Editorial

Dr. Coffey's visionary contributions to urological research in China and Japan

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In deep mourning for Dr. Coffey, we want to bring to readers some of the untold stories from our personal experience of how an extraordinarily talented and kind American scientist of unwavering vision and conviction profoundly influenced urological research and education in China and Japan. This article understandably addresses only a fraction of Dr. Coffey's legacy in science and education, but the tales told here are vivid and memorable, and hopefully will resonate with thousands of others who also mourn the loss of Dr. Coffey, our Chief, mentor and friend.

Dr. Coffey's contribution to urological research and education in China (contributed by Leland WK Chung and Haiyen E Zhau)

Dr. Coffey's curiosity about prostate cancer in Chinese eunuchs was inspired by a conversation he had with Dr. Chieh-Ping Wu, the leading urologic surgeon in China. Dr. Wu was trained by Dr. Charles Huggins from the University of Chicago Ben-May Laboratory, and returned China to serve as the Director of the prestigious Beijing Urologic Institute. Dr. Wu is considered the "father of urology" in China, for several decades the visionary leader and educator of Chinese urologists. He had a special relationship with Dr. Coffey at the Brady Urological Institute of Johns Hopkins University along with Drs. William Scott, Paul Talalay and Guy Williams-Ashman, all trained by Dr. Huggins and all recruited from the University of Chicago. At a scientific conference in the U.S., Dr. Wu told Dr. Coffey that he had examined 26 eunuchs from the Qing Dynasty palace still living in Beijing. He revealed the following remarkable findings [1] "....a general physical examination, including palpation of the prostate, for every one of them. Their average age then was 72 years (59-83 years). They became eunuchs at the age of 10-26 years. The prostate was impalpable in 21 (81%) and 1-2 cm in width rectally in five, with a flat surface. At the time of the examination, they had been eunuchs on the average for 54 years (41-65 years). This is probably the largest series of human beings followed for such a long period of time to confirm that testicular hormone is essential for the development and preservation of the prostate....". Based on Dr. Wu's observation, Dr. Coffey was convinced that exposure to testicular hormones in the pre-pubertal, pubertal or adult period could have profound effects on the development of both benign and malignant diseases of the prostate gland. When Leland Chung finished his postdoctoral fellowship with Dr. Coffey and moved from the Brady Urological Institute at Johns Hopkins to McGill University, we tested this hypothesis by setting up mouse studies to determine the effects of neonatal androgens and estrogens on the development of accessory sex organs and hepatic cytochrome P-450 drug metabolism systems [2-4]. We continued this work at the University of Colorado, further characterizing the effects of sex steroids on prostate epithelial-stroma interaction, and used a tissue recombinant technique to reveal that prostate epithelial growth and differentiation were qualitatively and quantitatively driven by male hormones, androgen receptor, and mesenchymal stromal components in the tissue recombinants [5-7]. These



Figure 1. Drs. Donald S. Coffey and Chieh-Ping Wu's visit of the University of Texas MD Anderson Cancer Center in April, 1991 where Drs. Coffey and Wu presided discussion of the future research and education collaboration between U.S. and China. The participants of this discussion were, from left, Haiyen E Zhau, Wu Chieh-Ping, John McConell, James Bowen, Margaret Spitz, Andrew von Eschenbach, Gary Miller and Donald S. Coffey.

initial findings paved the way for later concepts that prostate cancer growth and metastasis can be promoted by stromal fibroblasts, and that adjacent cells secreted soluble factors and provided insoluble matrices in the tumor microenvironment [8-15]. This concept gained traction, became popular and is now well-accepted by the scientific community and has been adopted comprehensively for the development of new biomarkers and therapeutics to improve the management of cancer in general and prostate cancer specifically [16-20].

While our lab studies went smoothly and produced promising results, our discussions with the late Dr. G. Miller, a leading genitourinary pathologist, pointed toward an early question we had: Are there fundamental molecular, biochemical and pathologic differences in benign and malignant prostate diseases between the East (China, Japan and Vietnam) and the West (U.S. and European countries)? This question was raised after significant debate with Dr. Miller, in which we were able to convince him that Chinese pathologists indeed had knowledge and expertise in diagnosing prostate cancer. In 1986 we were recruited from the University of Colorado to the University of Texas M. D. Anderson Cancer Center to join Dr. Andrew von Eschenbach to develop a uro-oncology research program. We were most excited when

