Concepts for Banking Tissue in Urologic Oncology— The International Bladder Cancer Bank

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Advances in understanding cancer at the molecular level have identified numerous genomic and proteomic alterations associated with cancer development and progression. The efforts in evaluating these putative biomarkers in clinical studies of patients with cancer are increasing, reflecting the great potential of molecular phenotyping to improve screening, diagnosis, and treatment (1). The translation of new markers to the clinic is often hampered by the fact that they are typically evaluated in single institutional settings, making comparison with other markers difficult due to differences in study design, experimental methods, and data analysis. There are no well-recognized guides that the urologic researcher can use to develop marker studies.

There is a clinical need for markers that will identify patients with a high risk for progression or predict tumor response to specific therapeutic regimens. Eighty percent of patients presenting with bladder cancer have superficial tumors that do not invade the muscular layer of the bladder wall and generally have a good prognosis (2). Nevertheless, 25% to 30% of these patients will eventually experience progression of their tumor into the muscle and 50% of them will die of their disease (3), translating into a mortality rate of 4 cases per 100,000 total population per year (4). Despite the description of high-risk and low-risk groups in superficial bladder cancer, clinical or pathologic prognostic factors cannot predict progression on an individual basis (5). Validated markers could enable patient-specific treatment decisions (6).

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The measurement of p53 is an example of the difficulty in marker development. Research on p53 in bladder cancer began with its discovery more than two decades ago (7, 8) and includes the original studies of its biological role in bladder cancer (9, 10), continuing to studies that examined the use of p53 to predict bladder cancer recurrence and progression (11–14) to the current use of p53 status to select patients for treatment within clinical trials (15). Several studies have shown that p53 alterations are present in a substantial proportion of bladder tumors. However, despite promising data suggesting that p53 expression by immunohistochemical analysis is a useful marker for bladder cancer (16, 17), the evaluation of this marker has been hampered by differences in study design, assay, and analysis (18, 19).

The Bladder Cancer Marker Network, under the sponsorship of the National Cancer Institute, was formed to develop and assess biomarkers for diagnostic and prognostic use. This core of investigators initiated the first International Workshops on Diagnostic and Prognostic Markers in Bladder Cancer (20) resulting in the formation of the International Bladder Cancer Network (http://www.uni-essen.de/urologie/ibcn/index.html). This group defined four phases through which markers are developed.

> Phase 1: Assay development and evaluation of clinical prevalence
> Phase 2: Evaluation studies for clinical utility
> Phase 3: Prospective confirmation and validation studies
> Phase 4: Application studies, technology transfer, and quality control

Phase 1 and 2 studies are often done at single institutions that can rapidly develop laboratory techniques and obtain preliminary information regarding the potential of new markers. However, it is rare that a single institution has the resources to achieve the required subject diversity or the large number of specimens to complete properly designed phase 3 or 4 studies. In addition, a multi-institutional approach offers advantages even in the initial phases of marker discovery, because samples obtained from multiple sources may help identify causes of variability. The essential interactions required by phase 3 and 4 evaluations and the need to gain access to greater resources are clearly facilitated by collaborative networks. Tumor banks and procedures are in place in many institutions, and there are several important existing networks and collaborations (21, 22) that have established procedures for data and tissue collection. However, only few groups have established general methodologic principles as guidelines and use discrete phases of marker development as an integral part of their collaboration.

The formation of an International Bladder Cancer Bank (IBCB) was a logical but an ambitious proposal arising from the International Workshops on Diagnostic and Prognostic Markers in Bladder Cancer held in Barcelona and Trento. The IBCB is designed to (*a*) obtain access to tumor specimens from a large number of patients with bladder cancer, including rare entities;

(*b*) standardize methods of tissue procurement and biomarker assay performance; (*c*) establish consistent methods of obtaining and coding patient information, end point definitions, and data management; and (*d*) serve as a resource for participating institutions to evaluate the biological and prognostic significance of potential "markers" in bladder cancer development and progression. It will coordinate and exploit the capabilities and resources offered by the current participating institutions while recruiting other new institutions to expand the resource and knowledge base, and it will complement efforts of cooperative groups by focusing on bladder cancer and collecting specimens from patients who are treated on standard regimens but are not part of large clinical trials.

Tissue and data procurement are the fundamental components in this infrastructure, whereas execution of the biomarker assays—analysis and interpretation—is the core of any marker study. A detailed description of the IBCB was introduced recently (23). In brief, samples will be identified and stored at each participating institution using agreed-upon protocols and procedures. Two basic models are used to process tissue and perform assays in the multicenter setting. Identified samples are either transferred to a core facility for analysis or analyzed locally with predefined standardized protocols and techniques. For statistical analysis, results are transferred to a study core center. In addition, the use of tissue microarrays can be used to great advantage, as it allows tissue to be collected centrally with minimal loss of the tissue at the contributing institution (24). Common software will facilitate local data management of a standard, minimal set of patient and pathologic information and allow transfer to a central database. All contributing centers will have an overview of the available tissue within the bank and some of their clinical and pathologic characteristics. In summary, the advantages of this infrastructure include consistency among participating institutions regarding procurement and processing of specimens and collecting and managing the associated information. The IBCB will provide prospectively collected data sets with long-term follow-up that are linked to specimens. This will simplify the process of finding collaborating partners as well as provide accurate prediction of the number of available specimens to facilitate study design. As a result, studies can be completed much sooner than would be possible with a conventional prospective study in which follow-up begins at the time of specimen acquisition. For this multi-institutional approach to marker development and its supporting infrastructure, there is a recognized need to combine knowledge from different scientific fields, such as computer technology, statistics, epidemiology, pathology, ethics, oncology, and urology.

The process to convert this concept into practice has already begun. The International Bladder Cancer Network established a collaboration with the National Cancer Institute Specialized Program of Research Excellence program and the Genitourinary Specialized Program of Research Excellence in Bladder Cancer at the University of Texas M.D. Anderson Cancer Center to create an international multi-institutional tissue resource and database by sharing bladder tumor specimens and establishing tissue microarrays to conduct highly powered multivariate biomarker studies to improve our understanding of the biology of bladder cancer. These efforts will enhance the development of more effective therapy. The IBCB/National Cancer Institute consortium will address pertinent translational research questions that cannot be adequately addressed by a single research institution. These investigations will foster the integration of new tools and strategies that will help standardize their use in pathologic and clinical applications.

The recent publication of the multisector report entitled "National Biospecimen Network Blueprint" reflects a growing consensus on the need to establish a biorepository system that will provide investigators with the highest-quality biospecimens that are uniformly collected, stored, and annotated. The National Biospecimen Network Blueprint also includes a bioinformatics platform that would allow broad access to data and data analysis tools to the scientific community. This blueprint offers the opportunity to establish standardized operating procedures for specimen processing that would minimize preanalytic variability, facilitating the comparison of biomarker data derived from the analysis of specimens from different institutions. The development of an IBCB within the context of the National Biospecimen Network system may enhance the ability of public and private researchers to access many high-quality and well-annotated bladder cancer specimens without intellectual property restrictions.

Modern genomics and proteomics are yielding an ever-increasing number of potential markers. The comprehensive infrastructure of the IBCB has the potential to be an effective resource that addresses the multiple methodologic difficulties that occur during all phases of marker development. Multi-institutional and interdisciplinary networks with a robust infrastructure, such as the proposed IBCB, will provide the resources enabling the evaluation of novel markers in an accurate and efficient fashion.

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Clin Cancer Res 2005;11:413-415.

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