish and *Caenorhabditis elegans* systems show promise.

As significant as the above-discussed issues may be, we wish to emphasize that target identification and validation—focusing on identified relevant pathways for bladder and kidney cancers—represents a major area of further expansion. Fostering collaborative industry-academic interactions conducive to discovery and validation, mainly in the areas of drug discovery, development, and manufacturing, is a requirement identified to further advance the field.

In the post-genome era and in view of the advent of high-throughput methods of molecular analysis, it will soon be possible to associate a specific tumor type with a distinct gene-expression profile and to define the molecular lesions characteristic of any given cancer. The development of new methods of manipulating the mouse genome has revolutionized the ability to unravel gene function and dissect molecular pathways relevant to the neoplastic process

in vivo, generating faithful mouse models of human cancer. Elucidation of the molecular pathogenesis of tumors and the events involved in tumor progression is leading directly to the discovery and application of molecular tumor markers. The diagnosis and prognosis of certain neoplasms are in many cases enhanced by the use of markers, which may constitute therapeutic targets. Detailed molecular knowledge of the natural history of tumors will yield biological determinants for inherited and acquired risks, which, in turn, are expected to make improved design and monitoring of prevention a reality.

Priority 1: *Generate and characterize transgenic models, including conditional knockout and knockin strategies, of bladder and kidney cancers, focusing on the use of tissue-specific promoters and targeting genetic events related to human disease.*

Rationale

The advent of transgenic technologies has enabled specific targeting of well-defined genetic alterations into the tissue of interest. Such systems will enable understanding of gene function, dissecting of molecular pathways, and generation of faithful models of human cancer. This knowledge will also provide targets for drug discovery and chemoprevention. Kidney and bladder cancers, however, lag behind other organ systems in the development and use of these models.

Priority 2: *Establish and determine the phenotype and genotype of a) normal uroepithelial and proximal tubular epithelial cells, including stem cells, as cultured lines and b) precursor early-stage and metastatic bladder and kidney cancer cell lines from human tissues and animal models.*

Rationale

Kidney tubular cells are among the most difficult epithelial cell types to cultivate *in vitro*. Access to these normal cells will enable understanding of the mechanisms of malignant transformation. Similarly, the further development of early- and late-stage bladder and kidney cancer cell lines will have a major impact on the elucidation of multistep tumor progression.

Priority 3: *Develop cell and animal models to credential predictive and therapeutic targets relevant to human bladder and kidney cancers.*

Rationale

Despite extensive efforts, few effective chemotherapeutic modalities are available for kidney and metastatic bladder cancers. There is a need to identify targets for the development of efficacious therapeutic agents. High-throughput cell-based and *in vivo* assays are needed to validate novel targets of potential clinical relevance in human kidney and bladder cancers. These efforts should be paralleled by the development of surrogate biological markers to correlate with *in vivo* tumor response.

Resources

To achieve the above-mentioned priorities, it will be crucial to have access to standardized and well-established low-throughput technologies, such as microscopic examination, as well as high-throughput technologies, including cDNA, genomic, and tissue arrays. Applying noninvasive imaging technologies (microPET [positron-emission tomography],

microMRI [magnetic resonance imaging]) will enable evaluation of the *in vivo* efficacy of therapeutic modalities. Critical to success in these studies will be the integration of statistical analyses and information technology, mainly in the area of computational genomics.

Translational Research Subgroup 2A—Preparing for Human Studies

Co-Chairs: *Bin Tean Teh, M.D., Ph.D., David McConkey, Ph.D.*

Participants:

William Benedict	James Resau
Rosemary Green	Craig Webb
Edmund Lattime	Bart Williams
W. Marston Linehan	Robert Wiltrout

BACKGROUND—STATE OF THE SCIENCE

Although surgery and other current therapeutic approaches are effective in superficial bladder cancer and early-stage kidney cancer, few effective regimens exist for more advanced disease. This failure may best be explained by the fact that most currently available therapeutic agents used to treat these cancers interact with nonspecific targets (e.g., T cells, DNA, RNA) that are not uniquely relevant to the biology of kidney and bladder cancers; as a result, these agents often cause life-threatening toxicities. In addition, efforts to optimize the efficacy of these agents have focused on empiricism, rather than on targeting specific biological and molecular defects present in tumors. Cancer formation is a multistep process involving many pathways. A targeted approach should result in improved efficacy with decreased side effects. Targeting tumor biological characteristics requires an arsenal of therapeutic regimens that does not currently exist as well as new strategies to measure the effects of therapy in preclinical models and in patients enrolled in clinical trials.

High-throughput screening technologies have identified an enormous number of potential molecular targets—components of pathways controlling proliferation, cell death, angiogenesis, invasion, immortalization, and insensitivity to growth inhibitors. With such a large number of potential agents, it is vital that we use an informed and reasoned method for identifying, prioritizing, and selecting the chemical and biological agents that should be tested in patients. This will require validation in *in vitro* and animal model systems that recapitulate critical aspects of disease progression and response to therapy.

When testing a therapy in human trials, clinical researchers must be able to confirm the biological mechanism and activities of a drug or biological agent. Functional imaging techniques, which enable detection by noninvasive means of the presence or activity of specific target molecules in the tissue of interest, could enable such determinations. Several such techniques offer possibilities for both directing and monitoring therapy in both experimental animals and human subjects. Examples include positron-emission tomography (PET) and magnetic resonance imaging

(MRI). PET imaging as conventionally performed with F-18 fluorodeoxyglucose (FDG) has shown promise in several small series for monitoring renal carcinomas, including Wilms tumor, as well as for monitoring carcinomas of the urinary bladder. In both settings, FDG-PET has shown anecdotal value for detecting metastatic lesions.

Unfortunately, because of the high levels of FDG activity in the normal kidney and urinary bladder, primary tumors in these organs are more difficult to evaluate with FDG-PET than are primary malignancies originating elsewhere; issues such as this have limited the popularity of FDG-PET imaging in kidney and bladder cancers. However, if suitable new target molecules for kidney and bladder cancers emerge, as expected, from ongoing and proposed gene expression microarray-based searches, it might become feasible to synthesize positron-emitting probes for those targets that would bring PET imaging into a more prominent functional imaging role in this field.

In the area of conventional nuclear imaging, both new radiopharmaceuticals and new instrumentation have the potential to provide functional imaging of kidney and bladder cancers. Radioimmunoscintigraphy and radioimmunotherapy with the monoclonal antibody G250 appear to be useful approaches in early clinical testing in patients with clear-cell renal cancer, and additional monoclonal antibodies should certainly be prepared against new molecular targets as they emerge and are brought toward clinical testing.

In addition, functional imaging techniques should also permit the development of minimally invasive biopsy procedures. For example, radioimmunoguided surgery with hand-held gamma probes to detect nodes and metastatic lesions of high radiotracer uptake intra-operatively has shown promise in the setting of colorectal carcinoma; there is no compelling reason that this approach cannot be adapted for surgical management of kidney or urinary bladder cancer. These minimally invasive biopsy procedures would enable serial biopsies, which could provide an invaluable source of information about the effectiveness of a therapy and about more general aspects of tumor biology. This information can be gleaned from, for example, gene expression profiles from cDNA microarray chips. Thousands of gene expression mRNAs in a tumor can be evaluated, and changes in the profiles before and after treatment can be studied.

Because the physician-scientist serves as the bridge between the laboratory and patients in clinical trials, there is an urgent need to train and provide incentives to physicians to participate in clinical research. Physicians must be introduced to clinical research during residency to ensure that the next-generation physician-scientist is prepared to take advantage of the flood of opportunities afforded by current technologies. In addition, basic researchers would be more effective if they received training in relevant aspects of clinical medicine.

Priority 1: *Develop functional imaging technologies to:*

- Facilitate early diagnosis and identify subsets of prospective patients for clinical trials,
- Follow responses with the goal of identifying early response criteria,
- Guide serial biopsies and obtain critical tissues for analysis while enabling minimally invasive procedures, and

- Confirm that the treatment affects its target and leads to a clinical response.

Rationale

At present no systematic effort is under way to confirm that investigational and conventional therapies produce desired biological effects *in vivo*. Better, validated functional imaging strategies (PET, ultrasound, MRI, etc.) are required to confirm targeting in preclinical models and in patients in clinical trials to establish agent efficacy and target relevance. Clinical MRI or PET units cost in the low millions of dollars to purchase and require a large staff to properly operate and maintain as well as a significant investment in facility space to house them. Companies will contract to bring in portable units and operate them for a fee, which for many hospitals is more cost-effective than buying their own unit. Conventional nuclear cameras and ultrasound units cost about $250,000 and upward and are less expensive than MRI or PET units to house, staff, and operate. A rough estimate of the time and cost to bring a single imaging agent from synthesis or derivation through animal models and Food and Drug Administration approval to its first clinical testing would be, at a minimum, 5 years and $1 million.