Dr. von Eschenbach shared with us his vision of bridging gaps in our knowledge in the West by studying populations in the East that are exposed to very different dietary, environmental and socioeconomic conditions. At that time China was trying hard to move ahead from a socialistic to a more modern capitalistic country. In April 1991, we had the honor of welcoming Dr. Chieh-Ping Wu as a visitor to the M.D. Anderson Cancer Center. Dr. Donald S. Coffey from Johns Hopkins kindly joined us and we shared our visions and exchanged ideas about how to advance the field of urologic science in the U.S. and China (Figure 1). Dr. Wu graciously brought us a rare copy of the

Atlas of Cancer Mortality in the People's Republic of China, published in December 1979. The study was the result of a directive from the late Premier Zhou En-lai. The survey took three years and involved 800 million participants from 29 provinces, with the work conducted by epidemiologists, biostatisticians, and one million medical workers, the so called "barefoot doctors" who literally walked from place to place to interview and record survey data. The surveyed cancers included stomach, esophagus, liver, cervix, lung, colon and rectum, leukemia, breast, nasopharynx, brain, lymphoma, bladder, penis, and choriocarcinoma. There was no kidney or prostate cancer to be found! Dr. Wu and Dr. Coffey sparked an in depth discussion of how to formally establish research collaboration between China and U.S. On the U.S. side, the question most often raised was why Chinese men rarely have prostate cancer, when prostate cancer is so prevalent in the U.S. and other western countries? Is this difference contributed by genetic, dietary, environmental, life-style or socioeconomic factors? With our visiting scholars from China, including the pathologists Lian-Sheng Zhao, Hua Yang, and Tongli Xia who worked closely with U.S. genitourinary pathologists Drs. Gary Miller, Patricia Troncoso, and Henry Frierson, we convinced Dr. Miller that indeed Chinese pathologists know how to read pathological slides of prostate cancer!

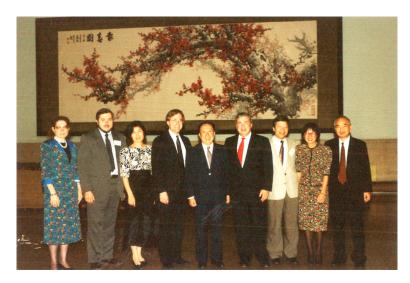


Figure 2. U.S. delegates participated UCUR meeting at the Great Hall of the People in Beijing in September, 1991. The participants were from left to right: Ellen Shapiro, Gary Miller, Haiyen E Zhau, Herbert Lepor, Chieh-Ping Wu, Andrew von Eschenbach, Leland WK Chung, Marion Lee, and Gu Fanliu.



Figure 3. After UCUR group meeting and discussion, the Prostate Cancer Biology and Pathology breakout session got together.

Shortly after Dr. Wu's visit, we organized a U.S. delegation consisting of physicians and scientists from three research areas in the urologic sciences (**Figure 2**): 1) Prostate cancer biology and pathology, Drs. Gary Miller, Andrew von Eschenbach, Haiyen E Zhau, Leland WK Chung, Isabell Sesterhenn and F. K. Mostofi. 2) Benign prostate hyperplasia, Drs. John McConnell, Herbert Lepor and Ellen Shapiro. 3) Prostate cancer epidemiology, Dr. Marion Lee. The Chinese leaders from each group were: Prostate cancer biology and pathology, Drs. T.

L. Xia and Y. C. Na; Benign prostate hyperplasia, Drs. Ying-Lu Guo and Z. Y. Xue; Epidemiology, Drs. Fangliu Gu, R.T. Wang, and K. H. Han. Based on the vision of Dr. Coffey and Dr. Wu, we formed the first such organization, the U.S.-China Urologic Research (UCUR) Group, with the primary goals of exchanging students and faculty to foster close research collaborations between the U.S. and China. We had our first meeting on Sept. 16-19, 1991 in Beijing, China. Dr. Chieh-Ping Wu presided, assisted by his two highly accomplished students, Drs. Fangliu Gu, Ying-Liu Guo, and their colleagues (Figure 3). The delegates from the U.S. were guided by Dr. Coffey behind the scenes. He wrote to all the delegates on August 21, 1991 (Figure 4). This warm encouraging letter from Dr. Coffey showed the depth of his vision and his deep conviction that collaboration with China would bring new knowledge from the East, and his confidence that we as delegates would understand that this was a difficult mission requiring much patience. History shows that Dr Coffey's visions and predictions came true. 1) The explosion of research collaborations between the U.S. and China in recent decades resulted in significant exchanges of knowledge

at every level in the urological sciences. 2) The active exchanges of faculty and students between the U.S. and China profoundly moved the scientific culture of China toward a more western model and improved our understanding of how research can be translated for the best patient care. 3) As Dr. Coffey foresaw, the success of joint papers published, joint grants funded, and U.S. training for new generations of urologic scientists all over China has been tremendous. One of the ripple effects of these cultural changes is that, in sharp contrast to early

