東京医科歯科大学

Tokyo Medical and Dental University (TMDU)
International Summer Program 2009
7th～9th September, 2009

PROGRAM

Recent Advances in Cancer Research

Dr. Takashi Ohyama

President
Tokyo Medical and Dental University

Message from the President

What makes Tokyo Medical and Dental University unique?
Is it the amount of research grants we obtain or the high citation index per researcher?
Yes, those aspects of TMDU are important, but I also would like you to know that our world-class researchers embrace the passion to save patients who are suffering from a disease against which we don't have an effective treatment at present.

Is it our facilities located in the center of Tokyo?
Yes, that is a fact which we feel proud of, but I rather wish people will admire our health care professionals who won't compromise in offering the best of medical and dental care to our patients, and those who stay beside the patients and their family members to help them maintain hope even in a dire moment of their life.

Through major structural changes in the past ten years, TMDU has become a national university corporation focusing on research and education in its graduate schools. In our history we have treasured the experience of teaching international students, which I believe served not only for the development of medicine and dentistry in students' home countries but also for the development of our own faculty in terms of appreciating different cultures and cultivating intellectual sympathy. It is our honor and pleasure to know that our international alumni encourage their friends or students to join us in our academic endeavor.

This year we are able to invite those who are so far not necessarily familiar with TMDU to the International Summer Program 2009. I hope this year's program will enable the participants to find out the unique features of our university as well as to satisfy their academic curiosity.

Dr. Sei Sasaki

Trustee and Vice·President, Strategic Planning and International Exchange
Tokyo Medical and Dental University

Message of Welcome

Dear Participants,

It is our great pleasure to welcome you to the Tokyo Medical and Dental University (TMDU) International Summer Program 2009.

Reflecting the rapid globalization of every aspect of life today, it is necessary for universities to become truly international institutions. The International Summer Program (ISP), launched this year, is one of the most important ways that we at TMDU are accelerating our international outreach. The aim of the ISP is to bring together students and young scientists from Asia, to study fundamental and emerging topics with leading scientists. To that end, we provided a total of 35 scholarships for attendance at the ISP. We hope that these future leaders will have a good chance to familiarize themselves with TMDU through this program and realize how their educational career may be enriched by overseas study.

The theme for ISP 2009 is “Advances in Cancer Research” and the program consists of two parts. The Lecture Course will feature lectures by leading researchers from abroad and from Japan and a poster session by students and young scientists from Asia. The second part, the International Symposium, will feature presentations by specially invited researchers from overseas. In addition, a joint program with the 8th Surugadai International Symposium, sponsored by the Medical Research Institute of TMDU, will be held in the afternoon of the final day of the ISP.

TMDU is located in the center of Tokyo and is a convenient base from which to explore the city, with its mix of exciting new places and historical, traditional areas. We thus arranged the Tokyo Excursion social program to help introduce the city to you.

We hope that the ISP 2009 will be both academically and socially beneficial for you. Thank you for your participation, and best wishes for your future career.

Sei Sasaki, M.D., Ph.D.

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ISP 2009 schedule

Date/Time	*Event*	*Venue*

Sunday, 6th September

17:00	**Registration**	Auditorium
17:30	**Orientation**	Auditorium
	MC: Prof. Kevin Cleary	
	Welcome Address: Dr. Sei Sasaki, Trustee, Starategic Planning and International Exchange	
	Introduction to the International Summer Program: Dr. Yasuhito Yuasa (TMDU)	
	Program Schedule: Dr. Ikuko Morio, Director, International Exchange Center	
18:00-20:00	**Welcome Reception**	**"Arumeida"**
	MC: Prof. Kevin Cleary	

Monday, 7th September

8:50-9:00	**Opening Remarks**	Auditorium
	Dr. Junji Tagami, Dean, Faculty of Dentistry (Tokyo Medical and Dental University)	
9:00-12:00	**Lecture Session 1**	Auditorium
	Chair: Dr. Yoshio Miki (Tokyo Medical and Dental University)	
9:00-9:45	• Dr. Yasuhito Yuasa (Tokyo Medical and Dental University)	
	Genetic and Epigenetic Involvement in Gastric Carcinogenesis	
9:45-10:30	• Dr. Masanobu Kitagawa (Tokyo Medical and Dental University)	
	Pathological Approach for Cancer Research: Recent Advances in Morphological Analysis	
	(Coffee Break, 15 min)	
	Chair: Dr. Yasuhito Yuasa (Tokyo Medical and Dental University)	
10:45-11:30	• Dr. Minetta C. Liu (Georgetown University Hospital, USA)	
	Molecular Diagnostics and Staging of Breast Cancer	
11:30-12:15	• Dr. Yoshio Miki (Tokyo Medical and Dental University)	
	Large-scale Genomic Studies of Cancer Patients for Personalized Medicine	
12:15-13:30	**Lunch Break**	
13:30-15:00	**Lecture Session 2**	Auditorium
	Chair: Dr. Masanobu Kitagawa (Tokyo Medical and Dental University)	
13:30-14:15	• Dr. Charlotte L. Bevan (Imperial College London, UK)	
	Endocrine Approaches to Treating Prostate Cancer	
14:15-15:00	• Dr. Yoshihiro Sasaki (Tokyo Medical and Dental University)	
	Drug Delivery System for Cancer Therapy	
	(Coffee Break, 15 min)	