Resources

- Clinical trials using functional imaging biopsies will need to be adequately funded.

- Investigator-initiated and National Cancer Institute-supported efforts are necessary to develop the methods that will enable investigators to detect relevant biochemical and molecular changes.

- Bioinformatics support and clinical databases are needed to process the information and store relevant data.

Priority 2: *Identify and prioritize agents that target known cancer growth and progression pathways.*

- Discover, develop, and evaluate therapies in physiologically relevant models that are organ- and tissue-specific for kidney and bladder cancers and are broad enough to accommodate new therapeutic modalities for early and advanced cancers.

- Identify surrogate markers of disease progression and response to therapy.

- Develop delivery strategies for targeted therapeutics.

Rationale

High-throughput genomic and proteomic technologies have enabled identification of a large number of potential molecular targets that are components of cancer growth and progression pathways. There is an urgent need to validate the roles of these targets and their potential as therapeutic agents.

Resources

- *In vivo* and *in vitro* models for screening and validation of pathways in kidney and bladder cancers, and small-molecule inhibitors.

- A series of tissue banks—tumor, urine, serum—linked to complete clinical data. Such tissue banks will require bioinformatics products to analyze the wealth of data.

- A system to facilitate communication and sharing of information among scientists with expertise in various fields.

Priority 3: *Train physician-scientists with a special interest in kidney and bladder cancers.*

Rationale

There is a unique need in the fields of kidney cancer and bladder cancer to develop trained physician-scientists to collaborate with basic and other scientists in studying the human model of cancer (i.e., patients) and transfer promising strategies such as image-based therapies and molecular therapeutics to patients. Unlike basic scientists, physician-scientists have the required medical qualifications and training (e.g., medical oncology, urology) to work with patients. Participation in patient-related research will enable them to devote time to developing and applying new paradigms of treatment. Unfortunately, most residents in training programs are preparing for board certification examinations, which test on the current standard of care and practice and not on new and improved methods. Trained physician-scientists can also help patients to understand the clinical trial process.

At the same time, many basic researchers, who may be less comfortable with patient-related research, can make major contributions to clinical research. The funding of basic researchers to enable them to embark on clinically related research will improve clinical medicine. A human trial is fraught with unknowns and variables that involve many aspects of research unrelated to clinical medicine (e.g., statistics). The involvement of basic researchers with different areas of expertise is necessary to ensure the highest quality of clinical research.

Resources

- Training grants for residency programs (e.g., in medical oncology and urology).
- Training grants for basic researchers to engage in clinical research.
- Recruitment of appropriate research mentors and academic centers for residents.
- Involvement of patient advocates, who are a vital resource for training residents in patient issues related to clinical research.

Translational Research Subgroup 2B—Correlative Science

Co-Chairs: *Michael Atkins, M.D., Robert Getzenberg, Ph.D., James Finke, Ph.D.*

Participants:

Peter Carroll	Robert Parker
James Hunter	Raymond Petryshyn
James Mier	David Swanson
Augusto Ochoa	James Thomas

BACKGROUND—STATE OF THE SCIENCE

There is a clear need to conduct translational studies for both kidney and bladder cancers. Novel therapeutic approaches are needed, and in many cases the basic knowledge by which to guide treatment is incomplete. These cancer types are excellent targets for conducting translational studies that take into account the diseases' unique natures. As is evident from the priorities outlined below, many common approaches can be taken to address these diseases. Additionally, there are aspects unique to each tumor type that provide excellent opportunities for novel correlative studies. For example, bladder cancer provides a system in which tumors can be studied and sampled longitudinally before, during, and after therapy. Urine provides a unique opportunity to study cells, protein, and DNA from the bladder and kidney, which may reflect the altered cell states, or markers that exist within the diseased tissues. Although several urine-based tumor markers have been identified in bladder cancer, no such markers have yet been identified in kidney cancer.

Genetic mutations and altered pathways have been identified in each cancer type, providing ample novel therapeutic targets. Kidney cancer is quite vascularized and, therefore, provides an opportunity to detect blood-based markers. Despite these apparent advantages, few markers are available for these diseases. In addition, kidney cancers are relatively resistant to most of the therapies that have been applied against them, with the possible exception of immunotherapies, which are only effective in a relatively few patients.

Priority 1: *Examine blood, urine, and tumor tissue before therapy to identify predictors and mechanisms of response or resistance.*

Such predictors and mechanisms include:

- Immunologic competence (e.g., T cells and dendritic cells),
- Mechanisms of tumor resistance, such as susceptibility to apoptosis and altered signaling pathways,
- Histopathologic features, and
- Molecular profiles (e.g., gene expression and proteomics).

Rationale

Because existing therapies benefit only a small proportion of patients, we must identify patient populations most likely to

respond. We also need to identify mechanisms of resistance in order to facilitate the development of alternative approaches for those who are unlikely to respond.

Some unique features of kidney and bladder cancers should be emphasized. There is evidence that in kidney cancer, the immune response is not well developed, partly because of tumor-induced down-regulation of immune function. The study of immunologic competence is a priority in kidney cancer. The role of the immune response in bladder cancer is less clear. These studies will ask whether the immunologic competence of an individual patient relates to the patient's ability to respond to immune-based therapies.

There is also a lack of information about the mechanisms of resistance to immunologic and chemotherapeutic agents for both diseases, although bladder cancer is typically more responsive than kidney cancer to chemotherapeutic agents. It is important to assess the mechanisms of resistance to therapy, which may include resistance to apoptosis and abnormalities in signal transduction pathways related to growth regulation. Information about immunologic competence and resistance mechanisms may be used to tailor therapeutic approaches to the individual patient. Such research will require the collection of blood, urine, and tissue samples in which to study individual immune competence and identify novel predictors of response and resistance to therapies.

Kidney and bladder cancers consist of multiple tumor types, and studies may require modification for each type. These studies will use the latest approaches to identify markers, including microarray and proteome analysis. These complex studies will need to be supported by bioinformatic techniques to determine the most relevant targets. Targets can be validated through several mechanisms, including the use of tissue arrays that provide the opportunity to screen a number of potential targets with a large number of samples.

Priority 2: *Facilitate development and utilization of noninvasive or minimally invasive techniques and novel clinical strategies to assess the biological effects of targeted therapeutics.*

Such techniques and strategies include:

- Functional imaging of tumor and tumor/host vasculature,
- Minimally invasive biopsies,
- Better use of biopsy material,
- Neoadjuvant treatment approaches, and
- Surrogate markers of clinical effects (e.g., target inhibition in blood, urine, skin, or other tissue that is easily and repetitively sampled).

Rationale

We must be able to serially sample patients during therapy to:

- Demonstrate biological efficacy before assessing clinical efficacy in Phase III trials,
- Determine the optimal biological dose rather than routinely using the maximum tolerated dose, and
- Discriminate between failure to inhibit the putative target and clinical failure

attributable to the fact that the inhibited pathway is not biologically critical.

Because renal tumors cannot be easily sampled, noninvasive and minimally invasive techniques are needed to assess the effect of therapies. There has been little development of noninvasive or minimally invasive procedures that can be used to provide information on the biological responsiveness of the tumor to therapy. New imaging techniques may provide an opportunity to address this important area. One approach would be to examine functional imaging of the tumors to determine their sensitivity to the therapy. Positron-emission tomography (PET) imaging with probes could focus on aspects of the biology of these tumor types. (Many PET agents are concentrated in the urine, which makes imaging of the bladder difficult but not impossible.) Imaging of the vasculature of both tumor and host can provide information about the particular response to antiangiogenic compounds. These imaging approaches can also be used to provide a means for more accurate biopsies of viable tumor tissue for analysis.

New methods need to be developed to obtain as much information as possible from current biopsies. This may involve study of small amounts of DNA or RNA obtained from biopsy samples.

Tumor response and resistance can also be studied by treating individuals before nephrectomy and then analyzing the harvested kidney tissue obtained from the nephrectomy specimen. This may require large patient populations and would be necessary when no biopsy or inadequate or insufficient material is available. This method also provides a source of viable tissue for analysis, which allows for many studies that cannot be performed on small biopsy samples, as well as studies to investigate adjacent normal tissue. When tumor or biopsy material is not available, surrogate markers of therapeutic efficacy would be useful. For example, one could study a pathway antagonist in a blood sample or easily obtainable normal body tissue such as skin.