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August 21, 1991

All Members of the Initial U.S.-China Urological Research Group

As you, I also have a very deep and abiding belief that the international interaction of urological research should now be realized and that China is a central colleague in this most important endeavor. The opportunities in China to form research collaborations that will answer and test many important questions tremendous potential. Each of you represents an established dynamic aspect of urological research. You are the premier new leaders in American Urology and will initiate the research directions with China that you believe will be most fruitful. It is therefore not appropriate for me at this time, as a more senior leader who is not actually in the trenches, to detract in any way or complicate any initial interactions that are embryonic and that will form the backbone of this future program. I will certainly work with you and the China program once these contacts are initiated but it must be supportive and not interfere or disturb what you will be building. I salute you for your efforts and I hope you are aware of the long range importance and meaning of this and we all realize how difficult this mission will be. These interactions will call for the utmost patience, wisdom and understanding, and you will be dealing with a great deal of frustration and confusion as you initiate these joint research efforts. Your leadership and determination will certainly be tested to the fullest extent. On behalf of all in urological research, we that you, wish you the best in this difficult mission and send our prayers for a safe and successful visit.

Sincerely, Your Friend and Colleague, Donald S. Coffey

Figure 4. The letter from Dr. Coffey expressed his sincere wishes for a successful meeting with our Chinese colleagues in Beijing. He told us it will be a difficult meeting, advised us to have patience and understanding. He placed his full trust and confidence in us, the U.S. delegates.

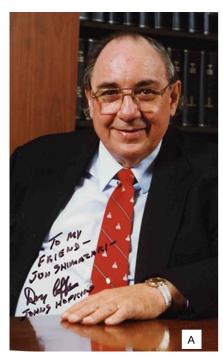








Figure 5. Dr. Coffey and Japanese urological doctors and scientists from Chiba University. A. Dr. Coffey's picture as a souvenir for Dr. Shimazaki. B. Dr. Coffey between Dr. Tomohiko and Ms. Yayoi Ichikawa on June 1, 1991, a couple of weeks before going back to Japan. C. Dr. Coffey and Suyama in front of Dr. Coffey's Portrait at Suyama's farewell lunch on Mar 5, 2010. D. Dr. Lupold and Dr. Kurozumi in front of Dr. Coffey's Portrait just after the lab meeting on February 6, 2018.

years where the professors presided and led all presentations and discussions, now young Chinese urologic surgeons and researchers are leading the way to building the future of urologic science in China.

Dr. Coffey's impact on urological research at Chiba University, Japan (contributed by Jun Shimazaki and Tomohiko Ichikawa)

As the first postdoctoral fellow working directly with Dr. Coffey at the Department of Pharmacology and Experimental Therapeutics at Johns Hopkins University from 1965 to 1967, I started my experimental work first with Drs. H. G. Williams-Ashman and Paul Talalay, and a few months later, Dr. Coffey started to work with me on biochemical research on the pathophysiology of the prostate gland. He kindly taught me many biochemical techniques and explained the principles behind these assays. He was extremely kind and caring, and escorted me late at night to my car parked only two blocks away from the main entrance of the hospital. We did what may have been the first molecular biologic experiment elucidating how DNA

