

Department/Division:

Department of Urology

Theme of research:

Heterogeneity of bladder cancer

Name of main researcher, title, and e-mail address:

Tatsuo Morita, Professor

Brief explanation of research activity:

Heterogeneity of bladder cancer has been well documented with respects to biologic, cytogenetic, and histologic properties. These evidences suggest the clonal evolution which can sometimes be seen as heterogeneity within the tumor mass as the tumor grows. Namely, in the process of tumor progression, acquisition of genetic alterations results in divergent clones with heterogeneity in genotypes and phenotypes. We previously reported that human bladder cancer cell line JMSU1 established from malignant ascitic fluid in advanced bladder cancer patient showed morphological heterogeneity at the initial culture in vitro. Therefore, JMSU1 at the first passage seems to contain divergent clones which would reflect the clonal evolution developed during the tumor progression in the bladder cancer patient. The purposes of our project are to establish the clones from the first passage of human bladder cancer cell line JMSU1, to examine clonal heterogeneity in terms of genotypes and phenotypes, and to evaluate the divergent clonal evolution in the process of tumor progression.

Department/Division: Department of Urology

Theme of research: Effect of the inhibitors on calcium oxalate crystallization

Name of main researcher, title, and e-mail address:

Masayuki Yuzawa Assistant Professor

Brief explanation of research activity:

Calcium oxalate is the major crystalline component of the urinary tract calculi. Two hydrates of calcium oxalate, calcium oxalate monohydrate (COM) and calcium oxalate dihydrate (COD), are found in urinary calculi. When calcium oxalate stones are divided into COM stones and COD stones, COM stones are less easily disintegrated than COD stones with ESWL because of the size and consistency. It is known that COD readily undergo transformation to the COM. It is considered the treatment of the stone disease is more easily if we can avoid the change of COD to COM. It is shown that the substances that inhibit the transformation of COD to COM have the potency to prevent the growth of calcium oxalate stone. We evaluate the effects of these inhibitors on calcium oxalate crystallization using microscopy and X-ray diffraction.

Department/Division: Department of Urology

Theme of research: Gene therapy for renal cancer – Enhancement of transgene efficacy with topical gene delivery using catheter and histone deacetylation inhibitor.

Name of main researcher, title, and e-mail address:

Minoru Kobayashi Instructor

Brief explanation of research activity:

Gene therapy for renal cancer has been done mainly for metastatic sites. In addition, cytokine therapies are effective for metastatic sites to some extent; however, they hardly work on primary sites. Therefore, currently, there is no non-invasive and effective treatment for patients who cannot undergo an operation for primary site because of poor conditions such as low performance status or severe complications, and imperative cases with single kidney or insufficient renal function. Vector selection and the way of delivery are essential for effective and safe gene treatment. We firstly developed a rat renal cancer model using chemical carcinogenesis, and established topical gene delivery method into kidney by transarterial approach using catheter. We used cationic polymer for the vector together with in vivo electroporation. In addition, combination of histone deacetylation inhibitor with adenoviral vector has been focused to enhance transgene efficiency. We also apply this chemical to our method to introduce therapeutic genes into primary site more efficiently, and investigate anti-tumor and anti-metastatic effect.

Department/Division: Department of Urology

Theme of research: Research on neuroendocrine and hormone refractory properties of prostate cancer

Name of main researcher, title, and e-mail address:

Masahiro Yashi Instructor

Brief explanation of research activity:

