1. INTRODUCTION

Even as we hail the arrival of the 21st century, we must realize that prostate cancer and prostate cancer metastasis will soon threaten a greater percentage of the US population than ever before (43). Prostate cancer and all its associated costs will be on the rise in the next decades, impacting the health industry and the productivity of the general economy as the baby boomers of World War II add to the general trends of the aging population. Faced with this uncertain future, the NIH and Congress have increased funding for prostate cancer research in recent years in the expectation that researchers will conduct translational research from bench to bedside. The opportunity exists to reduce the incidence of prostatic diseases through innovative prevention trials, to delay disease progression, and to treat men with hormone refractory, recurrent, and metastatic lymph node or bone diseases by specific hormonal, radiation, and chemotherapeutic strategies with clearly defined molecular targets. Future endeavors to identify additional critical molecular targets and develop therapeutic approaches exploiting these targets and processes have begun. Our intentions here are to review and summarize:

1. Our past research developing a molecular understanding of stromal and epithelial interaction in prostate growth and development.
2. The establishment of human prostate cancer progression models addressing the reciprocal roles of stromal and epithelial interaction and the expression by tumor epithelium of androgen independent and metastatic characteristics in host animals.
3. The use of human prostate cancer models to screen for therapeutic agents that can block local tumor growth and its distant metastases.
4. The dissection of genetic and phenotypic changes of prostate cancer cells during disease progression, and the categorization and validation of novel biomarkers to predict clinical prostate cancer development and disease progression, and
5. The designing of Phase I clinical trials, based on preclinical animal studies, to translate the findings from bench to the bedside for therapeutic targeting of men who have hormone-refractory primary prostate cancer and metastases to lymph nodes and skeleton.
2. STROMAL-EPITHELIAL INTERACTION IN PROSTATE DEVELOPMENT AND PROSTATE CANCER PROGRESSION

Reciprocal cellular interactions between stroma and epithelium are involved in fetal prostate development, postnatal prostate growth and maturation, maintenance of differentiation status, hormonal responsiveness, and the aging and senescence of the prostate gland in adulthood (16,21). During neoplastic progression, stromal-epithelial interactions have been shown to accelerate local tumor growth (11,15) and distant metastasis (67), and increase the genetic instability of the tumor epithelium (70) and its subsequent androgen independent progression (28,66,67). The intricate intercellular communication between stromal and epithelial cells involves cell-cell, cell-insoluble extracellular matrices (ECMs), cell-soluble factors, and cell-androgen receptor-mediated processes—all of which are the subject of intensive investigation. To understand the molecular pathways that may affect intercellular communication and subsequent intracellular signaling, we must first identify key cell types, soluble factors, and insoluble ECMs participating in these communication processes between tumor epithelium and stroma. The next step involves identifying key metabolic and signaling pathways that may mediate the functions of regulatory molecules in tumor epithelium in a rate-limiting manner. Obviously, these are complex, interactive, and often redundant pathways whose regulation is highly cell-background and cell-microenvironment interaction dependent. The challenge is to determine how the cells mediate, integrate, interpret, and organize intercellular communications, and how the signals ultimately dictate the structure, function, and behavior of the cells. The reciprocal nature of the stromal-epithelial interaction can be clearly seen in pathologic specimens obtained from primary prostate tumors and in prostate tumors metastasized to bone (Fig. 1: arrows represent areas of stromal-epithelial interaction).

Three important features of stromal-epithelial interactions are noteworthy. First, whereas androgen receptor (AR), a key nuclear transcription factor in the stromal cells, is responsible for regulating fetal prostate development (19,22), AR in the epithelium could assume the regulatory role and determine the ultimate growth and differentiation potential of the adult normal and tumor epithelium (17,37). Experimental evidence using cocultured human BPH-derived stromal and epithelial cells indicates that the expression of AR, PSA and 5α-reductase in the epithelial cells relies on the inductive influence of neighboring stromal cells (6,32). Similarly, in cocultured rat prostate epithelial and fibroblast cells, the androgen responsiveness of prostate epithelial cells can be conferred by the presence of fibroblastic cells (12). However, studies using transplantable PC-82 human prostate cancer xenografts in athymic mice clearly indicated that once prostate cancer cells acquire the ability to grow autonomously (as exhibited by their ability to be passaged and grown in competent hosts), AR in the epithelium rather than the stroma is responsible for controlling the androgen responsiveness of prostate tumors in vivo (25).

Second, genetic changes in the tumor epithelium are required, but are not sufficient in themselves to drive the metastatic cascade. Using a human prostate cancer epithelial cell line, LNCaP as a model, we demonstrated that despite its extensive chromosomal changes, this cell line remains nontumorigenic and nonmetastatic in castrated hosts (67). By interacting in vivo with prostate or bone fibroblasts followed by in vitro cell cul-