

Department of Pathology and Diagnostic Pathology

Professor

Masashi Fukayama, M.D., Ph.D.

Associate Professor

Shumpei Ishikawa, M.D., Ph.D., Junji Shibahara, M.D., Ph.D.

Lecturer

Yutaka Takazawa, M.D., Ph.D.*

Lecturer (Hospital)

Tetsuo Ushiku, M.D., Ph.D.* (visiting researcher, USA)

Associates

Rumi Hino, M.D., Ph.D.,

Yukako Shintani, M.D., Ph.D.,

Akiko Kunita, Ph.D.,

Mariko Tanaka, M.D., Ph.D.,

Aya Ushiku-Shinozaki, M.D., Ph.D. (visiting researcher, USA)

Teppei Morikawa, M.D., Ph.D.*,

Masako Ikemura, M.D., Ph.D.*,

Daichi Maeda, M.D., Ph.D.*,

Keisuke Matsusaka, M.D., Ph.D.*

Naoko Yamauchi, M.D., Ph.D. (Global COE Program)

Technical Support Specialist

Yasuyuki Morishita, M.T., Shinichi Harada, Kei Sakuma

Homepage <http://pathol.umin.ac.jp/>

Introduction and Organization

Department of Pathology and Diagnostic Pathology is responsible for the practice of diagnostic pathology, education, and research in conjunction with Division of Diagnostic Pathology of the University Hospital*. Our aim is the construction of “pathology as clinical medicine” as well as “next-generation pathology for translational research”.

Dr. Ushiku and Dr. Ushiku-Shinozaki worked at Massachusetts General Hospital, USA as a visiting researcher in 2012. Associate Professor, Dr. Shumpei Ishikawa, moved to Tokyo Medical and Dental

University as Professor of Department of Genome Pathology, Tokyo, on October, 2012. Dr. Hino moved to Department of Pathology, Cancer Institute, Japanese Foundation of Cancer Research, on January, 2013, and Dr. Aya Ushiku returned to the job on February.

Five postgraduate students (Abe, Ito, Morita, Yoshimoto, and Miyazaki) finished the course and received Ph.D. In the new fiscal year, 2013, five new students will enter the postgraduate course, and there will be 17 postgraduates (including one foreign student).

We are responsible for the pathology practice of the University Hospital, and are carrying forward the

morphology-based research targeting human diseases. As for the education for the medical students, we take charge of the following courses; General Pathology Course for the 1st grade students in collaboration with Department of Molecular Pathology, Systemic Pathology for the 2nd grade, Clinical Clerkship for the 3rd grade, and Bedside-learning (BSL) for the 4th grade students. Programs for postgraduates and junior residents are also included in our education activities.

The year 2012 was the 125th anniversary of the Department of Pathology. We held the memorial lecture meeting on May 19, and speakers were Dr. Tetsuichiro Muto, President Emeritus of Cancer Institute Ariake Hospital, and Dr. Kohei Miyazono, President of Postgraduate School of Medicine, the University of Tokyo. We also invited Dr. Kadowaki, the President of Tokyo University Hospital as a main guest, and had the celebration party.

Clinical activities (diagnostic pathology and autopsy)

Together with Division of Diagnostic Pathology, we are responsible for the pathologic diagnosis and autopsy in the University Hospital (see the corresponding section of Division of Diagnostic Pathology).

Surgical pathology conferences are regularly held with each clinical division, and the cases of various tumors are discussed, including thoracic organs, liver and pancreato-biliary tract, urology, gynecology, breast, and orthopedics, as well as biopsy cases of kidney, skin and GI tract.

Clinico-pathological conferences (CPCs) for two autopsy cases are held every month in the hospital. Both CPCs and weekly autopsy conferences are useful for the education of clinical residents. Digest versions of CPC slides are now open in the hospital, and we also started e-learning programs for interns to facilitate the understanding of the CPC contents. (Dr. Takazawa and Dr. Ikemura).

A model project for the survey analysis of deaths related to medical treatment (DRMT) has been in operation since September 2005, and we continue to be a member of the autopsy inspection of the project.

Teaching activities

We take on General Pathology Course for the 1st grade of undergraduate students, especially in its morphological field.

Each class of Systemic Pathology Course and exercises are held in parallel with that of Systemic Medicine Course. Handouts are available in every half course of the pathological exercises, and all slides used in the course are accessible on our website as virtual slides (digital images of the slides).