synthesis in the rat prostate is controlled by testosterone treatment [21, 22]. In addition to my own experience with Dr. Coffey, I can say unequivocally that Dr. Coffey was a dear friend of mine (Figure 5A), and he had a huge influence and impact on the thought processes of many Japanese urological doctors and scientists from Chiba University. After returning to Chiba, I decided to send Japanese doctors and scientists to Johns Hopkins to work with Dr. Coffey's protégées, Drs. John and Bill Isaacs, Dr. Steven Ward, Dr. Robert Getzenberg, and Dr. Shawn Lupold. We successfully completed the training of three generations of clinicians and scientists from Chiba at Johns Hopkins. After the trainees returned to Japan, they also successfully achieved their personal goals as academicians or practitioners. Tomohiko Ichikawa, MD., Ph.D. (Figure 5B) from 1989 to 1991, was trained under the mentorship Dr. John Isaacs [23-42]. Tomohiko is now the Professor and Chairman of the Department of Urology, Graduate School of Medicine, Chiba University. Yuzo Furuya, MD., Ph.D. [43-51] mentored by Dr. John Isaacs from 1992 to 1995 is now the Director of a private clinic. Hiroyoshi Suzuki, MD., Ph.D., [52-57] mentored by Drs. John and Bill Isaacs from 1996 to 1998, is now Professor and Chief of Urology, Toho University Sakura Medical Center. Akira Komiya, MD., Ph.D. [58-60] was mentored by Dr. Bill Isaacs from 2000 to 2003. Akira is currently the Associate Professor, Department of Urology, Graduate School of Medicine, Chiba University, Takahito Suvama, MD., Ph.D., [61, 62] mentored by Dr. Robert Getzenberg from 2008 to 2010, and he has a picture taken with Dr. Coffey before his departure then (Figure 5C). He is now an Assistant Professor in the Department of Urology at Teikyo University Chiba Medical Center, Most recently, Akira Kurozumi, MD., Ph.D., mentored by Dr. Shawn Lupold from 2017 to present, will also return to Japan with the offer of an academic position (Figure 5D).

Beside exciting academic interactions with Dr. Coffey and the Brady faculty, the students from Japan also enjoyed intimate interactions with Dr. Donald and Eula Coffey and the Brady bunch through parties, getting together and networking to support each other. Dr. Coffey's passing is a shock to all of us but he and Eula Coffey will live on in our memories.

Memorable moments with Dr. Donald and Mrs. Eula Coffey (provided by Haiyen E Zhau and Leland WK Chung)

In the summer of 2000, Dr. Donald and Mrs. Eula Coffey took a trip with us to Hong Kong, Taiwan, Xian and Beijing, China primarily for scientific conferences. At our first stop in Hong Kong, Dr. Coffey was amazed by the streamlined public transit system, the luxury hotels and restaurants and he proclaimed, "Who said this is a developing country, we Americans are from a developing country!" Dr. Coffey believed in meditation and practiced this art in the basement of his home. While we were in Taiwan, he asked to visit the monks in a Buddhist temple. In Xian, both he and Eula enjoyed Shaanxi Provincial Museum and the famous Terracotta Warriors. Dr. Coffey and Eula were attracted by an oval wooden table set with detailed engravings depicting a scene from Dream of the Red Chamber, a master piece of classical Chinese literature. They acquired the table set and had it shipped to Baltimore. Dr. Coffey enjoyed Chinese food everywhere he went. In Xian, Dr. Dalin He, our highly accomplished student and one of the leaders in the urologic sciences in China, catered a dinner in the Eastern Hotel which was prepared by his close friend, a nationally renowned chef. Dr. Coffey was impressed by every dish, none of which are to be found in Chinese restaurants in the U.S. The last night of his stay in Xian, Dalin asked Dr. Coffey what kind of food he would like. "The same food your friend made the night before", Dr. Coffey replied. To his and Eula's amazement, the renowned chef presented them with completely different and equally delicious dishes, and years later they still talked about the Xian meals. Dr. Coffey was deeply inspired by a Zen-Taoist poetry classic by Han Shan, one of the leading poets of the Tang Dynasty. Han Shan retired to Cold Mountain and took its name for his own. He wrote about his solitary Buddha-nature internal life on Cold Mountain, yet cared profoundly about educating the young to prepare them to lead a full life. Dr. Coffey's practice of deep meditation helped connect him with the nature. Once, driving along Lake Tahoe, he said to us, "Chinese look at the mountains from distance, beyond the cloud, and sink in their minds. We Americans on the other hand want to climb and to 'conquer' the mountains". On many occasions he surprised us with his profound understanding of eastern philosophy. Dr. Coffey's wisdom, humor and humanity will forever inspire us!