Priority 3: *Develop and apply urine and serum markers for tumor burden, assessment of tumor behavior, and early detection of relapse.*

Rationale

Using markers sufficiently sensitive to detect disease that is undetectable by radiologic methods, we can identify patients in whom treatment may be more effective. Such markers will also enable testing of the hypothesis that early treatment is more effective as well as monitoring of treatment response and early detection of relapse.

We must also test the hypothesis that limited tumor volume makes early treatment of recurrent kidney and bladder cancers more effective. To accomplish this goal, markers must be developed to detect these diseases before we can detect them by conventional methods. Thus we must identify and apply markers that would recognize individuals with disease early. In addition, these markers can be used to differentiate between tumors of various levels of aggressiveness. This information could alter the treatment approach to the individual patient. These markers can also be used to assess individual response to therapy. A marker, which may be as simple as a measure of tumor burden, could be valuable in providing rapid feedback to determine whether an agent can reduce tumor size without the use of potentially invasive approaches.

Resources

To accomplish the above research priorities, resources must be developed that include the following:

- Assay standardization and clinical validation,
- Multidisciplinary cooperation,
- Tissue banking and multi-institutional access, and
- Human subject issues, such as flexible consent and links to clinical databases.

Translational Research Subgroup 2C—Clinical Trials

Co-Chairs: *Walter Stadler, M.D., Robert Motzer, M.D., Michael O'Donnell, M.D.*

Participants:

Dean Bajorin
Robert Dreicer
Daniel George
David Nanus
Lorna Patrick
Katherine Phillion
Marsha Rosner

BACKGROUND—STATE OF THE SCIENCE

Until recently, the most significant difficulty in developing new therapies for bladder and kidney cancers was the lack of potential targets and agents. Currently, many of the molecular pathways in bladder and kidney cancer pathogenesis have been elucidated and maturation of high-throughput genetic and epigenetic analyses will likely further refine this knowledge. Two likely consequences of these efforts will be the definition of multiple tumor subtypes and multiple putative therapeutic targets. Continued sophistication in chemistry and biochemical assay systems means that agents will likely be identified for each of these targets. It has also become more evident that successful eradication of either kidney or bladder cancer will likely require inhibition of several molecular pathways, and the precise site at which inhibition is most likely to be effective may differ among tumor subtypes and perhaps even among individual patients. These pathways and tumor subtypes may well be defined by a longitudinal analysis of patient material obtained during the course of therapy.

Two examples illustrate new opportunities for targeted intervention. First, von Hippel-Lindau (*VHL*) mutations and alterations have been identified as components of a critical pathway in development of clear-cell renal carcinoma. These mutations and alterations lead to inhibition of hypoxia-inducible factor (HIFα) degradation, upregulation of vascular endothelial growth factor (VEGF), and the florid angiogenesis seen in kidney cancer. It would thus seem that this pathway is an appropriate target for mechanism-driven clinical trial research. A number of agents targeting this pathway are available or are in development, including an anti-VEGF antibody, various VEGF receptor antagonists, and HIFα transcriptional inhibitors. Although the VHL pathway is not relevant in other kidney cancer subtypes, other pathways in those cancers have been identified as putative therapeutic targets.

The second example relates to the well-described alteration of the p53 pathway in approximately 50 percent of bladder cancer patients. It has been hypothesized that dysregulation of this pathway may make tumors susceptible to certain chemotherapeutic approaches. Validation of this hypothesis is currently being examined in the adjuvant setting following cystectomy, where the use of chemotherapy is common but of marginal benefit. Patients

with T1 or T2 disease post-cystectomy are enrolled and stratified by *TP53* mutational status. Those with *TP53* mutations are randomly assigned to adjuvant chemotherapy or observation, with time to recurrence as the primary endpoint. Tumor tissue collected in this study is being evaluated for other cell cycle targets. In addition to p53 and the cell cycle, other well-known pathways amenable to targeted therapies have been described.

To take advantage of known and to-be-discovered critical pathways in kidney and bladder cancers, we have identified three research priorities appropriate to clinical trial translational efforts as well as the resources required to support these efforts.

Priority 1: *Develop clinical trials using mechanism-based agents that take into account known prognostic variables and molecular characteristics of tumors.*

Rationale

A commonly shared scientific knowledge base must be developed to improve current clinical approaches and evaluate new therapeutic agents. Clinical trials need to use agents that have clear mechanisms and that interact with pathways critical for kidney and bladder cancer oncogenesis. These trials should recognize and take into account previously described clinical prognostic variables—including histology, tumor grade, and clinical staging systems—to adequately assess outcome in relatively homogeneous populations. The molecular characteristics of tumors, including expression of the target, need to be assessed as part of the trial.

Priority 2: *Identify the features in the tumor or host that define response or non-response to therapy.*

Rationale

Preclinical studies have identified molecular alterations in the tumor and host that are associated with stage and outcome. Preclinical hypotheses require validation, and new hypotheses will be generated from these studies. The acquisition of materials before, during, and after therapy is critical to measuring the effect of treatment and to defining features that may predict outcome.

Priority 3: *Facilitate acquisition and evaluation of novel agents, singly and in combination, specifically for use in bladder and kidney cancer targets.*

Rationale

Kidney cancer should be considered a priority for the study of new agents because of the current lack of effective therapies and the poor survival associated with metastatic disease. The same problem exists in advanced bladder cancer, and the economic burden of early bladder cancer is disproportionately greater than the current research effort. Drugs with potential for efficacy in these diseases may not be readily available for study, either alone or in combination, in preclinical models and early-phase clinical trials. Although these agents may be available within industry, the National Cancer Institute, or academia, barriers exist to the study of these agents specifically in kidney or bladder cancers and to the study of agents that may interact with pathways specific to kidney or bladder cancer. One approach to overcoming these barriers might be to create centers or networks of clinical research that provide opportunities to recruit dispersed patient populations with these diseases and to use multidisciplinary expertise in the conduct of mechanism-based clinical trials.

Resources

- Preclinical data: Preclinical data that identify and validate appropriate targets in kidney and bladder cancers must be generated and made available to researchers.

- Specimen bank: Pretreatment and posttreatment patient specimens with assessment of optimum methods for procurement, preservation, and analysis must be made available to basic and clinical researchers. The availability of urine and serial, accessible primary and metastatic tumor (and normal) samples provides unique opportunities for study in these diseases.

- Drug bank: New and developing agents (including drugs generated by industry and academia) with a potential impact on kidney and bladder cancers should be made available to basic and clinical researchers.

Treatment Subgroup 3A—Risk-Directed Treatment of Localized Disease

Co-Chairs: *Anthony Zietman, M.D., M.R.C.P., F.R.C.R., Martin Resnick, M.D., Eila Skinner, M.D.*

Participants:

Arie Belldegrun	Fray Marshall
Jean deKernion	Michael Redden
S. Machele Donat	Dan Theodorescu

BACKGROUND—STATE OF THE SCIENCE

Experience indicates that 30 to 70 percent of patients presenting with localized kidney and bladder cancers will develop either local or distant recurrence after local therapy. Various local treatment approaches are used, ranging from organ-sparing maneuvers to radical extirpative surgery.

For kidney cancer, the standard of care over the last 50 years has been the radical nephrectomy. Since the 1980s, however, nephron-sparing techniques have been developed. Though these techniques were originally intended for patients with one kidney, chronic renal disease, or bilateral tumors, their use has been extended to patients with a normal contralateral kidney. This trend has been encouraged by a stage shift caused by the identification, by modern imaging techniques, of increasing numbers of patients with small tumors. Most recently, cryosurgery and radiofrequency ablation have been used either percutaneously or laparoscopically, although the exact role of each of these less-invasive techniques remains undefined.

At the other end of the spectrum, there exists a group of kidney cancer patients who are at high risk for metastatic recurrence after radical local therapy. However, conventional surgical and pathological criteria cannot predict the risk of metastatic recurrence for each individual. Although identified high-risk patients have been targeted for adjuvant therapy, to date no trials have shown clear benefit. There is a critical need to develop new techniques for better identifying high-risk patients and to test immunotherapeutic and other novel agents in the adjuvant setting.

