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Editorial

Biology and therapy of urological cancer metastasis

From the early roots of modern urology to today, genitourinary (GU) cancers have been an important part of the fields of urology and cancer biology. As medical science has advanced, newer clinical and basic viewpoints have impacted the thinking and practice in this important field. As such, GU oncology has been consistently seen as an area of rapid evolution both in biological understanding and clinical care. GU cancers continue to rise in incidence worldwide. Moreover, they represent a significant portion of cancer mortality in Asia and the western world. These facts have been met with some of the boldest and most important advances in cancer biology and therapy that have reshaped this field.

The idea of this special issue was conceived one year ago at joint meeting of the Chinese Urological Association and the Asian Urological Association in Shanghai. At this meeting, a special session was convened on the topic of urological cancer metastasis and therapeutic resistance. Here, basic and clinical urological scientists and investigators met and enthusiastically shared their ideas and discoveries with the goal of improving the future of patient care through research. We, the guest editors, were greatly impressed by the quality and depth of the science presented at the meeting and unanimously agreed to volunteer time and energy to develop this special issue for the *Asian Journal of Urology* (*AJU*). In this spirit, we invited some of the preeminent scientists and clinicians from the United States and Asia to share their perspectives and successes in their respective areas of work with the hope of stimulating even more discoveries with the promise for clinical translation.

We have collected fourteen articles in this special issue including both original research articles and reviews focused on clinically-relevant models of prostate, kidney, and bladder cancers. The articles cover a wide range of topics currently considered to be of prime interests to the field of uro-oncology. Topics covered by our contributors range broadly while retaining great depth. These works include the three manuscripts on the functionality of the androgen receptor (AR) and the mechanisms underlying the development of therapeutic resistance. Three articles focus on the plasticity of cancer cells within the tumor microenvironment and how this may present challenges and new opportunities for the development of improved therapeutics. Three original and review articles using clinically relevant materials to develop new biomarkers predictive of clinical outcome, new patient-derived xenografts (PDXs) to study cancer bone metastasis and *ex vivo* expanded circulating tumor cells (CTCs) and the CTC-derived xenografts (CDXs) from liquid biopsies for personalized oncology. And five highly clinically translatable reviews focusing on the use of CTCs to study the progression and evolution of cancer cells in blood, clinical application of new knowledge learned from urothelial cancer, recent advances in the development of immune-based therapeutics for GU tumors, and new concept of developing cancer therapeutics based on site of cancer metastasis. As guest editors, we have made significant efforts in reviewing all of the articles and providing special comments to provide the readership of *AJU* with high quality papers with a particular focus on the translational potential of these topics from the bench to the bedside.

Dr. Jun Luo [1] is a pioneer who discovered spliced AR-V7 mRNA in CTC as a biomarker predictive of androgen antagonist therapy in prostate cancer patients. He highlighted a number of other noninvasive actionable prognostic biomarkers that could prove to be highly valuable in seeking further improvement of monitoring clinical responses of metastatic castration-resistant prostate cancer (CRPC) patients. Dr. Yun Qiu and her colleague Jin Xu [2] provided mechanistic insights on the expression and the role of AR spliced variants in driving the progression of metastatic CRPC and how they contribute to disease relapse and therapeutic resistance. Dr. Allen Gao and colleagues [3] proposed the concept of adaptive pathways that enable prostate cancer cells to survive androgen-deprivation therapy, and they developed new strategies to overcome therapeutic resistance, particularly in prostate cancer patients who relapsed following therapy with androgen antagonists.

The question of tumor cell plasticity and heterogeneity is addressed by three excellently prepared reviews. Dr. Yuzhuo