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References

- [1] Wu JP, Gu FL. The prostate 41-65 years post castration. An analysis of 26 eunuchs. Chin Med J (Engl) 1987; 100: 271-272.
- [2] Wu JP, Gu FL. The prostate 41-65 years post castration. An analysis of 26 eunuchs. Chin Med J (Engl) 1987; 100: 271-272.
- [3] Chao H, Chung LW. Neonatal imprinting and hepatic cytochrome P-450. Immunochemical evidence for the presence of a sex-dependent and neonatally imprinted form(s) of hepatic cytochrome P-450. Mol Pharmacol 1982; 21: 744-52.
- [4] Chung LW, Ferland-Raymond G. Ferland-Raymond, Differences among rat sex accessory glands in their neonatal androgen dependency. Endocrinology 1975; 97: 145-53.
- [5] Chung LW, Anderson NG, Neubauer BL, Cunha GR, Thompson TC, Rocco AK. Tissue interactions in prostate development: roles of sex steroids. Prog Clin Biol Res 1981; 75A: 177-203.
- [6] Cunha GR, Chung LW. Stromal-epithelial interactions—I. Induction of prostatic phenotype in urothelium of testicular feminized (Tfm/y) mice. J Steroid Biochem 1981; 14: 1317-24.
- [7] Chung LW, Cunha GR. Stromal-epithelial interactions: II. Regulation of prostatic growth by embryonic urogenital sinus mesenchyme. Prostate 1983; 4: 503-11.
- [8] Chang SM, Chung LW. Interaction between prostatic fibroblast and epithelial cells in culture: role of androgen. Endocrinology 1989; 125: 2719-27.
- [9] Camps JL, Chang SM, Hsu TC, Freeman MR, Hong SJ, Zhau HE, von Eschenbach AC, Chung LW. Fibroblast-mediated acceleration of human epithelial tumor growth in vivo. Proc Natl Acad Sci U S A 1990; 87: 75-9.
- [10] Chung LW. Fibroblasts are critical determinants in prostatic cancer growth and dissemination. Cancer Metastasis Rev 1991; 10: 263-74.
- [11] Chung LW, Gleave ME, Hsieh JT, Hong SJ, Zhau HE. Reciprocal mesenchymal-epithelial interaction affecting prostate tumour growth and hormonal responsiveness. Cancer Surv 1991; 11: 91-121.

- [12] Freeman MR, Song Y, Carson DD, Guthrie PD, Chung LW. Extracellular matrix and androgen receptor expression associated with spontaneous transformation of rat prostate fibroblasts. Cancer Res 1991; 51: 1910-6.
- [13] Gleave M, Hsieh JT, Gao CA, von Eschenbach AC, Chung LW. Acceleration of human prostate cancer growth in vivo by factors produced by prostate and bone fibroblasts. Cancer Res 1991; 51: 3753-61.
- [14] Chung LW, Li W, Gleave ME, Hsieh JT, Wu HC, Sikes RA, Zhau HE, Bandyk MG, Logothetis CJ, Rubin JS, et al. Human prostate cancer model: roles of growth factors and extracellular matrices. J Cell Biochem Suppl 1992; 16H: 99-105.
- [15] Gleave ME, Hsieh JT, von Eschenbach AC, Chung LW. Prostate and bone fibroblasts induce human prostate cancer growth in vivo: implications for bidirectional tumor-stromal cell interaction in prostate carcinoma growth and metastasis. J Urol 1992; 147: 1151-9.
- [16] Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nat Rev Clin Oncol 2018; 15: 234-248.
- [17] Devignes CS, Aslan Y, Brenot A, Devillers A, Schepers K, Fabre S, Chou J, Casbon AJ, Werb Z, Provot S. HIF signaling in osteoblast-lineage cells promotes systemic breast cancer growth and metastasis in mice. Proc Natl Acad Sci U S A 2018; 115: E992-E1001.
- [18] Wu JB, Yin L, Shi C, Li Q, Duan P, Huang JM, Liu C, Wang F, Lewis M, Wang Y, Lin TP, Pan CC, Posadas EM, Zhau HE, Chung LWK. MAOA-dependent activation of Shh-IL6-RANKL signaling network promotes prostate cancer metastasis by engaging tumor-stromal cell interactions. Cancer Cell 2017; 31: 368-382.
- [19] Yang W, Bai Y, Xiong Y, Zhang J, Chen S, Zheng X, Meng X, Li L, Wang J, Xu C, Yan C, Wang L, Chang CC, Chang TY, Zhang T, Zhou P, Song BL, Liu W, Sun SC, Liu X, Li BL, Xu C. Potentiating the antitumour response of CD8(+) T cells by modulating cholesterol metabolism. Nature 2016; 531: 651-5.
- [20] Makohon-Moore A, lacobuzio-Donahue CA. Pancreatic cancer biology and genetics from an evolutionary perspective. Nat Rev Cancer 2016; 16: 553-65.
- [21] Coffey DS, Ichinose RR, Shimazaki J, Williams-Ashman HG. Effects of testosterone on adenosine triphosphate and nicotinamide adenine dinucleotide levels, and on nicotinamide mononucleotide adenylytran sfersee activity, in the ventral prostate of castrated rats. Mol Pharmacol 1968; 4: 580-90.
- [22] Coffey DS, Shimazaki J, Williams-Ashman HG. Polymerization of deoxyribonucleotides in relation to androgen-induced prostatic growth. Arch Biochem Biophys 1968; 124: 184-98.

