Preface

PROSTATE CANCER RESEARCH HAS ACCELERATED over the past decade because of our better understanding of the human genome, more sophisticated model systems, renewed and improved efforts in targeting the androgen receptor, and the introduction of next-generation sequencing technologies coupled with computational methods, which provide new insights into prostate cancer disease progression. In particular, genomic research has begun to define subclasses of prostate cancer, including ETS-overexpressing tumors due to common gene fusions, SPOP and IDH mutated tumors, and androgen-indifferent prostate cancer (e.g., neuroendocrine or FGFR mutated tumors) that arises after therapy.

Clinically, there have been vast improvements owing to newer imaging modalities, including high-resolution MRI and molecular imaging, as well as the readout of important clinical trials in the setting of both localized and advanced cancer. Numerous studies have focused on the epidemiology and clinical outcome of localized disease to better assess risks of treatment as well as lack of treatment. In the setting of advanced prostate cancer, important results using second-generation androgen-deprivation therapy (ADT), PARP inhibitors, and taxanes have indicated prolonged quality of life and survival for men with castration-resistant prostate cancer (CRPC). In addition, the emerging understanding that up to 10%–15% of men with advanced prostate cancer have defects in DNA repair genes (most commonly *BRCA1/2*, *ATM*, or mismatch repair genes) has led the way to recommendations for routine genomic and genetic testing of men with advanced prostate cancer. However, unlike melanoma, lung, and bladder cancer, prostate cancer has not responded well to immune modulation with checkpoint inhibitors. Thus, greater understanding of how to modulate the tumor microenvironment is clearly needed.

This wide range of exciting developments is covered in the chapters that make up this book, which are written by established experts in the field. To provide a general background in prostate cancer biology, we have included chapters that discuss the comparative anatomy and histology of the mouse and human prostate (Ittmann), prostate organogenesis (Francis and Swain), and the histopathology and staging of prostate cancer (Humphrey). The origins of prostate cancer are covered in chapters on stem cells and cancer stem cells (Li and Shen) and pre-neoplastic lesions (Trabzonlu et al.). Chapters on prostate cancer epidemiology (Pernar et al.) and disparities research (Rebbeck) help define the extent of disease and ethnic considerations for cancer aggressiveness and outcomes. Prostate cancer risk is covered in a review of the genetics of prostate cancer (Dias et al.), which includes discussions on common but low-penetrance as well as rare high-penetrance germline variants (e.g., *HOXB13*).

Several chapters on the molecular analysis of prostate cancer provide up-to-date reviews of prostate cancer genomics (Rubin and Demichelis), transcriptional regulation (Labbé and Brown), and epigenetics (Yegnasubramanian et al.). We also include a chapter describing the unusual features of prostate cancer metabolism (Zadra and Loda). These new molecular insights have been complemented by the establishment of novel genetically engineered mouse models (Arriaga and Abate-Shen), as well as xenografts, organoids, and other explant models (Risbridger et al.), which have provided the basis for preclinical studies (Chen and Pandolfi).

The importance of androgen receptor signaling remains paramount in consideration of disease progression. Chapters are devoted to the androgen receptor (Centenera et al.) and androgen signaling (Dai et al.), providing insights into basic biology as well as novel therapeutic approaches. A chapter on chemoprevention explores lessons learned since the prostate cancer screening trial (Rivero et al.). Recent clinical trials using PARP inhibitors and emerging genomic data reveal the increasing

importance of the DNA damage response (Schiewer and Knudsen). Improved approaches for clinical and molecular imaging are helping to define both localized and advanced disease (Miller et al.). Furthermore, the identification of biomarkers for localized prostate cancer is of fundamental importance for distinguishing indolent from aggressive disease (Udager and Tomlins).

The emergence of advanced prostate cancer and its treatment is a central topic of investigation, and thus we include novel perspectives for the origins of metastasis (La Manna et al.). The emergence of treatment-related neuroendocrine and other androgen-indifferent variants is also covered (Puca et al.). Moreover, the tumor microenvironment is a critical partner for tumor progression (Levesque and Nelson), and potentially represents a major obstacle for immunotherapy (Venturini and Drake). Finally, we provide a chapter on the development of therapies for advanced disease (Sumanasuriya and de Bono).

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