Patients with clinically localized bladder cancer demonstrate a very broad spectrum of stages, ranging from superficial tumors through locally invasive and occult metastatic disease. Eighty percent of patients have superficial disease at initial diagnosis. Bladder cancer is a lifelong disease whose pattern of relapse after initial treatment is characterized by multiple local recurrences and eventual phenotypic progression of disease. More health care dollars are currently spent on the surveillance and treatment of superficial bladder cancer than on the treatment of prostate cancer. Large randomized trials of intravesical immunotherapy and chemotherapy have shown that recurrence and progression can be delayed but not necessarily prevented. Once patients have progressed to muscle-invasive disease, the standard therapy is a radical cystectomy, with its quality-of-life

implications. Though there have been attempts at organ preservation using limited surgical techniques, either alone or in combination with chemotherapy or radiation, the role of organ-sparing approaches in the management of patients with muscle-invasive disease has not been established. Better markers are required to define those subpopulations that can be appropriately treated with more limited therapy. Despite effective local therapy, half of bladder cancer patients with muscle-invading tumors ultimately develop distant metastases. Adjuvant trials have demonstrated modest efficacy using conventional chemotherapeutic regimens. These trials have, however, been difficult to complete because of limited patient numbers, therapeutic toxicity, and physician bias.

The therapeutic dilemmas encountered in patients with localized kidney and bladder cancers thus have many similarities. The following priorities focus on research initiatives and goals common to these seemingly distinct diseases.

Priority 1: Develop molecular biomarkers and functional imaging techniques to improve our ability to select patients for appropriate therapy. Such markers and imaging techniques may be used to increase the accuracy of staging, predict tumor behavior, and predict an individual's response to therapy.

Rationale

Kidney and bladder cancers are biologically heterogeneous diseases. It is clear that many patients can be managed with less invasive therapy, while others need more aggressive treatment. Better predictors of behavior and response are needed to more appropriately guide treatment and predict prognosis for the individual patient.

Key resources for accomplishing this priority are (a) development of high quality tissue, serum, and urine banks and (b) development and application of novel imaging techniques, including functional and molecular imaging.

Priority 2: *Support innovative trial design for rapid evaluation of new treatment options using surrogate markers.*

Rationale

Evaluation of new treatment options now proceeds slowly because of limited patient numbers, unnecessary delays in trial design and approval, and insufficient funding. The current system of clinical studies is inadequate to assess the large numbers of novel therapies in development. Many organ-conserving strategies exist and are used empirically, and many new technologies are being developed. Support must be provided for formal assessment of the efficacy, safety, cost, and impact on quality of life of these approaches. Support should also be provided for innovative organ-conserving strategies such as novel intravesical agents or novel combinations or sequences of currently available agents. One suggested approach for localized disease is neoadjuvant treatment with surgical, radiographic, and biological monitoring of response using validated surrogate markers. The response would determine whether organ preservation is feasible. This approach could also allow initial testing of novel agents such as biological modifiers in patients with localized disease without having to first prove efficacy in diffuse metastatic disease.

Resources

- Expand the definition of Specialized Programs of Research Excellence (SPORE) to encourage multi-institutional consortia of centers of excellence in clinical research. We recommend as a goal the establishment of three to five SPOREs in kidney and bladder cancers. This mechanism would enhance the performance of high-priority translational projects and facilitate investigations of targeted palliative-care approaches. It would also encourage the Recruitment of scientists into kidney and bladder cancer research.

- Increase public awareness and education about kidney and bladder cancers to encourage patient and physician participation in clinical trials.

- Develop the K08 mechanism to support physician-scientist career development in kidney and bladder cancer research.

- Develop specimen repositories (including tumor and normal tissue, serum, and urine) to allow future correlations with clinical trial outcomes.

- Develop a centralized database management system for patients participating in clinical trials sponsored by National Cancer Institute cooperative groups, and the pharmaceutical industry, as well as in investigator- or institution-initiated pilot trials.

Treatment Subgroup 3B—Treatment and Palliation of Advanced Disease

Co-Chairs: *Janice Dutcher, M.D., Ronald Bukowski, M.D., Mellar Davis, M.D.*

Participants:

Arie Belldegrun
Deborah Collyar
Robert Dreicer
Robert Figlin
Mary Gospodarowicz
Alan Poland
James Yang

BACKGROUND—STATE OF THE SCIENCE

Kidney and bladder cancers together account for about 88,000 new cases of malignancy annually. Annual mortality figures indicate that over 24,000 patients die from these two diseases each year.

Current treatment approaches use immunotherapy for metastatic kidney cancer and chemotherapy and radiation therapy for metastatic bladder cancer. Nevertheless, less than 10 percent of treated patients with advanced disease survive long term (more than 5 years). However, subsets of patients with advanced kidney and bladder cancers have complete responses and long-term disease-free survival. At present, clinical criteria are the only way to prospectively identify patients with potential for long-term survival. The current staging systems and prognostic factors have recently been combined, allowing for improved prediction of disease recurrence and outcomes for individual patients.

Recently, awareness has developed that each of these diseases is heterogeneous in its pathologic and molecular characteristics. These new insights may lead to individualized therapeutic approaches. For example, in clear-cell renal cancer, 70 percent of sporadic tumors contain deletions of chromosome 3p and mutations of the von Hippel-Lindau (*VHL*) gene, indicating loss of tumor suppressor function and activation of growth stimulating pathways. Additionally, there is evidence for silencing of the *VHL* gene by promoter hypermethylation, which is potentially reversible by appropriate drug treatment. These findings suggest that a specific defect causes clear-cell renal cancer and may lead to the identification of specific targets for new therapeutic approaches. In bladder malignancies, although no such specific early molecular target has been identified to date, *TP53* mutations can occur in early dysplastic lesions; *TP53* status is currently being tested as a means to direct treatment.

Ninety-five percent of patients with advanced kidney or bladder cancer develop progressive disease despite initial therapy. Up to 30 percent of patients with metastatic kidney cancer develop symptomatic bone metastases that require specific therapies. Evidence-based approaches to and guidelines for the management of symptom clusters of advanced disease (e.g., anemia, anorexia, and fatigue) are lacking.

Priority 1: *Develop innovative therapeutic strategies that will eradicate disease, preserve organ function, and maintain quality of life.*

- Investigate the role of *VHL* mutations and their associated pathways that may identify molecular targets for novel therapeutic interventions. This is an extraordinary opportunity for molecular targeted therapy.

- Identify and validate novel targets for treatment in bladder and kidney cancer and, where appropriate, integrate new molecular therapies into existing treatment approaches.

- Support innovative trial designs for rapid evaluation of new treatment options using surrogate markers.

- Identify and target mediators of paraneoplastic syndromes.

Rationale

- *VHL* mutations are associated with 70 percent of clear-cell renal cancers, which represent 60 percent of all kidney cancers. Targeting this pathway represents a unique opportunity to develop specific therapy for a causative pathway.

- Current systemic therapy is inadequate. Identification of molecular targets may lead to improved therapy. Such targets (e.g., the endothelial growth factor receptor, vascular endothelial growth factor, and m-Tor) have not been well explored in kidney and bladder cancers.

- The current system for completing clinical studies is inadequate to assess the large numbers of novel therapies currently being developed. Many organ-conserving strategies exist and are used empirically, and many new technologies are in development. Support must be provided for rapid assessment of the efficacy, safety, cost, and impact on quality of life of these approaches to treating advanced disease. One suggested approach is earlier use of novel agents in untreated patients with advanced disease (window of opportunity therapy).

- Mediators of paraneoplastic events may influence disease outcome and management. Examples include anemia, fever, hypercalcemia, and anorexia/cachexia syndrome, all of which are mediated by endogenous factors.

Priority 2: *Develop and improve approaches to risk assessment of advanced disease.*

- Develop molecular biomarkers and functional imaging techniques to improve our ability to select patients for appropriate therapy. These tools may be used to increase the accuracy of staging, predict tumor behavior, and predict an individual's response to therapy.

- Develop methodologies to refine existing and new prognostic classifications, to enable better evaluation of therapeutic outcomes and for use in clinical trials.

Rationale

Kidney and bladder cancers are biologically heterogeneous diseases. Patients with advanced disease have disparate characteristics that affect therapeutic

outcomes. Better predictors of behavior and response are needed to more appropriately guide treatment of the individual patient and predict prognosis.

Priority 3: *Develop evidence-based, hypothesis-driven research efforts in palliative care for patients with advanced kidney and bladder cancers.*

- Identify, characterize, and evaluate symptom clusters for both diseases and their impact on disease outcome and quality of life.

- Develop pharmacological, non-pharmacological, and complementary/ alternative strategies for targeted palliation through evidence-based approaches.

