Even though the aetiology of cancer is complicated by several risk factors contributing to cancer genesis, the detection as well as treatment options for urogenital cancers (including prostate, bladder, and cervical cancers, and renal cell carcinoma) has been greatly modified in recent years with a number of nonsurgical interventions now generally available. Notwithstanding the great conceptual breakthroughs in our understanding about the nature as well causes of cancer, modifications of existing urologic techniques and discovery of novel powerful molecular therapeutic targets have contributed to additional improvement in patient outcome. Environmental factors such as smoking, drinking, food intake, viral (or other) infections, chronic inflammation and genetics are considered to be contributors in tumor progression. Many critical aspects of our understanding of these contributors that underlies the urogenital cancers has been described in this useful volume, split into seven key sections converging the unified research in the last few years.

Genetic and epigenetic factors contribute a significant fraction, producing inherited predispositions to the development of various types of urogenital cancers. In the early days, a failure to appreciate the hereditary aspects of urogenital cancer has delayed our knowledge and prevented obvious therapeutic advances in this area. Nonetheless, high-throughput gene expression analysis and next-generation sequencing (NGS) have been at the forefront of dissecting the genetic component, which has allowed the molecular analysis of the entire human genome in a matter of hours. These high throughput techniques have undoubtedly revolutionized our understanding of the disease and hold great promise for improving diagnostic and prognostic accuracy and may be now termed as Clinomics. To this effect, the first chapter (Section 1) of the book by Wenz *et al.* summarizes a genomic classifier based on expression of predefined biomarkers to identify prostate cancer patients who may benefit from aggressive therapy in order to "hit early and hit hard". Similarly, genomic scores could help us shortlisting patients who don't need any aggressive treatment and are great candidates for active surveillance (Ploussard *et al.*). Nonetheless, these studies and also a study summarised by Tosoian *et al.* reminded us about the tumor multiclonality and tumor heterogeneity and questioning if the genomic classifiers are not yet ready for the clinic. In an effort to provide solutions Trapani *et al.* in this section suggested that circulating tumor DNA analysis may allow a more comprehensive assessment of the molecular heterogeneity of the patient's prostate cancer, which also can lead to a personalized and combinatorial treatment with targeted therapies. Segovia *et al.* have very well reviewed the complexity of EZH2 as treatment target covering its mutations, different roles and acquired resistance in bladder cancers. Last but not least, Manley *et al.* in this section has covered the novel genomic studies of renal tumors with sarcomatoid variant histology. These results have demonstrated that progressive dedifferentiation is the source of the sarcomatoid elements in renal carcinomas. Overall, these genomic studies are paving pathways towards clinical translation. More thorough studies of medical histories, family backgrounds, tumor heterogeneity and environmental exposure are now being carefully compiled and reported to enhance our comprehension of genetics of urogenital cancer.

Amalgamation of molecular biology with disease pathology has already started to bear its fruits. Consequently, firmly establishing molecular pathology in oncology practices. Development of high throughput genomic, proteomic and epigenome technologies have gradually extended the molecular diagnostic armamentarium of urogenital cancers helping early cancer detection and tumors subclassification. To this effect, in Section II, Matin *et al.* summarized a miRNA panel for the diagnosis of aggressive prostate cancer. Intriguingly, the elementary research has identified several molecular mechanisms communal to multiple cancers, while others are very subjective and uniquely confined to only specific cancer. For example, epithelial mesenchymal transition (EMT) is one of the key steps for fibrogenesis and cancer metastasis and several studies including the one described by Kanlaya *et al.* in Section II of this book has tried to understand the molecular mechanisms underlying EMT and its regulation. In the process, oncometabolite fumarate has been discovered as a potent agent inducing epigenetic regulation of EMT in kidney cancers. Similarly, rapamycin complex 1 (mTORC1) pathway has been identified as a common pathway in several cancers controlling anabolic and catabolic processes with appropriate checkpoints and balances to maintain cellular homeostasis. Jones *et al.* in summarizes a novel molecular mechanism by which oncogenic MiT/TFE transcription factors support cell growth/proliferation of cancer cells through their transcriptional regulation of the upstream of mTORC1 activator, RagD. On the other hand, pathways such as Androgen receptor (AR) pathways are not confined but specific to prostate cancer genesis. Based on this, inhibiting the production of androgens by castration or their effects by using anti-AR agents are employed as a treatment of advanced prostate cancer. El-Sayed *et al.* commented on elevated fibroblast growth factor (FGF) and downstream mitogen-activated protein kinase (MAPK) pathway activity as the main cellular and molecular determinants driving underlying escape of AR-directed therapy, which is also connected to EMT. Recently efforts have been

made to understand the molecular mechanisms behind rare and more aggressive form of urogentital cancers. For example, Pinto and Monn *et al.* have molecularly dissected the role of N-myc and their disruption by aurora kinase A inhibitors as a potential therapeutic target for treatment of small cell prostate cancer. Monn *et al.* and Husain *et al.* have commented on the emerging molecular pathways involved in a rare form, micropapillary variant urothelial carcinoma. These studies undoubtedly suggest that molecular pathology has evolved into a novel focus of clinical pathology. A combination of traditional pathology and molecular pathology is bound to give rich dividend in term of guiding tumor therapy explicitly discussed in Section VII of the current book