In BSL for 4th grade medical students, following courses are included; autopsy pathologic practices with a case presentation for paired students, surgical pathologic practices using various tumor sections, and a tour of the pathology laboratory. The past examination questions for graduation and Systemic Pathology for the second grade students are referred to the website. Two students chose the clinical clerkship course for 3rd grade medical students.

As for the free quarter program, we received four students of M0 and three of M1 in this fiscal year.

We also set up the lecture series of tumor pathology for the Cancer Profession Training Program in postgraduate school.

Research activities

The first major theme is “chronic inflammation and neoplasms”, especially Epstein-Barr virus (EBV) associated gastric carcinoma (GC) (Drs. Ushiku, Hino, Ushiku-Shinozaki, Matsusaka, and Kunita). We are focusing on the mechanisms of abnormalities in CpG island methylation and microRNA molecules in the development and progression of EBV-associated GC (ref.10). Mutations of ARID1A gene, a constituent protein of chromatin remodeling complex of SWI/SNF, were reported in various types of cancer, and the frequencies were rather high in two GC subtypes, EBV-associated and microsatellite unstable GC. We demonstrated by immunohistochemistry that the mutation occurs characteristically in an early stage in EBV-associated GC, which is different from other types of GC (ref. 2).

The second major theme is ‘translational research pathology’. We are engaged in search of target molecules for cancer therapy by global analysis of

expression profiles of various cancers, in collaboration with Research Center for Advanced Science and Technology (RCAST), the University of Tokyo. In addition, we take part in a global COE program, “Comprehensive Center of Education and research for Chemical Biology of the Diseases” , in which we are investigating the morphological analysis of gene expression abnormalities of the key molecules for several diseases (Dr. Yamauchi, ref. 38).

Dr. Ishikawa’s group is engaged in developing the precisely analyzing methods for genome information to establish a new field of pathology. They introduced a quantitative analysis using digital PCR for the investigation of Merkel cell polyoma virus, which was recently discovered from human tumors (ref. 28).

The third theme is to re-evaluate the disease entities and tumor entities from the standpoint of classical histopathology. Dr. Ushiku reported that claudin 6 is expressed in germ cell tumors and subsets of cancers of stomach, lung and ovary (ref. 32).

Dr. Morikawa accomplished a significant achievement in molecular epidemiology of colon cancer in USA, and participated in the basic research of microenvironment of cancer, demonstrating the contribution of cancer-associated fibroblast in drug resistance of cancer (ref. 31). Dr. Tanaka received the 100th Anniversary Memorial Award for Young Pathology Investigator for her thesis research about the carcinogenesis of the pancreas.

The research works closely related with pathology practice are described in Diagnostic Pathology Division.

References

(including those of Diagnostic Pathology Division)