Rationale

Therapy fails in 95 percent of patients with advanced kidney or bladder cancer. In both of these tumor types, the distribution of symptom clusters in advanced disease is relatively unknown and the prognostic significance and impact on quality of life of these symptom clusters are not well studied. For example, it would be useful to evaluate different strategies for managing bone metastases and the effects of these different strategies on mobility, function, and pain.

Resources

- Expand the definition of Specialized Programs of Research Excellence (SPORE) to encourage multi-institutional consortia of centers of excellence in clinical research. We recommend a goal of three to five SPOREs in kidney and bladder cancers. This mechanism would enhance the performance of high-priority translational projects and facilitate investigations of targeted palliative care approaches. It would also encourage the recruitment of scientists into kidney and bladder cancer research.

- Increase public awareness and education about kidney and bladder cancers to encourage patient and physician participation in clinical trials.

- Develop the K08 mechanism to support physician-scientist career development in kidney and bladder cancer research.

- Develop specimen repositories (including tumor and normal tissue, serum, and urine) to allow future correlations with clinical trial outcomes.

- Develop a centralized database management system for patients participating in clinical trials sponsored by National Cancer Institute cooperative groups and the pharmaceutical industry, as well as in investigator- or institution-initiated pilot trials.

Cancer Control Subgroup 4A—Screening and Prevention

Co-Chairs: *H. Barton Grossman, M.D., Edward Messing, M.D., Robert Flanigan, M.D.*

Participants:

Samuel Cohen	Levy Kopelovich
Michael Droller	Howard Parnes
Wayland Eppard	Jaye Viner
Susan Groshen	Xifeng Wu

BACKGROUND—STATE OF THE SCIENCE

Bladder cancer—the fourth most common cancer in men and eighth most common in women in the United States—is uniquely suitable for screening because of its easy accessibility by means of cystoscopy and urinary markers. Metastases are almost invariably associated with concomitant or previous muscle-invading cancers. The vast majority of patients with muscle invasion have it at initial presentation; few have evidence of previous superficial tumors. Moreover, because autopsy series show no incidentally found bladder cancer, it is very likely that even early bladder cancers will cause symptoms to appear rapidly, leading to diagnosis and treatment. Because all tumors arise on the urothelial surface, there is a window of time (before muscle invasion occurs) during which they can be detected and treated with strategies that are highly successful and relatively nonmorbid. Because bladder cancers grow quite rapidly (otherwise, many more would be detected incidentally at autopsy), studies to enhance early detection are imperative to improve outcomes. Screening aimed at early detection in people without a history of prior bladder tumors holds great promise for reducing mortality from bladder cancer.

High-risk populations for bladder cancer include cigarette smokers and persons with exposure to industrial or environmental carcinogens. However, the duration between exposure and the development of bladder cancer can be 20 years or more.

Although few screening studies have been conducted in kidney cancer, evidence suggests that earlier detection and treatment will result in improved outcomes. The evolution of less-invasive treatment modalities for small tumors makes this an especially opportune time to pursue screening studies. Recent advances in understanding the molecular bases of kidney cancers provide exciting potential new biomarkers for early detection and prognosis.

Preclinical and limited clinical data demonstrate that bladder cancer is responsive to primary and secondary preventive efforts; few similar data exist for kidney cancer. Although improved understanding of the pathways of both bladder and kidney carcinogenesis present new targets for prevention, the lack of identifiable high-risk populations (particularly for sporadic kidney cancer) and of surrogate endpoint biomarkers (for both malignancies) limits our ability to

implement prevention studies. Barriers to patient enrollment and specimen acquisition are significant impediments to progress. To move prevention of both these diseases forward, sample sizes that provide sufficient statistical power and access to specimens with appropriate clinical follow-up are essential.

Priority 1: *Identify, characterize, and validate biomarkers that can be used to assess risk of disease, enhance early detection, and predict response to chemoprevention.*

Rationale

Biomarkers can be used to select high-risk subjects for screening, resulting in more statistically powerful screening studies with smaller numbers of subjects than could be obtained by general population screening. New markers are available that have high sensitivity and specificity, and others are being developed. Furthermore, bladder cancer is ideally suited to secondary prevention. Validated surrogate endpoints will facilitate the evaluation of novel chemopreventive agents and strategies.

Early excision of small renal cell carcinomas cures almost all patients. Identification of novel biomarkers could enhance the detection of small tumors (less than 2 cm); newly developed, minimally invasive treatments permit ablation of these lesions with relatively low morbidity. Biomarkers can also be used to identify patient subgroups according to their risk of progression and to determine targets for emerging therapies.

Resources

Previously identified biomarkers lack the sensitivity and specificity to be useful as tools for early detection and screening. Promising new markers are now available and in development, and their clinical utility for screening needs to be validated. Because screening trials require large populations to be followed over long periods, adequate infrastructure designed with input from patient advocates is critically needed. The increasing availability of multiple biomarkers requires rigorous bioinformatic assessment. Novel and economical trial designs will require statistical tools capable of analyzing multiple variables assessed in a small data set.

Priority 2: *Develop models and study unique populations to assess risk and improve detection and prevention efforts for kidney and bladder cancers by incorporating genetic, epidemiologic, and clinical data.*

Rationale

Unique populations have contributed dramatically to our understanding of the genetic and molecular bases of kidney cancers (VHL syndrome, hereditary papillary renal cancer, Wilms tumor, etc.). This knowledge has also revolutionized our understanding of the far more common sporadic forms of the disease. Other unique populations—such as young adults with bladder cancer, patients with end-stage renal disease, and posttreatment cancer patients who continue to smoke—offer the potential to provide similarly valuable knowledge with broad applicability. Studies of such populations are likely to yield insights into risk factors for renal and bladder cancers. Additionally, preclinical, mathematical, and other models are essential to the development and testing of successful, cost-effective strategies for screening and prevention.

Resources

In both kidney and bladder cancers, the relative rarity of many of these unique subgroups limits the capacity of a single institution to conduct studies with meaningful statistical power. Multi-institutional collaborations and specimen banks with associated clinical longitudinal data, focused on these unique populations, would address this barrier. New genetically engineered animal models now in use for mechanistic studies in kidney and bladder cancers offer unique opportunities for prevention research.

Priority 3: *Identify and test novel chemopreventive agents and strategies.*

Rationale

Bladder cancer is an attractive target for prevention efforts because renal excretion of oral agents allows for prolonged exposure to high concentrations of drugs and because the urothelium is easily evaluated and monitored with relatively noninvasive techniques. Additionally, the frequent recurrence of superficial bladder cancer with low occurrence of muscle-invasive disease permits the safe and efficient assessment of strategies to prevent secondary bladder cancers with a modest number of patients and short follow-up. New and more effective preventive agents, combinations, and strategies are urgently needed because even the most effective intravesical agent (bacillus Calmette-Guerin) has local toxicity and a high rate of long-term failure. With improved understanding of molecular oncology, patients with hereditary kidney cancer syndromes and lesions provide excellent opportunities to test chemoprevention strategies. Advances in this arena will translate immediately to sporadic kidney cancers and will result in improved quality of life and outcomes for a much larger number of patients.

Resources

Unfortunately, few resources are being directed toward new agents for prevention of kidney and bladder cancers because of the relatively small numbers of patients at risk and the likelihood of poor economic returns on such investments. Moreover, chemopreventive compounds are currently often tested as single agents, although data suggest that such drugs exert greater impact when they are directed in combination against different molecular pathways. Furthermore, novel intervention strategies directed toward blocking the proximate carcinogen may prevent the disease.

Finally, epidemiologic studies imply that natural products, such as vitamins and herbal combinations, may provide preventive benefit in both diseases, but these agents are not being studied because they cannot easily be patented and are available over the counter in unregulated formulations. Such natural products can have unknown interactions that confound clinical trial data.

The National Cancer Institute and the Food and Drug Administration must jointly develop mechanisms to encourage research in the above areas. Secondly, mechanisms must be developed to encourage combination strategies. This may require increased collaboration between governmental agencies and industry. Finally, it should be brought to the attention of industry that bladder cancer, in particular, is a highly prevalent disease that should be economically attractive as a subject of study.

Cancer Control Subgroup 4B—Quality of Life

Co-Chairs: *Susan Leigh, B.S.N., R.N., Geraldine Padilla, Ph.D., Judith Shell, Ph.D.*

Participants:

Karen Basen-Engquist	Brian Rini
Marlene Frost	Julia Rowland
Deborah Lubeck	Charles Scott
David Penson	John Wei

BACKGROUND—STATE OF THE SCIENCE

No single, commonly accepted definition of health-related quality of life (HRQOL) exists. However, a number of definitions share the concepts of well-being, multidimensionality—including the domains of physical, functional, psychological, social and spiritual well being—and the subjective value of one's life.

