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EDITORIAL

Global advances in prostate cancer diagnosis and therapy

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There is a lot to learn from transnational research collaboration, and the Prostate Cancer Foundation (PCF) is dedicated to building bridges around the world to address complex scientific and clinical issues related to the development of improved diagnostics and therapeutics for metastatic prostate cancer. With the goal of improving patient care for men with prostate cancer globally, the multidisciplinary Sixth Annual Forum of Prostate Disease (6th FPD) was convened during 8–9 June 2012 in Shanghai, China. This conference provided an opportunity for scientists and clinicians from major medical centers in the United States and China to share data and forge new professional relationships. This special issue of the *Asian Journal of Andrology (AJA)* provides an overview of the major presentations at the 6th FPD, which highlighted prostate cancer biology, genetics, new clinical therapies, imaging technologies and the biotechnology of new diagnostic tests capable of identifying patients destined for unfavorable outcomes.

Recent advances in next generation sequencing have defined prostate cancer as a collection of molecularly distinct subclasses instead of a single uniform disease. This massive underlying disease heterogeneity is the reason why prostate cancer patients respond variably to a given treatment. Each prostate tumor develops a unique combination of genomic alterations, some of which drive tumor development and progression, while others are passenger changes. This unique combination of driver and passenger alternations will determine ultimate clinical outcome. It is this vast molecular heterogeneity of prostate cancer that has confounded attempts to develople improved life-extending therapies and a new generation of predictive diagnostic methods. The disease complexity necessitates the development of analytical methods that can potentially help 1) discriminate indolent from aggressive disease to avoid overtreatment of non-lethal tumors; and, 2) guide clinical therapeutic decisions by appropriate patient selection based on their sensitivity/resistance to a particular treatment modality.

The following series of articles highlights some of the most important areas of biomedical research capable of prolonging prostate cancer patient survival. The reader will appreciate the ushering in of a new era of predictive diagnostics that will report underlying tumor heterogeneity and more accurately stratify patients for treatments they will benefit from, sparing those whose prostate cancer is indolent. 'Precision' medicine will also help address another key clinical challenge; that of defining rational therapeutic strategies for prostate cancer drug combinations as well as sequencing.

This special issue aims to provide a comprehensive overview of our current understanding of prostate cancer biology and genetics detailing promising biomarkers that hold the potential to improve the specificity of prostate cancer diagnoses as well as guide clinical management of the disease for maximal patient benefit.

The first article in this special issue by Wyatt *et al.*[1] elegantly summarizes the tremendous progress made in recent years in identifying molecular events underlying cancer initiation, progression, metastasis and resistance to therapy. The authors dissect molecular aberrations such as genomic rearrangements (heterogeneous copy number alterations, genome breakpoints, chromothripsis and polygene fusions); mutations (SPOP); and mechanisms that increase transcriptomic complexity (splicing, non-coding RNA, epigenetic modifications), all of which come together to generate massive molecular heterogeneity of prostate cancer.

The cover art for this issue of *AJA* depicts a Circos Plot of the 90 significantly recurrent molecular alterations in prostate cancer from an analysis of 372 prostate tumors (green-loss; red-gain) discussed in the Wyatt *et al.* Review article.[1] Significantly mutated genes from studies of large tumor cohorts are annotated by black dots around the outside, with dot size proportional to the level of significance. Recurrent fusion genes involving ETS transcription factors are shown in the center of the plot, as are recently identified non-ETS fusions genes.

The second Review article by Dean and Lou[2] assesses prostate cancer causes and risk factors, and their underlying genetic associations. The etiology of prostate cancer is largely unknown; however, advanced age, African ethnicity and positive family history have been consistently associated with an increased risk for prostate cancer. The influence of genetics on prostate cancer susceptibility, incidence and mortality have spurred several genome-wide association studies (GWAS); however, the authors caution that to draw meaningful conclusions from these studies, it is important that these results are generated, annotated and combined in a rational fashion using statistically significant large numbers of samples that are properly collected and annotated. Dean and Lou[2] emphasize that prostate cancer molecular studies and epidemiological investigations need to focus on exome and genome sequencing, copy number analysis, epigenome analysis, and expression and chromatin studies.

Particularly insightful in this context is Jianfeng Xu *et al.* Review[3] summarizing prostate cancer risk-associated single nucleotide polymorphisms (SNPs) identified through GWAS in prostate cancer patients and controls. These studies have identified >50 prostate cancer risk-associated SNPs in Caucasians, African Americans, Japanese, and Chinese populations tabulated in this review. This data set includes more genetic polymorphisms than have been identified in any other solid tumor type. This article elegantly discusses the potential clinical utility of these implicated genetic markers in the screening, diagnosis, prevention, and treatment of prostate cancer. Though most of the common SNPs identified by GWAS confer a relatively small to

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moderate effect, and can only account for ~25% of genetic susceptibility to prostate cancer, they help in better understanding the etiology of the disease.