- [23] Ichikawa T, Kyprianou N, Isaacs JT. Genetic instability and the acquisition of metastatic ability by rat mammary cancer cells following v-Hras oncogene transfection. Cancer Res 1990; 50: 6349-57.
- [24] Steinberg GD, Brendler CB, Ichikawa T, Squire RA, Isaacs JT. Characterization of an N-methyl-N-nitrosourea-induced autochthonous rat bladder cancer model. Cancer Res 1990; 50: 6668-74.
- [25] Ichikawa T, Ichikawa Y, Isaacs JT. Genetic factors and metastatic potential of prostatic cancer. Cancer Surv 1991; 11: 35-42.
- [26] Ichikawa T, Schalken JA, Ichikawa Y, Steinberg GD, Isaacs JT. H-ras expression, genetic instability, and acquisition of metastatic ability by rat prostatic cancer cells following v-H-ras oncogene transfection. Prostate 1991; 18: 163-72.
- [27] Ichikawa T, Ichikawa Y, Isaacs JT. Genetic factors and suppression of metastatic ability of prostatic cancer. Cancer Res 1991; 51: 3788-92
- [28] Ichikawa T, Ichikawa Y, Isaacs JT. Genetic factors and suppression of metastatic ability of v-Ha-ras-transfected rat mammary cancer cells. Proc Natl Acad Sci U S A 1992; 89: 1607-10.
- [29] Bussemakers MJ, van Moorselaar RJ, Giroldi LA, Ichikawa T, Isaacs JT, Takeichi M, Debruyne FM, Schalken JA. Decreased expression of Ecadherin in the progression of rat prostatic cancer. Cancer Res 1992; 52: 2916-22.
- [30] Ichikawa T, Lamb JC, Christensson PI, Hartley-Asp B, Isaacs JT. The antitumor effects of the quinoline-3-carboxamide linomide on Dunning R-3327 rat prostatic cancers. Cancer Res 1992; 52: 3022-8.
- [31] Ichikawa T, Ichikawa Y, Dong J, Hawkins AL, Griffin CA, Isaacs WB, Oshimura M, Barrett JC, Isaacs JT. Localization of metastasis suppressor gene(s) for prostatic cancer to the short arm of human chromosome 11. Cancer Res 1992; 52: 3486-90.
- [32] van Moorselaar RJ, Ichikawa T, Schaafsma HE, Jap PH, Isaacs JT, van Stratum P, Ramaekers FC, Debruyne FM, Schalken JA. The rat bladder tumor model system RBT resembles phenotypically and cytogenetically human superficial transitional cell carcinoma. Urol Res 1993; 21: 413-21.
- [33] Ichikawa T, Nihei N, Suzuki H, Oshimura M, Emi M, Nakamura Y, Hayata I, Isaacs JT, Shimazaki J. Suppression of metastasis of rat prostatic cancer by introducing human chromosome 8. Cancer Res 1994; 54: 2299-302.
- [34] Rinker-Schaeffer CW, Hawkins AL, Ru N, Dong J, Stoica G, Griffin CA, Ichikawa T, Barrett JC, Isaacs JT. Differential suppression of mammary and prostate cancer metastasis by human