Cancer metabolism is an emerging hallmark of cancer, capable of segregating urogenital cancer patients into a distinctive molecular classes with variable clinical outcome. The alterations in intracellular and extracellular metabolites that can accompany cancer-associated metabolic reprogramming have profound effects on oncogene expression, cellular differentiation, and the tumor microenvironment. Protein catabolic pathways via macro autophagy is considered a critical metabolic rewiring in cancer cells. In the section III, Barakat *et al.* have commented on the role of autophagy in the PTEN-loss driven mouse prostate cancer *in vivo* model. Similarly, Watt *et al.* and Blee *et al.* have commented on the role of altered lipid metabolism mostly via secretion of adipose tissue derived proteins called "adipokines", focussing on the effects of CCR3/CCL7-mediated cell migration. McDonald *et al.* summarized a study which followed bioinformatics analysis to shortlisted key regulators of prostate cancer cell metabolism, and identified peroxisome proliferator-activated receptor gamma co-activator 1 alpha (PGC1α) as a key transcriptional network regulator with a role in prostate cancer metastasis suppression. In addition to metabolism of macromolecules, drug metabolism pathways are attracting special attention to improve patient outcome in drug resistant tumors. Obst *et al.* have covered the metabolism of abiraterone, describing six previously unknown metabolites and their effect on both androgen metabolism and tumor progression in hope to improve the treatment for castration resistant prostate cancer (CRPC).

The need for a predictor of malignancy is universally recognized. While some of the previous sections of this book has covered the use of genomics, gene expression including that of miRNA and epigenetics signatures to be at the forefront of clinical translation of biomarker discovery for early diagnosis and prognosis of urogentital cancers, Section IV amess the role of cancer-derived exosomes in tumor progression and metastasis, including that in intracellular communications (Panfoli *et al.*) using mediators in the forms of protein, DNA and assorted RNA molecules. Once referred to as a "rubbish bag" to wrap up and dump out waste, the term "exosome" in also gaining a newfound glory as potential novel easily accessible urine based biomarker of cancer diagnosis and prognosis (covered by Liu *et al.*). As of this year a urine-based, non-invasive test has become commercially available for prostate cancer to improve discrimination between indolent and aggressive disease. On the other hand, Yamada *et al.* have brought back the value in understanding the role of content of exosomes and their potential clinical usage. Following which Vetterlein *et al.* summarized a study published in JAMA suggesting the pre-biopsy use of an exosome-derived gene expression signature to avoid unnecessary invasive procedures. The study described by Donovan *et al.* in this section goes beyond exosomes describing the use of liquid biopsy which relies on the isolation of cellular components found in post-digital rectal exam of total urine samples of prostate cancer patients. Despite the challenges, such as streamlining the collection process, identification of a stable urine normalization control, exosomes provide a novel platform for liquid biopsy for disease diagnosis and following disease progression and recurrence. Exosomes also hold exquisite promise in the delivery of therapeutics given their low immunogenicity, the environmental protection provided by their lipid bilayer membranes, and potential for targeting to cell types of interest. Blackwell *et al.* have summarised their efficiency in delivering siRNAs and chemotherapeutic agents into cancer cells.

Personalized medicine is the new Buzz word in the cancer world. As per Wikipedia personalized medicine, precision medicine, or theranostics is a medical model that separates people into different groups—with medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease. The section V thus provides the clinical nutshell of the above described sections mostly incorporating genetic stratification such as polygenic risk scores (Randazzo *et al.*) and/or mutation profiles (Ciccarese *et al.*), gene signature (Lombardi *et al.*—for response to radiotherapy) and MRI guided biopsy (Shoji *et al.*) to eventually direct patient's therapeutic regime for prostate cancer. Similarly, Roshan-Moniri *et al.* suggested an ERG directed therapy based on ERG and other oncogenic ETS family members expression profile as alternative or complimentary agents for the current chemotherapeutics to treat therapy resistant prostate cancer. Mennitto *et al.* focussed their comments on Urachal cancer, a rare and extremely aggressive

malignancy, suggesting its shared genomic alterations with colorectal carcinoma based on a case study with the presence of EGFR amplification. Matteucci *et al.* explored the role of the prostate-specific membrane antigen as both a diagnostic and therapeutic agent in renal cell carcinoma based on its expression dysregulation. Although these studies are highly encouraging, the results should be interpreted with pinch of salt for the validity of these signatures for the multiethnic populations.