A comprehensive kidney and bladder cancer research program needs to include investigations into the HRQOL of patients with these cancers for a number of reasons. HRQOL is a critical outcome in studies of the burden of kidney and bladder cancers**,** of new treatment modalities, of positive and negative treatment side effects, and of new or different treatments that may have a minimal or negligent impact on survival. Most importantly, patient preferences, decisions, and behaviors regarding treatment and disease management occur in the context of quality-of-life evaluations.

The vast majority of persons who develop kidney or bladder cancer are diagnosed with early-stage disease. As a consequence, they can expect long-term survival. Unfortunately, we know very little about the late or chronic effects of potentially curative therapeutic interventions. Of the few studies that exist, patient reports usually focus on sexual and urinary dysfunction and chronic fatigue. In addition, early diagnosis can be associated with long-term surveillance demands, including procedures that may have a negative impact on quality of life.

For those with advanced disease, understanding the impact of their cancer on individual functioning and well-being is important in the management of their care. Because current treatment options for advanced disease do little to prolong life, HRQOL information is needed to help patients make decisions about therapies, to tailor therapies to reduce morbidity, and to improve adherence to prophylactic and surveillance regimens. Maintaining or improving quality of life becomes a primary goal of treatment and care in advanced disease.

A number of barriers confront investigators who seek to study the HRQOL of persons with kidney and bladder cancers. The health care community, particularly surgeons and primary care providers, lacks education about the importance of behavioral and health-related quality of life issues that face persons with kidney and bladder cancers.

Patients lack education about the legitimacy of their concerns surrounding the management of their care. Patients also lack education about risk factors for kidney and bladder cancers, such as smoking and obesity. Reliable, valid instruments that target kidney and bladder disease- and treatment-specific HRQOL do not exist. Further, the field lacks a critical mass of investigators and clinicians devoted to working in these populations.

Data suggest that kidney cancer, like melanoma, may be immunologically driven. Other data show that immune vaccines such as bacillus Calmette-Guerin have a role in the control of bladder cancer. The existence in both of these tumors of an association between a potential immune mechanism and disease progression has important ramifications for behavioral scientists. Specifically, research has shown that cognitive and behavioral interventions can change the immune milieu in healthy individuals who are under great stress, as well as in cancer survivors. The effectiveness of these interventions in mediating immune response raises provocative questions about their potential for improving response to disease and treatment in patients with kidney and bladder cancers.

In addition, the known association between smoking and bladder and kidney cancers and the potential association between obesity and kidney cancer suggests an important role for behavioral interventions in both primary and tertiary risk reduction.

We know that patterns of care for kidney and bladder cancers are different for older patients, who tend to receive less aggressive treatment and to have poorer outcomes. As the U.S. population ages with better health, this pattern of under-treatment needs to be addressed. Further, it has been reported that women with bladder cancer tend to be diagnosed at a later stage than men. It is hypothesized that this delay is due to the failure of physicians to recognize the early signs of this disease. Women who present with hematuria are more likely than men to be treated with antibiotics for a presumed urinary tract infection, thereby delaying a cancer diagnosis. These concerns point to the need for research that examines the role in treatment decisions of patient and physician biases that may adversely affect outcomes for women and older persons with bladder and kidney cancer.

Currently, there are approximately 550,000 survivors of kidney and bladder cancers in the United States. The National Cancer Institute's grant portfolio supports few, if any, projects that address the quality of life for these survivors. Numerous gaps exist in the science of quality of life in kidney and bladder cancers. These gaps include:

- A lack of measurement tools and information, such as:
  - Treatment- or symptom-specific measures of quality of life,
  - Qualitative studies that may reveal currently unknown domains of quality of life uniquely affected by these diseases,
  - Psychometric studies to develop measures (both descriptive and preference-based) specific to bladder and kidney cancers, and
  - Research to clarify clinically significant differences in quality of life within and between groups.

- An absence of studies that:
  - Use standardized, reliable, and valid measures;
  - Assess quality of life prospectively over the survival continuum;
  - Address variables that are potentially related to quality of life (e.g., decision-making; role of family; different perspectives of patients, providers, and family members; insufficient collaboration between urology and oncology on issues related to patient care); and
  - Identify the effects of specific treatments and the distress associated with invasive surveillance procedures.
- A dearth of studies of the effect of treatment and disease outcomes on quality of life—mediated by such variables as adherence to treatment, surveillance, immune function, and smoking.
- A shortage of randomized, controlled trials or long-term cohort studies that test the effectiveness of interventions to improve quality of life and ameliorate symptoms.

All kidney and bladder cancer studies should assess the effects of socioeconomic status, ethnicity, language, age, gender, and culture on quality of life.

Priority 1: *Describe quality of life along the survivorship continuum (including persons at high risk) for persons with kidney and bladder cancers and their families.*

Research studies addressing this priority need to consider:

Instruments

- Identify disease- and treatment-specific measures of health-related quality of life for use in the collection of prospective data across the continuum of care.
- Develop or refine new tools or refine existing tools; test the reliability and validity of these tools.
- Develop gender-specific questions concerning urinary and sexual function.
- Encourage the use of common, standardized instruments across studies.
- Use descriptive and preference-based instruments.
- Test and validate existing, standardized instruments.
- Develop criteria for measures of clinically significant change in quality of life.
- Assess patient satisfaction with treatment outcomes.

Types of Studies

- Prospective, longitudinal trials.
- Cross-sectional studies.

Predictor and Outcome Variables

- Symptoms, symptom management, morbidity, and mortality.
- Treatment, surveillance, and adherence.
- Socioeconomic status, ethnicity, and gender.

- Comorbidity.
- Stage of disease.
- Access to care.
- Patterns of care.
- Patient/provider attitudes to care decisions.
- Health behaviors (e.g., smoking).
- Neuroendocrine and immune function.
- Satisfaction with care.

Rationale

- Quality of life is a highly valued component of care for persons with kidney or bladder cancer. Although cure or increased life expectancy is a primary goal of medical treatment, patients and those who care for them agree that improving quality of life is also a high priority.
- In advanced kidney and bladder cancers, current treatment options do little to prolong life. Therefore, maintaining or improving quality of life becomes a primary goal of treatment and care.
- When kidney or bladder cancer is diagnosed at an early stage, a longer life expectancy is likely. However, early diagnosis can be associated with long-term treatment-related side effects and distress caused by continued surveillance, all of which may have a negative impact on quality of life. Common distressing problems include sexual and urinary dysfunction and invasive follow-up procedures.
- Decreased quality of life—mediated by such variables as adherence to treatment, surveillance, immune function, and smoking—may have an impact on treatment and disease outcomes.
- Data on quality of life have an impact on treatment choice and are needed to inform patient and provider decision-making.
- Patients increasingly expect that their quality of life will be considered in their plan of care. This expectation has an impact on their satisfaction with care.
- Non-congruity among patient, provider, and family assessments of the patient's quality of life can lead to difficulties in decision-making about treatment choices.
- Initial quality of life is a predictor of later quality of life and survival, making it critical to continuously monitor quality of life.

Priority 2: *Develop and assess treatments—medical and surgical, complementary and alternative, psychosocial, and behavioral—that will improve survival, optimize health-related quality-of-life outcomes, increase health status, and promote healthy behavior in persons who have or are at risk for kidney and bladder cancers.*

Possible topics for these studies include:

- Quality of life as a primary endpoint in existing clinical trials,
- Psychosocial variables related to immune function,
- Compliance with treatment and surveillance,

- Smoking cessation,
- Symptom management related to sexual function, urinary function, fatigue, pain, depression and anxiety, and sleep,
- Fear of recurrence, and
- Provider and patient relationship.

Rationale

- Evidence-based interventions are needed to address disease- or treatment-related side effects (e.g., fatigue, sexual dysfunction, urinary dysfunction, depression, and anxiety).
- Because smoking is a risk factor for kidney and bladder cancers, smoking cessation and relapse prevention should be studied in patients who continue to smoke or have recently quit, as well as in populations at risk for disease development or recurrence.