- chromosomes 17 and 11. Cancer Res 1994; 54: 6249-56.
- [35] Dong JT, Lamb PW, Rinker-Schaeffer CW, Vukanovic J, Ichikawa T, Isaacs JT, Barrett JC. KAI1, a metastasis suppressor gene for prostate cancer on human chromosome 11p11.2. Science 1995; 268: 884-6.
- [36] Nihei N, Ichikawa T, Kawana Y, Kuramochi H, Kugo H, Oshimura M, Killary AM, Rinker-Schaeffer CW, Barrett JC, Isaacs JT, et al. Localization of metastasis suppressor gene(s) for rat prostatic cancer to the long arm of human chromosome 10. Genes Chromosomes Cancer 1995; 14: 112-9.
- [37] Ichikawa T, Nihei N, Kuramochi H, Kawana Y, Killary AM, Rinker-SchaefferCW, Barrett JC, Isaacs JT, Kugoh H, Oshimura M, Shimazaki J. Metastasis suppressor genes for prostate cancer. Prostate Suppl 1996; 6: 31-5.
- [38] Dong JT, Rinker-Schaeffer CW, Ichikawa T, Barrett JC, Isaacs JT. Prostate cancer-biology of metastasis and its clinical implications. World J Urol 1996; 14: 182-9.
- [39] Kawana Y, Komiya A, Ueda T, Nihei N, Kuramochi H, Suzuki H, Yatani R, Imai T, Dong JT, Imai T, Yoshie O, Barrett JC, Isaacs JT, Shimazaki J, Ito H, Ichikawa T. Location of KAI1 on the short arm of human chromosome 11 and frequency of allelic loss in advanced human prostate cancer. Prostate 1997; 32: 205-13.
- [40] Nihei N, Ohta S, Kuramochi H, Kugoh H, Oshimura M, Barrett JC, Isaacs JT, Igarashi T, Ito H, Masai M, Ichikawa Y, Ichikawa T. Meta-stasis suppressor gene(s) for rat prostate cancer on the long arm of human chromosome 7. Genes Chromosomes Cancer 1999; 24: 1-8.
- [41] Gao AC, Lou W, Ichikawa T, Denmeade SR, Barrett JC, Isaacs JT. Suppression of the tumorigenicity of prostatic cancer cells by gene (s) located on human chromosome 19p13.1-13.2. Prostate 1999; 38: 46-54.
- [42] Ichikawa T, Hosoki S, Suzuki H, Akakura K, Igarashi T, Furuya Y, Oshimura M, Rinker-Schaeffer CW, Nihei N, Barrett JC, Isaacs JT, Ito H. Mapping of metastasis suppressor genes for prostate cancer by microcell-mediated chromosome transfer. Asian J Androl 2000; 2: 167-71.
- [43] Berges RR, Furuya Y, Remington L, English HF, Jacks T, Isaacs JT. Cell proliferation, DNA repair, and p53 function are not required for programmed death of prostatic glandular cells induced by androgen ablation. Proc Natl Acad Sci U S A 1993; 90: 8910-4.
- [44] Furuya Y, Isaacs JT. Differential gene regulation during programmed death (apoptosis) versus proliferation of prostatic glandular cells induced by androgen manipulation. Endocrinology 1993; 133: 2660-6.

- [45] Isaacs JT, Furuya Y, Berges R. The role of androgen in the regulation of programmed cell death/apoptosis in normal and malignant prostatic tissue. Semin Cancer Biol 1994; 5: 391-400.
- [46] Armstrong DK, Kaufmann SH, Ottaviano YL, Furuya Y, Buckley JA, Isaacs JT, Davidson NE. Epidermal growth factor-mediated apoptosis of MDA-MB-468 human breast cancer cells. Cancer Res 1994; 54: 5280-3.
- [47] Furuya Y, Lundmo P, Short AD, Gill DL, Isaacs JT. The role of calcium, pH, and cell proliferation in the programmed (apoptotic) death of androgen-independent prostatic cancer cells induced by thapsigargin. Cancer Res 1994; 54: 6167-75.
- [48] Furuya Y, Isaacs JT. Proliferation-dependent vs. independent programmed cell death of prostatic cancer cells involves distinct gene regulation. Prostate 1994; 25: 301-9.
- [49] Furuya Y, Lin XS, Walsh JC, Nelson WG, Isaacs JT. Androgen ablation-induced programmed death of prostatic glandular cells does not involve recruitment into a defective cell cycle or p53 induction. Endocrinology 1995; 136: 1898-906.
- [50] Furuya Y, Krajewski S, Epstein JI, Reed JC, Isaacs JT. Expression of bcl-2 and the progression of human and rodent prostatic cancers. Clin Cancer Res 1996; 2: 389-98.
- [51] Furuya Y, Krajewski S, Epstein JI, Reed JC, Isaacs JT. Expression of bcl-2 and the progression of human and rodent prostatic cancers. Clin Cancer Res 1996; 2: 389-98.
- [52] George DJ, Suzuki H, Bova GS, Isaacs JT. Mutational analysis of the TrkA gene in prostate cancer. Prostate 1998; 36: 172-80.
- [53] Dong JT, Suzuki H, Pin SS, Bova GS, Schalken JA, Isaacs WB, Barrett JC, Isaacs JT. Down-regulation of the KAI1 metastasis suppressor gene during the progression of human prostatic cancer infrequently involves gene mutation or allelic loss. Cancer Res 1996; 56: 4387-90.
- [54] Suzuki H, Dong JT, Gao AC, Barrett JC, Isaacs JT. Identification of the rat homologue of KAI1 and its expression in Dunning rat prostate cancers. Prostate 1998; 37: 253-60.
- [55] Leinonen KA, Saramäki OR, Furusato B, Kimura T, Takahashi H, Egawa S, Suzuki H, Keiger K, Ho Hahm S, Isaacs WB, Tolonen TT, Stenman UH, Tammela TL, Nykter M, Bova GS, Visakorpi T. Loss of PTEN is associated with aggressive behavior in ERG-positive prostate cancer. Cancer Epidemiol Biomarkers Prev 2013; 22: 2333-44.