- (1) Asawa Y, Sakamoto T, Komura M, Watanabe M, Nishizawa S, Takazawa Y, Takato T, Hoshi K. Early-stage Foreign Body Reaction against Biodegradable Polymer Scaffolds Affects Tissue Regeneration during the Autologous Transplantation of Tissue Engineered Cartilage in the Canine Model. *Cell Transplant*. 2012;21(7):1431-42.
- (2) Abe H, Maeda D, Hino R, Otake Y, Isogai M, Ushiku AS, Matsusaka K, Kunita A, Ushiku T, Uozaki H, Tateishi Y, Hishima T, Iwasaki Y, Ishikawa S, Fukayama M. ARID1A expression loss in gastric cancer: pathway-dependent roles with and without Epstein-Barr virus infection and microsatellite instability. *Virchows Arch*. 2012;461(4):367-77.
- (3) Horst D, Chen J, Morikawa T, Ogino S, Kirchner T, Shivdasani RA. Differential WNT activity in colorectal cancer confers limited tumorigenic potential and is regulated by MAPK signaling. *Cancer Res*. 2012;72(6):1547-56.
- (4) Ikeda Y, Oda K, Nakagawa S, Murayama-Hosokawa S, Yamamoto S, Ishikawa S, Wang L, Takazawa Y, Maeda D, Wada-Hiraike O, Kawana K, Fukayama M, Aburatani H, Yano T, Kozuma S, Taketani Y. Genome-wide single nucleotide polymorphism arrays as a diagnostic tool in patients with synchronous endometrial and ovarian cancer. *Int J Gynecol Cancer*. 2012;22(5):725-31.
- (5) Imamura Y, Morikawa T, Liao X, Lochhead P, Kuchiba A, Yamauchi M, Qian ZR, Nishihara R, Meyerhardt JA, Haigis KM, Fuchs CS, Ogino S. Specific mutations in KRAS codons 12 and 13, and patient prognosis in 1075 BRAF-wild-type colorectal cancers. *Clin Cancer Res*. 2012;18(17):4753-63.
- (6) Ishiura H, Sako W, Yoshida M, Kawarai T, Tanabe O, Goto J, Takahashi Y, Date H, Mitsui J, Ahsan B, Ichikawa Y, Iwata A, Yoshino H, Izumi Y, Fujita K, Maeda K, Goto S, Koizumi H, Morigaki R, Ikemura M, Yamauchi N, Murayama S, Nicholson GA, Ito H, Sobue G, Nakagawa M, Kaji R, Tsuji S. The TRK-fused gene is mutated in hereditary motor and sensory neuropathy with proximal dominant involvement. *Am J Hum Genet*. 2012;91(2):320-9.
- (7) Ishibashi Y, Takara Y, Tsukamoto M, Kinugasa S, Sugaya M, Takazawa Y, Kume H, Fujita T. Epithelium is absent from the subcutaneous tunnel in long-term peritoneal dialysis patients. *Perit Dial Int*. 2012;32(6):652-6.
- (8) Ito T, Murakawa T, Sato H, Tanabe A,

- Maekawa M, Yoshida Y, Fukayama M, Nakajima J. Simple preoperative computed tomography image analysis shows good predictive performance for pathological vessel invasion in clinical stage IA non-small cell lung cancer. *Interact Cardiovasc Thorac Surg*. 2012;15(4):633-8.
- (9) Kaji Y, Oshika T, Takazawa Y, Fukayama M, Fujii N. Co-localisation of advanced glycation end products and D-β-aspartic acid-containing proteins in gelatinous drop-like corneal dystrophy. *Br J Ophthalmol*. 2012;96(8):1127-31.
- (10) Kaneda A, Matsusaka K, Aburatani H, Fukayama M. Epstein-Barr virus infection as an epigenetic driver of tumorigenesis. *Cancer Res*. 2012;72(14):3445-50.