Resources

- Develop and verify reliable, valid instruments to measure disease- and treatment-specific HRQOL outcomes.
- Actively involve advocates and survivors in efforts to develop instruments, identify key issues relevant to their HRQOL, and assist in the implementation and delivery of evidence-based interventions.
- Train physicians, nurses, and other providers in quality-of-life assessment and measurement and psychosocial and behavioral interventions.
- Establish multi-institutional, cross-disciplinary collaborations and networks.
- Develop and incorporate new technologies to facilitate data collection.
- Extend the support offered by kidney cancer advocacy groups to the bladder cancer arena.

Cancer Control Subgroup 4C—Health Care Delivery and Communication

Co-Chairs: *Harry Herr, M.D., F.A.C.S., Chan Leng Hunter, Richard Hara, Ph.D.*

Participants:

Linda Aldoory	Kelli Marciel
Robyn Anderson	Sarah Moody-Thomas
Donna Berry	Daniel Petrylak
Barbara Given	John Stein

BACKGROUND—STATE OF THE SCIENCE

Health care delivery and communication are important, yet often neglected, issues in the study of bladder and kidney cancers. Lack of communication with and suboptimal quality of care delivered to underserved populations often result in disparate outcomes. Examples of disparities related to kidney and bladder cancers include the differences in incidence of these diseases by geographic region and the differences in mortality rates by gender and race. In addition, there exist disparities in age of death between patients with bladder or kidney cancer. Research that addresses these disparities in terms of health care delivery and communication would ultimately improve quality of life and patient outcomes and reduce disparities in treatment.

Both kidney and bladder cancers are chronic diseases that primarily affect an elderly but increasingly healthy population. The incidence of both bladder and kidney cancers is expected to increase as the U.S. population ages. Currently, the median age for kidney cancer diagnosis is 60 years; for bladder cancer diagnosis, 72 years. On average, patients with kidney cancer die a decade earlier than those with bladder cancer, reflecting the younger age at diagnosis and the greater lethality of kidney cancer compared with bladder cancer.

Disparities exist among the elderly who develop bladder cancer. The majority of patients with bladder cancer are aged over 65; 35 percent, over 75; and 20 percent, over 80. People aged 80 to 85 are twice as likely to develop bladder cancer as their counterparts aged 60 to 65. Additionally, those over 80 are twice as likely to die from bladder cancer as those aged 60 to 65. This may reflect an increasing incidence of bladder cancer with age, a more malignant form of the disease in the elderly, or less aggressive treatment attributable to age and co-morbidities.

Bladder cancer is diagnosed later in women than in men. Particularly in women, hematuria and dysuria are often attributed to benign conditions, leading to clinically important delays in diagnosis of an underlying malignancy. In women, diagnosis of bladder cancer commonly occurs 9 months after the appearance of initial symptoms, whereas the disease typically is diagnosed in men within 3 to 6 months of the appearance of initial

symptoms. Women are nearly 50 percent more likely to die from bladder cancer than men, although men are diagnosed with the disease nearly three times as frequently. Since 1995, although death rates for bladder cancer have declined overall, death rates among white women have remained steady. Coincidentally, smoking is increasing only in this population subgroup. Very few population-focused studies address these issues.

Racial disparities are also evident. Black males have a lower incidence of bladder cancer but higher mortality from the disease than their white counterparts. Incidence of kidney cancer is rising more quickly in the black population for both males and females, and the mortality rate from kidney cancer is rising more rapidly among blacks than among whites.

Earlier evaluation of hematuria in all populations may lead not only to earlier diagnosis of bladder cancer but also to early diagnosis of kidney cancer. However, this outcome is dependent on increased awareness of both diseases as well as on the availability of adequate resources to implement standards of care for early diagnosis of kidney and bladder cancers. Few patients realize that bladder and kidney cancers are linked to smoking and that kidney cancer is linked to obesity and hypertension. Inconsistent access to specialty care—resulting from knowledge deficits among non-cancer specialists, care providers, and patients—is a barrier to quality of care.

Because both kidney and bladder cancers have a high rate of recurrence, these diseases should be regarded as lifelong conditions. As such, they require surveillance over an extended period of time. This ideally is a joint venture between the patient and health care provider. As patients move along the disease continuum, grow older, or otherwise change over time, their care and communication needs also change. Basic research to define how these needs change will serve as a foundation for developing communication products to improve the accuracy, clarity, and timeliness of cancer care decision making, which the National Cancer Institute has identified as a key priority in improving quality of care.

Advocacy groups may be key in reducing gaps and barriers between standards of practice and care received. However, a strong patient advocacy group for bladder cancer does not currently exist. Support services for kidney advocacy need to be enhanced. The involvement of advocates in decision-making bodies such as advisory groups, councils, and research teams will ultimately help to close the gap between consumers and health care providers. Future research can explore whether such involvement is effective and feasible.

Priority 1: *Identify and explore the gaps and barriers that lead to disparate outcomes for patients with kidney and bladder cancer patients who receive care that does not reflect standards of practice.*

These gaps and barriers include:

- Hematuria screening practices,
- Treatment delays,
- Lack of access to clinical trials,
- Less aggressive or potentially curative treatment of the elderly,

- Lack of understanding that smoking is related to bladder and kidney cancer, especially among women, and
- Differences in mortality by gender, race, ethnicity, and geographic location.

Rationale

- Bladder and kidney cancers are chronic diseases in an aging healthy population.
- Women are diagnosed with bladder cancer 6 to 9 months later than men, on average, and have a disproportionately higher death rate that appears to be correlated with delay in receiving treatment.
- People aged 80 to 85 are four times more likely to develop bladder cancer and twice as likely to die from it than their counterparts aged 65 to 69.
- Black males have a higher mortality rate for both bladder and kidney cancers despite lower incidence of both diseases.
- Incidence and mortality rates for kidney cancer are increasing among blacks more rapidly than among whites.

Resources

- Examine and analyze SEER (Surveillance, Epidemiology, and End Results Program)-Medicare linked databases to understand practice patterns that may create gaps and barriers in bladder and kidney cancer patient care.
- Enhance optimal treatment by creating a provider-patient partnership through the use of multimedia modalities and collaborative community outreach activities, especially utilizing centers of clinical research that specialize in kidney and bladder cancers.
- Reduce the regulatory barriers that impede the identification of patients at risk and their health conditions. These data currently are restricted by protection of human subject requirements.
- Target studies at identified populations with disparate outcomes to determine why barriers exist and to develop strategies to eliminate the gaps.

Appendix C

Kidney/Bladder Cancers PRG
Membership Roster

Kidney/Bladder Cancers PRG Membership Roster

Peter A. Jones, Ph.D.
PRG Co-Chair
University of Southern California

Nicholas J. Vogelzang, M.D.
PRG Co-Chair
University of Chicago

Jorge Gomez, M.D., Ph.D.
PRG Executive Director
National Cancer Institute

Michael B. Atkins, M.D.
Beth Israel Deaconess Medical Center

Arie Belldegrun, M.D.
School of Medicine, UCLA

Donna Berry, Ph.D., R.N., A.O.C.N.
University of Washington

Ronald M. Bukowski, M.D.
Cleveland Clinic Taussig Cancer Center

Wong-Ho Chow, Ph.D.
National Cancer Institute

Carlos Cordon-Cardo, M.D., Ph.D.
Memorial Sloan-Kettering Cancer Center

Richard J. Cote, M.D.
Norris Comprehensive Cancer Center

Janice P. Dutcher, M.D.
New York Medical College

H. Barton Grossman, M.D.
M.D. Anderson Cancer Center

Harry W. Herr, M.D., F.A.C.S.
Memorial Sloan-Kettering Cancer Center

Othon Iliopoulos, M.D.
Harvard Medical School
Massachusetts General Hospital

Margaret Knowles, Ph.D.
Imperial Cancer Research Fund
Clinical Centre at Leeds

Susan Leigh, B.S.N., R.N.
National Coalition for
Cancer Survivorship

W. Marston Linehan, M.D.
National Cancer Institute

Edward M. Messing, M.D.
University of Rochester Medical Center

Robert J. Motzer, M.D.
Memorial Sloan-Kettering Cancer Center

Cherie Nichols, M.B.A.
National Cancer Institute

Martin I. Resnick, M.D.
Case Western Reserve University

Raymond Ruddon, M.D., Ph.D.
Johnson & Johnson

Walter Stadler, M.D.
University of Chicago

Bin Tean Teh, M.D., Ph.D.
Van Andel Research Institute

Mimi Yu, Ph.D.
Norris Comprehensive Cancer Center

Anthony L. Zietman, M.D., M.R.C.P., F.R.C.R.
Harvard Medical School
Massachusetts General Hospital