The mutational landscape of prostate cancer is extremely complex and Ahmad *et al.*[4] do an excellent job of describing the interactions between key signaling molecules that promote tumorigenesis. The authors have modeled abnormal cellular signaling events *in vitro* and *in vivo*, and consider these findings in the context of developing targeted therapy for future clinical evaluation. Ahmad *et al.* suggest that stratifying patients according to their tumor PTEN and HER2 status holds potential in predicting their responsiveness to targeted therapy with MEK/ERK inhibition. They present data that suggest that MEK inhibitors are effective targeted therapy in prostate cancer tumors with high HER2 levels and low levels of PTEN. Further, they discuss that PI3K/AKT signaling significantly contributes to prostate carcinogenesis driven by SPRY2 and PTEN loss. Complex interactions among receptor tyrosine kinases (such as HER2/3 and EGFR tumor suppressor genes (including SPRY2 and PTEN) and their downstream effectors (PI3K and MAPK) exhibit a fine regulation of signaling networks, which may represent important targets for developing personalized treatments.

Neuroendocrine cells that lack the androgen receptor and are androgen-independent have been reported from benign prostate and prostate adenocarcinoma specimens. Recent studies have shown that these cells may contribute to disease progression and castration resistance. In their review, Jiaoti Huang and colleagues[5] discuss the molecular mechanisms of this neuroendocrine differentiation of prostate cancer which presents as small cell neuroendocrine carcinoma (SCNC) in prostate cancer patients whose disease recurs upon treatment (hormone therapy) failure. Their results show that a P53 mutation in the neuroendocrine cells disrupts the IL-8/CXCR2/P53 signaling pathway, causing the rapid proliferation of these cells and the development of SCNC.

The non-prostate cancer-specificity of PSA testing necessitates the discovery of suitable biomarkers that allow accurate diagnoses and can report on disease aggressiveness. Testing these biomarkers in urine samples holds potential due to the non-invasiveness of urinalysis, ease of collection, and the fact that prostate cells are directly released into the urethra through prostatic ducts after a digital rectal exam (DRE) or prostate massage. Daphne Hessels and Jack Schalken[6] present a comprehensive overview of urine biomarker analysis, describing the potential of using epigenetic modifications (GSTP1 and RASSF1A), genes uniquely expressed in prostate cancer (*PCA3, TMPRSS2-ETS* genes fusions, *AMACR, PSMA*), microRNAs (miR-107 and miR-574-3p) and exosomes (PSA, TMPRSS2-ERG gene fusion and PCA3 mRNA transcripts) as biomarkers for the non-invasive testing of prostate cancer in urine.

The manuscript by Eric Klein[7] describes a novel strategy for prostate cancer molecular profiling by assessing tumor aggressiveness using tumor tissue obtained at biopsy. Klein's study in association with the team at Genomic Health has generated a validated panel of genes that can predict clinical recurrence/adverse pathology at the time of prostatectomy and allow improved selection of prostate cancer patients for active surveillance. In the article, Klein notes that meaningful information on clinical outcomes is contained in the small amounts of tissue obtained at biopsy and gene-expression profiling of these tissue samples holds potential to better guide clinical management of the disease. This test, if fully validated, will predict the presence of adverse pathology in a prostate gland where low grade carcinoma was previously discovered by needle biopsy. High probability of adverse pathology will trigger active therapy while lack of this finding would be a gateway for active surveillance.

The evolving castration resistant prostate cancer (CRPC) treatment landscape is summarized by Paul Toren and Martin Gleave[8] who provide a comprehensive overview of several ongoing Phase II and III clinical trials and associated molecular targets (androgen synthesis, AR, cell signaling, stress-response, angiogenesis, bone metastases and the immune system). Table 3 in this review lists ongoing Phase III trials in metastatic CRPC. AR continues to play a critical role in prostate cancer progression even upon castration resistance, and is the target of several therapies. The authors discuss the significance of patient selection, therapeutic agent combinations and sequencing for maximal benefit.

The National Basic Research Program of China (973 Program) is a Chinese government-funded prostate cancer research program, which exemplifies the excellent application of next-generation sequencing to answer important biological questions in prostate cancer research in China. These recent advances have been summarized by Ren *et al.*[9] who discuss the results of the first GWAS in China that has revealed two new prostate cancer susceptibility loci in Chinese patients. The authors also discuss differences in the frequency of the *TMPRSS2-ERG* gene rearrangement seen in ~46% of prostate cancers from Caucasian men as against less than 20 of prostate cancers in China. Ren *et al.* summarize the personalized standard-of-care prostate cancer therapies in China that include nanotherapeutics and traditional Chinese medicine.

This special issue of *AJA* provides an overview of our current understanding of prostate cancer biology and how this knowledge may be applied to the development of suitable disease biomarkers that can report on the molecular underpinnings of the disease. These biomarkers will serve as tools for appropriate risk-stratification of prostate cancer patients facilitating identification of patients who will benefit most from either aggressive therapeutic approaches or active surveillance of their disease. The heterogeneity of the disease suggests that a combination/panel of these biomarkers will faithfully report underlying biology. This does seem daunting in light of prostate cancer and patient heterogeneity along with the multifocality with which the disease typically presents; however, we are optimistic that biomarkers/molecular reporters will change prostate cancer clinical management in the not too distant future.

This *AJA* special issue will hopefully serve as a useful guide for prostate cancer clinicians and researchers in understanding the current state of the science of prostate cancer biology and recent advances in validating suitable disease biomarkers. Global knowledge exchanges through conferences like the 6th FPD bring us closer to our common goal: improvement in clinical care of prostate cancer patients by sharing research findings without national borders.

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