- (11) Kaneko MK*, Kunita A*, Abe S, Tsujimoto Y, Fukayama M, Goto K, Sawa Y, Nishioka Y, Kato Y. (*; equal contributor) A chimeric anti-podoplanin antibody suppresses tumor metastasis via neutralization and antibody-dependent cellular cytotoxicity. *Cancer Sci*. 2012;103(11):1913-9.
- (12) Kitagawa H, Watanabe K, Kage H, Inoh S, Goto A, Fukayama M, Nagase T, Ohishi N, Takai D. Pulmonary venous invasion, determined by chest computed tomographic scan, as a potential early indicator of zygomycosis infection: a case series. *J Thorac Imaging*. 2012;27(4):W97-9.
- (13) Koga T, Maruyama K, Tanaka M, Ino Y, Saito N, Nakagawa K, Shibahara J, Todo T. Extended field stereotactic radiosurgery for recurrent glioblastoma. *Cancer*. 2012;118(17):4193-200.
- (14) Kuchiba A, Morikawa T, Yamauchi M, Imamura Y, Liao X, Chan AT, Meyerhardt JA, Giovannucci E, Fuchs CS, Ogino S. Body mass index and risk of colorectal cancer according to fatty acid synthase expression in the nurses' health study. *J Natl Cancer Inst*. 2012;104(5):415-20.
- (15) Liao X, Morikawa T, Lochhead P, Imamura Y, Kuchiba A, Yamauchi M, Nosho K, Qian ZR, Nishihara R, Meyerhardt JA, Fuchs CS, Ogino S. Prognostic Role of PIK3CA Mutation in Colorectal Cancer: Cohort Study and Literature Review. *Clin Cancer Res*. 2012;18(8):2257-68.
- (16) Liao X, Lochhead P, Nishihara R, Morikawa T, Kuchiba A, Yamauchi M, Imamura Y, Qian ZR, Baba Y, Shima K, Sun R, Nosho K, Meyerhardt JA, Giovannucci E, Fuchs CS, Chan AT, Ogino S. Aspirin use, tumor PIK3CA mutation status, and colorectal cancer survival. *N Engl J Med*. 2012;367(17):1596-606.
- (17) Lin JH, Morikawa T, Chan AT, Kuchiba A, Shima K, Nosho K, Kirkner G, Zhang SM, Manson JA, Giovannucci E, Fuchs CS, Ogino S. Postmenopausal hormone therapy is associated with a reduced risk of colorectal cancer lacking CDKN1A expression. *Cancer Res*. 2012;72(12):3020-8.
- (18) Lochhead P, Imamura Y, Morikawa T, Kuchiba A, Yamauchi M, Liao X, Qian ZR, Nishihara R, Wu K, Meyerhardt JA, Fuchs CS, Ogino S. IGF2BP3 (IMP3) expression is a marker of unfavourable prognosis in colorectal cancer. *Eur J Cancer*. 2012;48(18):3405-13.
- (19) Matsubara D, Kanai Y, Ishikawa S, Ohara S, Yoshimoto T, Sakatani T, Oguni S, Tamura T, Kataoka H, Endo S, Murakami Y, Aburatani H, Fukayama M, Niki T. Identification of CCDC6-RET fusion in the human lung adenocarcinoma cell line, LC-2/ad. *J Thorac Oncol*. 2012;7(12):1872-6.
- (20) Miyauchi M, Yoshimi A, Nannya Y, Takazawa Y, Ichikawa M, Fukayama M, Kurokawa M. Efficacy of pleural biopsy for diagnosis of pleural effusion due to chronic GVHD after hematopoietic stem cell transplantation. *Int J Hematol*. 2012;96(1):146-8.
- (21) Miyazaki H, Uozaki H, Tojo A, Hirashima S, Inaga S, Sakuma K, Morishita Y, Fukayama M. Application of low-vacuum scanning electron microscopy for renal biopsy specimens. *Pathol Res Pract*. 2012;208(9):503-9.
- (22) Morikawa T, Kuchiba A, Qian ZR, Mino-Kenudson M, Hornick JL, Yamauchi M, Imamura Y, Liao X, Nishihara R, Meyerhardt JA, Fuchs CS, Ogino S.