The next phase of personalized medicine is to develop molecularly targeted therapy with minimal side-effects, which could not always be effective as hitting the target does not always mean the tumor will respond to the drug due to genomic complexity and/or tumor heterogeneity and/or tumor microenvironment. For the same reasons, the response to treatment may be temporary. The design of molecular inhibitors is inspired by the expression, function and structural determinants of the molecules within the tumor mileu. Following these classical primes and virtual drug design/screening has led to the development of small molecules that can inhibit the interaction between SPOP and its interacting partners in kidney cancers as summarized by Hwang *et al.* in Section VI of this book. Santoni *et al.* and Chipollini *et al.* pointed that differences in responsiveness to adjuvant and/or salvage therapy in multiple clinical trial can be streamlined if the molecular and biological features can be examined to select the patients. Similarly, Stratton *et al.* summarizes that a group of penile cancer patients with high PD-L1 expression in HPV negative tumors may be susceptible to novel checkpoint inhibiting therapies, also supporting this dual pathway to malignant transformation. Notwithstanding, molecular inhibitors have witnessed success as adjuvant therapy in recent years at least in experimental models. In addition, understanding the molecular mechanism of action of a drug can help in drug repositioning. Testifying the same, Nijar *et al.* summarizes a study where clinically approved molecule/drug inhibitors of CYP17 were found to antagonize the androgen receptor and thus rationalize the clinical efficacies of "dual CYP17 inhibitors/AR antagonist" in the clinic in men with CRPC. During the last decades different immunotherapies, targeting at enabling the immune system towards recognizing cancer antigens and eliminate the tumor cells, have been trialed with some documented successes. Development of suitable *in vivo* models with intact immune system is a requisite to interrogate the tumor microenvironment and signaling pathways in response to single targeting agents given alone or in combination with immunotherapy agents such as checkpoint inhibitors. Slovin *et al.* and Ziranu *et al.* described the successful use of such models for assessing effectiveness of the combinatorial immunotherapy against infiltrating Myeloid-derived suppressor cells for CRPC. Menzer *et al.* have extended their comments on using combination therapy with ipilimumab and nivolumab for kindey cancer. Three studies in this section have covered the persistent toxicity due to Bacillus Calmette-Guerin immunotherapy for urothelial carcinoma and strategies to minimize the side effects- all pointing towards in-depth molecular characterization of the selective response.

A large volume of work presented in this book has been concerted to prostate cancer, a disease of major concern across developed countries with 1.1 million cases being diagnosed per year. Although early detection of urogenital cancers is key to better prognosis by starting early therapy; prostate cancer falls in a unique spectrum due to the availability of Prostate Specific Antigen (PSA) as a non-invasive biomarker for disease diagnosis. Since the discovery of PSA almost 40 year ago, the number of clinically reported prostate cancer cases have increased exponentially. PSA test has been recently criticized for not being able to distinguish indolent disease from aggressive prostate cancer leading to over-diagnosis and over-treatment. Given the perils of a prostate biopsy including infection, cost and diagnosis of low-risk, indolent prostate cancer, hunt for a highly specific prognostic biomarkers continues in the 21st century and is well documented in the last section of our book covering the use of gene expression profiles (Choudhury *et al.*) to genomic profiling including mutilations in AR genes during (CTC) (Martignano *et al.*), splicing of *Uridine diphosphate glucuronosyltransferase 2B type 28* (Toit *et al.*) and circulating tumor cells (Marshall *et al.*). Interestingly, no differences were observed between robotic assisted laparoscopic radical prostatectomy on intraoperative levels of prostate cancer CTCs contemplating the hypothesis that the introduction of CTCs during surgery may promote cancer progression. Mian *et al.* summarizes the molecular markers for basal and luminal subtypes of prostate cancer and these molecular signatures could be predictive classifier in identifying the subgroup who might benefit from androgen deprivation therapy. Based on these studies, it is well anticipated that not just single but integrative molecular and classical pathology biomarkers will play an increasingly important role in risk stratification for clinical decision making not just in prostate cancer but other urogenital cancers.

It is an exciting time of translation from bench to bedside in cancer personalized medicine and molecular pathology have the potential to be the guiding hand in determining optimal treatment regimen of targeted therapies for patients with advanced diseases. Through this book, we intended to cover the recent developments in urogenital cancers at the research

and at the clinical trial fronts bringing our readers' up to speed. We hope that the material and overview of the current state of research covered in this book will provide sufficient intellectual stimulations for our readers to venture new ideas into their research and clinical practices.

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