Neuroendocrine system is another endocrine pathway for normal and neoplastic prostate growth, but little was unveiled about its physiological function to date. Our prostate cancer study group considers the controversial issue around the neuroendocrine prostate, whether it correlates with androgen-independent disease progression, depends on the profile in neuropeptide expression and its cleaving enzyme (CD10). Bombesin/gastrin-releasing peptide (GRP) is a peptide growth factor produced from the neuroendocrine phenotype, and a recent proteomics analysis investigating advanced prostate cancer suggests it should be one of the key peptides. We had an interest in the peptide growth factors and performed a large-scale study using the measurement of serum progastrin-releasing peptide (ProGRP), a carboxy-terminal region common to three precursors for GRP, in cases with prostate cancer. The serum status steadily shifted toward predominant expression of ProGRP with the progression of prostate cancer into metastatic and androgen-independent stages. Serum ProGRP level had positive correlation with the serum prostate-specific antigen (PSA) level and bone-related factors (alkaline phosphatase, EOD grade). Prognostic analysis revealed that serum ProGRP level held an independent predictive value for progression-free survival. Interestingly, the ProGRP-positive neuroendocrine cells showed a distribution that is similar but not identical to that of chromogranin A-positive cells. The clinical results suggest serum ProGRP is a promising marker to know the neuroendocrine milieu in advanced prostate cancer, and the prognostic value implies the possibility of causative link between serum ProGRP level and disease progression. Several clinical and experimental therapies using somatostatin analogue or GRP antagonist base on the positive role of neuropeptide in androgen-independent disease progression, and these therapies may advance the standard therapy for metastatic prostate cancer.

Department/Division: Department of Urology

Theme of research: Tissue engineered bladder

Name of main researcher, title, and e-mail address:

Shinsuke Kurokawa Instructor

Brief explanation of research activity:

Augmentation cystoplasty or bladder reconstruction using autologous intestinal flaps, a widely accepted method, may induce severe complications which are related to the use of intestinal mucosa. Therefore, we try to replace the intestinal mucosa with urothelial cells. After the urothelial cell expansion on temperature-responsive culture dishes, viable cultured urothelial cell sheets are harvested from these dishes. The cell sheets are autografted on demucosalized intestinal flaps, and then the bladder is augmented using these flaps. Transplantable urothelial cell sheets are obtained by utilizing temperature-responsive culture dishes covalently bonded with the thermally sensitive polymer, poly(N-isopropylacrylamide), and harvested from these dishes by reducing the temperature. In addition, we product smooth muscle cell sheets, and try to construct three-dimensional muscle layer by laminating smooth muscle cell sheets.

Department/Division: Department of Urology

Theme of research: mRNA expressions of factors in tumor progression and anti-cancer drug sensitivity in prostate cancer

Name of main researcher, title, and e-mail address:

Akinori Nukui Instructor

Brief explanation of research activity:

Expression levels of thymidylate synthase(TS), dihydropyrimidine dehydrogenase(DPD), thymidine phosphorylase(TP) and orotate phosphoribosyltransferase(OPRT) genes in prostate cancer tissues are evaluated to confirm whether they may be predictive parameters for tumor progression or the efficacy of anti-cancer drugs. We extract total RNA of harvested cells from areas of tumor and benign gland in the prostatectomy specimens using laser captured micro-dissection to harvest cells, and then perform reverse quantitative transcriptase polymerase chain reaction. In addition, we semiquantify the expression levels of TS, DPD and TP in the prostatectomy specimens immunohistochemically.

Department/Division: Department of Urology

Theme of research: Clinical research of hot flush in prostate cancer

Name of main researcher, title, and e-mail address:

Kazumi Suzuki, Instructor

Brief explanation of research activity:

Hot flushes are the major side effect of endocrine therapy for Japanese prostate cancer patients. (Suzuki K, Kobayashi M and Tokue A, *Nippinyoukaishi*, 94:614-620, 2003.) A relationship between the elevation of circulating calcitonin gene-related peptide (CGRP) levels and hot flush has been reported. Moreover, usefulness of *Kampo*, steroidal antiandrogen (SAA), and serotonin secretion re-uptake inhibitor (SSRI) to hot flush are also reported. The purposes of the present include (1) evaluation of the relationship between serum CGRP (early morning sample) value and various clinical factors study in endocrine or non-treated prostatic cancer patients, and (2) the evaluation of clinical efficacy of *Kampo*, SAA and SSRI against hot flush.