- Prognostic significance and molecular associations of tumor growth pattern in colorectal cancer. *Ann Surg Oncol*. 2012;19(6):1944-53.
- (23) Morikawa T, Shima K, Kuchiba A, Yamauchi M, Tanaka N, Imamura Y, Liao X, Qian ZR, Brahmandam M, Longtine JA, Lindeman NI, Fuchs CS, Ogino S. No evidence for interference of H&E staining in DNA testing: usefulness of DNA extraction from H&E-stained archival tissue sections. *Am J Clin Pathol*. 2012;138(1):122-9.
- (24) Morikawa T, Tanaka N, Kuchiba A, Nosho K, Yamauchi M, Hornick JL, Swanson RS, Chan AT, Meyerhardt JA, Huttenhower C, Schrag D, Fuchs CS, Ogino S. Predictors of Lymph Node Count in Colorectal Cancer Resections: Data from U.S. Nationwide Prospective Cohort Studies. *Arch Surg*. 2012;147(8):715-23.
- (25) Morikawa T, Kuchiba A, Liao X, Imamura Y, Yamauchi M, Qian ZR, Nishihara R, Sato K, Meyerhardt JA, Fuchs CS, and Ogino S. Tumor TP53 expression status, body mass index, and prognosis in colorectal cancer. *Int J Cancer*. 2012;131(5):1169-78.
- (26) Morita K, Nakamura F, Nannya Y, Nomiya A, Arai S, Ichikawa M, Maeda D, Homma Y, Kurokawa M. Primary MALT lymphoma of the urinary bladder in the background of interstitial cystitis. *Ann Hematol*. 2012;91(9):1505-6.
- (27) Nagata M, Sakurai-Yageta M, Yamada D, Goto A, Ito A, Fukuhara H, Kume H, Morikawa T, Fukayama M, Homma Y, Murakami Y. Aberrations of a cell adhesion molecule CADM4 in renal clear cell carcinoma. *Int J Cancer*. 2012;130(6):1329-37.
- (28) Ota S, Ishikawa S, Takazawa Y, Goto A, Fujii T, Ohashi K, Fukayama M. Quantitative analysis of viral load per haploid genome revealed the different biological features of Merkel cell polyomavirus infection in skin tumor. *PLoS One*. 2012;7(6):e39954.
- (29) Satoh Y, Mori K, Kitano K, Kitayama J, Yokota H, Sasaki H, Uozaki H, Fukayama M, Seto Y, Nagawa H, Yatomi Y, Takai D. Analysis for the combination expression of CK20, FABP1 and MUC2 is sensitive for the prediction of peritoneal recurrence in gastric cancer. *Jpn J Clin Oncol*. 2012;42(2):148-52.
- (30) Soma K, Abe H, Takeda N, Shintani Y, Takazawa Y, Kojima T, Fujiu K, Semba H, Yamashita H, Hirata Y, Fukayama M, Nagai R. Myocardial involvement in patients with osteogenesis imperfecta. *Int Heart J*. 2012;53(1):75-7.
- (31) Straussman R, Morikawa T, Shee K, Barzily-Rokni M, Qian ZR, Du J, Davis A, Mongare MM, Gould J, Frederick DT, Cooper ZA, Chapman PB, Solit DB, Ribas A, Lo RS, Flaherty KT, Ogino S, Wargo JA, Golub TR. Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion. *Nature*. 2012;487(7408):500-4.
- (32) Sun M, Uozaki H, Hino R, Kunita A, Shinozaki A, Ushiku T, Hibiya T, Takeshita K, Isogai M, Takada K, Fukayama M. SOX9 expression and its methylation status in gastric cancer. *Virchows Arch*. 2012;460(3):271-9.
- (33) Ushiku T, Shinozaki-Ushiku A, Maeda D, Morita S, Fukayama M. Distinct expression pattern of claudin-6, a primitive phenotypic tight junction molecule, in germ cell tumours and visceral carcinomas. *Histopathology*. 2012;61(6):1043-56.
- (34) Watanabe K, Emoto N, Hamano E, Sunohara M, Kawakami M, Kage H, Kitano K, Nakajima J, Goto A, Fukayama M, Nagase T, Yatomi Y, Ohishi N, Takai D. Genome structure-based screening identified epigenetically silenced microRNA associated with invasiveness in non-small-cell lung cancer. *Int J Cancer*. 2012;130(11):2580-90.
- (35) Yamauchi M, Lochhead P, Morikawa T, Huttenhower C, Chan AT, Giovannucci E, Fuchs CS, Ogino S. Colorectal cancer: a tale of two sides, or a continuum? *Gut*. 2012;61(6):794-7.
- (36) Yamauchi M, Morikawa T, Kuchiba A, Imamura Y, Qian ZR, Nishihara R, Liao X, Waldron L, Hoshida Y, Huttenhower C, Chan AT, Giovannucci E, Fuchs CS, Ogino S. Assessment of colorectal cancer molecular features along bowel subsites challenges the conception of distinct dichotomy of proximal vs. distal colorectum. *Gut*. 2012;61(6):847-54.
- (37) Yamashiki N, Sugawara Y, Tamura S, Kaneko J,

Takazawa Y, Aoki T, Hasegawa K, Sakamoto Y, Koike K, Kokudo N. Living-donor liver transplantation for autoimmune hepatitis and autoimmune hepatitis-primary biliary cirrhosis overlap syndrome. *Hepatol Res*. 2012;42(10):1016-23.

- (38) Yamauchi N, Takazawa Y, Maeda D, Hibiya T, Tanaka M, Iwabu M, Okada-Iwabu M, Yamauchi T, Kadowaki T, Fukayama M. Expression levels of adiponectin receptors are decreased in human endometrial adenocarcinoma tissues. *Int J Gynecol Pathol*. 2012;31(4):352-7.
- (39) Yoshida A, Sekine S, Tsuta K, Fukayama M, Furuta K, Tsuda H. NKX2.2 is a useful immunohistochemical marker for Ewing sarcoma. *Am J Surg Pathol*. 2012;36(7):993-9.
- (40) Zong Y, Huang J, Sankarasharma D, Morikawa T, Fukayama M, Epstein JI, Chada KK, Witte ON. Stromal epigenetic dysregulation is sufficient to initiate mouse prostate cancer via paracrine Wnt signaling. *Proc Natl Acad Sci U S A*. 2012;109(50):E3395-404.