- [56] Whang YE, Wu X, Suzuki H, Reiter RE, Tran C, Vessella RL, Said JW, Isaacs WB, Sawyers CL. Inactivation of the tumor suppressor PTEN/ MMAC1 in advanced human prostate cancer through loss of expression. Proc Natl Acad Sci U S A 1998; 95: 5246-50.
- [57] Suzuki H, Freije D, Nusskern DR, Okami K, Cairns P, Sidransky D, Isaacs WB, Bova GS. Interfocal heterogeneity of PTEN/MMAC1 gene alterations in multiple metastatic prostate cancer tissues. Cancer Res 1998; 58: 204-9.
- [58] Xu J, Zheng SL, Komiya A, Mychaleckyj JC, Isaacs SD, Hu JJ, Sterling D, Lange EM, Hawkins GA, Turner A, Ewing CM, Faith DA, Johnson JR, Suzuki H, Bujnovszky P, Wiley KE, DeMarzo AM, Bova GS, Chang B, Hall MC, McCullough DL, Partin AW, Kassabian VS, Carpten JD, Bailey-Wilson JE, Trent JM, Ohar J, Bleecker ER, Walsh PC, Isaacs WB, Meyers DA. Germline mutations and sequence variants of the macrophage scavenger receptor 1 gene are associated with prostate cancer risk. Nat Genet 2002; 32: 321-5.
- [59] Xu J, Zheng SL, Komiya A, Mychaleckyj JC, Isaacs SD, Chang B, Turner AR, Ewing CM, Wiley KE, Hawkins GA, Bleecker ER, Walsh PC, Meyers DA, Isaacs WB. Common sequence variants of the macrophage scavenger receptor 1 gene are associated with prostate cancer risk. Am J Hum Genet 2003; 72: 208-12.
- [60] Narla G, Difeo A, Reeves HL, Schaid DJ, Hirshfeld J, Hod E, Katz A, Isaacs WB, Hebbring S, Komiya A, McDonnell SK, Wiley KE, Jacobsen SJ, Isaacs SD, Walsh PC, Zheng SL, Chang BL, Friedrichsen DM, Stanford JL, Ostrander EA, Chinnaiyan AM, Rubin MA, Xu J, Thibodeau SN, Friedman SL, Martignetti JA. A germline DNA polymorphism enhances alternative splicing of the KLF6 tumor suppressor gene and is associated with increased prostate cancer risk. Cancer Res 2005; 65: 1213-22.
- [61] Suyama T, Shiraishi T, Zeng Y, Yu W, Parekh N, Vessella RL, Luo J, Getzenberg RH, Kulkarni P. Expression of cancer/testis antigens in prostate cancer is associated with disease progression. Prostate 2010; 70: 1778-87.
- [62] Shiraishi T, Terada N, Zeng Y, Suyama T, Luo J, Trock B, Kalkarni P, Getzenberg RH. Cancer/ Testis Antigens as potential predictors of biochemical recurrence of prostate cancer following radical prostatectomy. J Transl Med 2011; 9; 153.