

To my beloved parents, Debatosh and Swapna Ghosh, had you not been by my side,

This work would not have been possible.

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PREFACE

According to the American Cancer Society, an estimated 218,890 new cases of prostate cancer will be diagnosed in United States in 2007. Prostate cancer remains the second leading cause of cancer related deaths in men in the United States, lung cancer being responsible for most number of cancer deaths. Over the years, a tremendous amount of research effort has resulted in groundbreaking discoveries, which improved our understanding of this disease. These advances of the scientific community have identified molecular targets for rational drug design, which can potentially lead to improved clinical management of prostate cancer. Unfortunately, in spite of all available treatment options, the fact remains that prostate cancer reappears after initially regressing following therapeutic intervention. This stage of the cancer, referred to as Androgen Independent Prostate Cancer (AIPC), is untreatable and ultimately metastasizes to a number of distant organs, resulting in morbidity and mortality. The major sites of prostate cancer metastasis are bone, lung, lymph nodes and liver. The molecular events driving this progression and metastasis of prostate cancer is not yet fully understood. In this project, we studied the role of stathmin, a microtubule destabilizing protein, in the progression of prostate cancer. Stathmin is upregulated in a variety of human malignancies like leukemia, breast and ovarian cancer. Previous reports suggest that stathmin expression is elevated in poorly differentiated prostate cancer. We have shown that increased stathmin expression correlates with high Gleason pattern in human prostate cancer. We have also established that androgens and anti-androgen treatment can modulate stathmin phosphorylation – a mechanism that can potentially drive progression

to AIPC. Furthermore, we have also demonstrated a role for stathmin in epithelial cell homeostasis. Transforming growth factor-beta (TGF β) is one of the most enigmatic molecules in the context of normal development and tumorigenesis, acting as growth inhibitor in normal cells and growth stimulator in cancer cells. We have shown that stathmin can modulate TGF β signaling to induce epithelial to mesenchymal transition in prostate cancer cells – a mechanism that makes the cancer cells more invasive, eventually leading to metastasis. Hence, this project establishes the regulation of stathmin expression and activity as a novel mechanism for prostate cancer progression to a more aggressive phenotype.

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LIST OF ABBREVIATIONS

AR.....	Androgen Receptor
AD.....	Androgen Dependent
AI.....	Androgen Independent
AIPC.....	Androgen Independent Prostate Cancer
BPH.....	Benign Prostatic Hyperplasia
CK.....	Cytokeratin
CHX.....	Cycloheximide
DHT.....	Dihydrotestosterone
EMT.....	Epithelial-to-mesenchymal Transition
HGPIN.....	High-grade Prostatic Intraepithelial Neoplasia
HPE.....	Human Prostate Epithelial (Cells)
LGPIN.....	Low-grade Prostatic Intraepithelial Neoplasia
LUTS.....	Lower Urinary Tract Symptoms
OHF.....	Hydroxy-flutamide
PB.....	Probasin
PCa.....	Prostate Cancer
PIN.....	Prostatic Intraepithelial Neoplasia
PSA.....	Prostate Specific Antigen
RTKs.....	Receptor Tyrosine Kinases
TGF β	Transforming Growth Factor-beta
TMA.....	Tissue Microarray