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Wang and colleagues [4] communicated a new perspective on the epithelial immune cell-like transition (EIT), where prostate cancer cells were shown to express molecules conventionally expressed by immune cells, hence evading immune surveillance and a suppressive microenvironment in human prostate cancer. Understanding the factors secreted by cancer cells could help combat the resistance of GU tumors towards immune checkpoint inhibitors. Dr. Jer-Tsong Hsieh and his colleagues [5] also presented their novel ideas of aggressive prostate cancer cells that assume pluripotency of stem cell phenotypes are also the cells that drive drug resistance. Their review summarizes a number of promising cell surface targets of stem cells responsible for the maintenance of stem cell self-renewal are the novel therapeutic targets for aggressive prostate cancer. Dr. Takashi Kobayashi [6] reviewed the plasticity of urothelial cancer that assumes epithelial-mesenchymal transition (EMT) and the cancer stemness and is closely linked to the metastasis of urothelial cancer. He suggested that in order to improve the survival of patients with urothelial cancer, we need to seek better understanding of the progression and metastasis of urothelial cancer by developing better models, better insights in regulatory biology, and better targets that could lead to improved treatment of patients with urothelial cancer.

The authors are all keenly aware of the fact that exploiting clinically relevant materials is a crucial element to advance new knowledge in GU oncology. Dr. Colm Morrissey and colleagues [7] conducted tissue microarrays using radical prostatectomy from CRPC patients. They found the absence of several mismatched repair protein expression is frequent and a predictor of poor outcome in CRPC patients. Dr. Christina Jamieson and her colleagues [8] presented an attractive new PDX model of prostate cancer bone metastasis. Their model has the advantage over the other PDXs in that the bone metastatic tumor cells can grow in culture as well *in situ* generating both osteolytic and osteoblastic lesions in mouse skeleton in an anatomical regional-dependent manner. Taking advantage of their original success in establishing CTCs from mouse model of prostate cancer metastasis, Dr. Ruoxiang Wang [9] shared his views and experience on culturing CTCs in a highly reproducible manner to obtain CTCs and CTC-derived PDXs, or CDXs from cancer patients. CTCs/CDXs could become the first step of studying the mechanisms underlying cancer metastasis and to address the molecular basis of how therapeutic resistance to chemo- and hormonal-therapy may be developed.

Perhaps the best examples linking closely the laboratory-based technologies could impact clinical care of patients came from the 5 expert contributors who mastered not only the knowledge of medical care of GU cancer patients, but also the cutting-edge of investigational sciences and technologies. Dr. Edwin Posadas [10] reviewed the advancement of CTC isolation and enumeration methods and predicted the future of personalized oncology will evolve from sensitive and reliable sequencing and computational technologies and understanding of the biology of CTCs captured from patients. Drs. David McConkey, Colin Dinney, and their colleagues [11] discussed the relevance of the newly-described intrinsic basal and luminal subtypes of urothelial cancers to metastasis and the use of neoadjuvant chemotherapy. Dr. Tian Zhang and colleagues [12] comprehensively reviewed recent progress in the use of immunologic approaches for the treatment of metastatic renal cell carcinoma urothelial carcinoma with agents that block cytotoxic T lymphocytes associated androgen 4 (CTLA-4), programmed death receptor 1 (PD-1), and programmed death-ligand 1 (PD-L1). They emphasized that a deeper understanding of the mechanisms of action of immune checkpoint inhibitors and selection of patients could further improve the therapeutic responses of patients to immunologic-based therapy. Drs. Ravi Madan and James Gulley [13] elegantly summarized the development of a number of emerging immunotherapies for metastatic prostate cancer, many of which are under development at National Cancer Institute in the United States in patients. Dr. Sumanta Pal and his colleagues [14] highlighted the biology of renal cell carcinoma and how this biology can lead to revolutions in the treatment of metastatic renal cell carcinoma based on the clinical patterns of organic-specific metastasis of this disease.

We are most grateful to the contributors of this special issue for lending their time, experience, and passion for their respective fields and the expert reviews of the submitted articles by Dr. Stephen Shiao and Dr. Sungyong You. All of our contributors are thought leaders in their fields ranging from the bench to the bedside with a single goal in mind: elimination of death and suffering from cancer. We look forward to the future with great anticipation as all of the authors who contributed to this issue are actively reshaping clinical oncology and cancer biology by exploring new frontiers that will ultimately help patients diagnosed with GU cancers to find hope, and ultimately a cure for their disease. Our special thanks also go to Shasha Wei who communicated diligently with the guest editors, the authors and the publishers and we do not believe it is possible to publish this special issue without her dedication and devotion!

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