Appendix D

Kidney/Bladder Cancers PRG
Roundtable Participants Roster

Kidney/Bladder Cancers PRG Roundtable Participants Roster

Peter A. Jones, Ph.D.
PRG Co-Chair
Norris Comprehensive Cancer Center

Nicholas J. Vogelzang, M.D.
PRG Co-Chair
University of Chicago

Jorge Gomez, M.D., Ph.D.
PRG Executive Director
National Cancer Institute

Linda Aldoory, Ph.D.
University of Maryland

Robyn Andersen, Ph.D**.**
Fred Hutchinson Cancer Research Center

Michael B. Atkins, M.D.
Beth Israel Deaconess Medical Center

Natasha Aziz, Ph.D.
EOS Biotechnology

Dean Bajorin, M.D.
Memorial Sloan-Kettering Cancer Center

Karen Basen-Engquist, Ph.D.
M.D. Anderson Cancer Center

Arie Belldegrun, M.D.
School of Medicine, UCLA

William Benedict, M.D.
M.D. Anderson Cancer Center

Donna Berry, Ph.D., R.N., A.O.C.N.
University of Washington

Bernard Bochner, M.D.
Memorial Sloan-Kettering Cancer Center

Susan Borghoff, Ph.D.
CIIT Centers for Health Research

Ronald M. Bukowski, M.D.
Cleveland Clinic Taussig Cancer Center

Paul Cairns, Ph.D.
Fox Chase Cancer Center

Kevin Callahan, Ph.D.
National Cancer Institute

Peter Carroll, M.D.
University of California, San Francisco

Wong-Ho Chow, Ph.D.
National Cancer Institute

Samuel Cohen, M.D., Ph.D.
University of Nebraska Medical Center

Deborah Collyar
PAIR: Patient Advocates In Research

Carlos Cordon-Cardo, M.D., Ph.D.
Memorial Sloan-Kettering Cancer Center

James Corrigan, Ph.D.
National Cancer Institute

Richard J. Cote, M.D.
Norris Comprehensive Cancer Center

Mellar Davis, M.D.
Cleveland Clinic Foundation

Jean deKernion, M.D.
University of California, Los Angeles

Carl Dixon, J.D.
Kidney Cancer Association

S. Machele Donat, M.D.
Memorial Sloan-Kettering Cancer Center

Robert Dreicer, M.D.
Cleveland Clinic Foundation

Michael Droller, M.D.
Mount Sinai Medical Center

Deborah Duran, Ph.D.
National Cancer Institute

Janice P. Dutcher, M.D.
Our Lady of Mercy Cancer Center
New York Medical College

Wayland Eppard
NCCTG—Mayo Clinic

Robert Figlin, M.D.
University of California, Los Angeles
School of Medicine

James Finke, Ph.D.
Cleveland Clinic Foundation

Robert Flanigan, M.D.
Loyola University Medical Center

Andrew Freedman, Ph.D.
National Cancer Institute

Marlene Frost, Ph.D.
Mayo Clinic

Daniel George, M.D.
Dana-Farber Cancer Institute

Robert Getzenberg, Ph.D.
Shadyside Medical Center

Barbara Given, Ph.D.
Michigan State University

Barry Gold, Ph.D.
University of Nebraska Medical Center

Mary Gospodarowicz, M.D.
Princess Margaret Hospital

Joyce Graff
VHL Family Alliance

Rosemary Green
Kidney Cancer Association

Susan Groshen, Ph.D.
Norris Comprehensive Cancer Center

H. Barton Grossman, M.D.
M.D. Anderson Cancer Center

Richard Hara, Ph.D.
Memorial Sloan-Kettering Cancer Center

Adrian Harris
University of Oxford

Mary Ellen Haisfield-Wolfe, M.S., R.N.
Johns Hopkins Hospital

David Hein, Ph.D.
University of Louisville School of Medicine

James Herman, M.D.
Johns Hopkins University

Harry W. Herr, M.D., F.A.C.S.
Memorial Sloan-Kettering Cancer Center

Chan Leng Hunter
Kidney Cancer Association

James Hunter
Kidney Cancer Association

Othon Iliopoulos, M.D.
Harvard Medical School

Karl Kelsey, M.D.
Harvard University

Margaret Knowles, Ph.D.
Imperial Cancer Research Fund
Clinical Centre at Leeds

Levy Kopelovich, Ph.D.
National Cancer Institute

Edmund Lattime, Ph.D.
Robert Wood Johnson Medical School
and Cancer Institute of New Jersey

John Lazo, Ph.D.
University of Pittsburgh School of Medicine

Susan Leigh, B.S.N., R.N.
National Coalition for Cancer Survivorship

Jonathan Li, Ph.D.
University of Kansas Medical Center

W. Marston Linehan, M.D.
National Cancer Institute

Deborah Lubeck, Ph.D.
University of California, San Francisco

Judith Manola
Dana-Farber Cancer Institute

Kelli Marciel
National Cancer Institute

Fray Marshall, M.D.
Emory University

David McConkey, Ph.D.
M.D. Anderson Cancer Center

Edward M. Messing, M.D.
University of Rochester Medical Center

James Mier
Beth Israel Deaconess Medical Center

Judith Mietz, Ph.D.
National Cancer Institute

Sarah Moody-Thomas, Ph.D.
Louisiana State University

Robert J. Motzer, M.D.
Memorial Sloan-Kettering Cancer Center

David Nanus, M.D.
Cornell University

Cherie Nichols, M.B.A.
National Cancer Institute

Perry Nisen, M.D., Ph.D.
Abbott Laboratories

Augusto Ochoa, M.D.
Louisiana State University

Michael O'Donnell, M.D.
University of Iowa Hospitals and Clinics

Geraldine Padilla, Ph.D.
University of California, San Francisco

Robert Parker, Sc.D.
Beth Israel Deaconess Medical Center

Howard Parnes, M.D.
National Cancer Institute

Lorna Patrick
National Cancer Institute

David Penson, M.D.
University of Washington
School of Medicine

Daniel Petrylak, M.D.
Columbia Presbyterian Medical Center

Raymond Petryshyn, Ph.D.
National Cancer Institute

Katherine Phillion
Patient Advocate

Alan Poland, M.D.
National Cancer Institute

Michael Redden, J.D.
Duke University

James Resau, Ph.D.
Van Andel Research Institute

Martin I. Resnick, M.D.
University Hospitals of Cleveland

Brian Rini, M.D.
University of California, San Francisco

Marsha Rosner, Ph.D.
University of Chicago

Ronald Ross, M.D.
University of Southern California

Julia Rowland, Ph.D.
National Cancer Institute

Raymond Ruddon, M.D., Ph.D.
Johnson & Johnson

Peter Scardino, M.D.
Memorial Sloan-Kettering Cancer Center

Mark Schoenberg, M.D.
John Hopkins Medical Institutions

Charles Scott, Ph.D.
American College of Radiology

Judith Shell, Ph.D.
Osceola Cancer Center

Matthew Sherman, M.D.
Wyeth/Genetics Institute

Debra Silverman, Ph.D.
National Cancer Institute

Eila Skinner, M.D.
Keck School of Medicine

Paul Skipper, Ph.D.
Massachusetts Institute of Technology

Frank Solano
Wyndam Hotels and Resorts

Walter Stadler, M.D.
University of Chicago

John Stein, M.D.
Norris Comprehensive Cancer Center

David Swanson, M.D.
M.D. Anderson Cancer Center

Bin Tean Teh, M.D., Ph.D.
Van Andel Research Institute

Dan Theodorescu, M.D., Ph.D.
University of Virginia

James Thomas, M.D.
University of Wisconsin
Hospital and Clinics

Annabelle Uy, M.S.
National Cancer Institute

Jaye Viner, M.D.
National Cancer Institute

Frederic Waldman, M.D., Ph.D.
University of California, San Francisco

Craig Webb, Ph.D.
Van Andel Research Institute

John Wei, M.D.
University of Michigan

Bart Williams, Ph.D.
Van Andel Research Institute

Robert Wiltrout, Ph.D.
National Cancer Institute

Xifeng Wu, M.D., Ph.D.
M.D. Anderson Cancer Center

Xue-Ru Wu, Ph.D.
New York University School of Medicine

James Yang, M.D.
National Cancer Institute

Mimi Yu, Ph.D.
Norris Comprehensive Cancer Center

Berton Zbar, M.D.
National Cancer Institute

Zhong Zhong, Ph.D.
Cell and Molecular Technologies, Inc.

Anthony L. Zietman, M.D., M.R.C.P., F.R.C.R.
Harvard Medical School
Massachusetts General Hospital

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