Date/Time	*Event*	*Venue*
15:15-15:45	**Introduction to the University** Dr. Ikuko Morio, Director, International Exchange Center	Auditorium
15:45–17:15	**Campus Tour**	Campus
17:30–19:30	**Poster Session** **Supervisors**: Dr. Yoshihiro Sasaki, Dr. Hiroyuki Kagechika (Tokyo Medical and Dental University)	Seminar Room

Tuesday, 8th September

9:00-11:15	**Lecture Session 3** **Chair**: Dr. Johji Inazawa (Tokyo Medical and Dental University)	Auditorium
9:00-9:45	• Dr. Masahiko Miura (Tokyo Medical and Dental University) *Radiation Oncology and Biology for Oral Cancer*	
9:45-10:30	• Dr. Michael S. O'Reilly (M. D. Anderson Cancer Center, USA) *Angiogenesis: From Discovery to Clinical Application*	
10:30-11:15	• Dr. Sumio Sugano (University of Tokyo) *Transcriptome Analysis Using Second Generation Sequencers*	
12:00-17:00	**Afternoon Excursion in Tokyo**	
18:00-20:00	**Social Hour** **MC:** Prof. Kevin Cleary **ISP 2009 Address:** Dr. Sei Sasaki, Trustee, Strategic Planning and International Exchange **Presentation of ISP 2009 Certificates:** President Takashi Ohyama	**"Tokyo Garden Palace Hotel"**

Wednesday, 9th September

9:30-12:00	**International Symposium**
9:30-9:40	**Opening Remarks**: Dr. Kikuo Ohno Dean, Faculty of Medicine (Tokyo Medical and Dental University)
9:40-12:00	**Morning Session "Frontiers in Cancer Research"** **Chair**: Dr. Masahiko Miura (Tokyo Medical and Dental University)
9:40-10:25	• Dr. Minetta C. Liu (Georgetown University Hospital, USA) *Circulating Tumor Cells (CTC): A Reliable Predictor of Treatment Efficacy in Metastatic Breast Cancer*
10:25-11:10	• Dr. Charlotte L Bevan (Imperial College London, UK) *Inhibiting the Androgen Receptor in Prostate Cancer*

Date/Time	*Event*	*Venue*
11:10-11:55	• Dr. Michael S. O'Reilly (M. D. Anderson Cancer Center, USA) *Antiangiogenesis as Part of a Combined Modality Approach for the Treatment of Lung Cancer*	
11:55-13:00	**Lunch Break**	
13:00- 17:50	**Afternoon Session (Joint Session with the 8th Surugadai International Symposium)** "New Waves Towards Personal Genomics"	
13:00-13:10	Opening Remarks: Dr. Ikuo Morita (Trustee, TMDU) **Chair:** Dr. Hiroshi Tanaka, Dr. Fumitoshi Ishino	
13:10– 14:00	• Dr. David Hawkins (Ludwig Institute for Cancer Research, UCSD, USA) *Global Analysis of the Human Stem Cell Epigenome*	
14:00-14:25	• Dr. Hidehito Kuroyanagi (Medical Research Institute, TMDU) *Regulation of Alternative Splicing in vivo*	
14:25-14:50	• Dr. Yoshihito Niimura (Medical Research Institute, TMDU) *Evolution of Olfactory Receptor Genes in Vertebrates: From the Viewpoint of Comparative Genomics* (Coffee Break, 20 min) **Chair:** Dr. Masatoshi Hagiwara, Dr. Yoshio Miki	
15:10-16:00	• Dr. Yong Zhang (Beijing Genomics Institute, China) *Application of Next-generation Sequencing Technology on Cancer Genomics and Personal Genomics*	
16:00-16:25	• Dr. Masaaki Muramatsu (Medical Research Institute, TMDU) *Genome Epidemiology of Common Diseases* **Chair:** Dr. Shigetaka Kitajima, Dr. Johji Inazawa	
16:25-16:50	• Dr. Issei Imoto (Medical Research Institute, TMDU) *Integrative Genomics and Epigenomics in Cancer*	
16:50-17:40	• Dr. Jan P. Dumanski (Uppsala University, Sweden) *How Common is Somatic Mosaicism for DNA Copy Number Variations (CNVs)?*	
17:40-17:50	**Closing Remarks:** Dr. Shigeteka Kitajima (Director, MRI, TMDU)	

Profiles and Abstracts of the Lecture Course Presenters

Dr. Yasuhito Yuasa
(Tokyo Medical and Dental University, Japan)

Biodata

Dr. Yasuhito Yuasa graduated from Tokyo Medical and Dental University Medical School, and was awarded the degree of M.D. in 1973. He then graduated from the Institute of Medical Science, University of Tokyo and was awarded the degree of Ph.D. in Microbiology in 1977. In April 1977 he was employed as an Assistant Professor at the Institute of Medical Science, University of Tokyo. During 1980-1983 he was a Visiting Fellow at the Laboratory of Cellular and Molecular Biology, National Cancer Institute, NIH, USA. He became Associate Professor at the Department of Hygiene, Gunma University School of Medicine in 1985. Prof. Yuasa joined the Tokyo Medical and Dental University School of Medicine in 1988 as a Professor in the Department of Hygiene and Oncology. Since 2000 he has been Professor at Department of Molecular Oncology, Graduate School of Medicine and Dentistry, Tokyo Medical and Dental University.

Professor Yuasa's research concentrates on cellular and molecular analyses of cancer-related genes, such as oncogenes and tumor suppressor genes, in gastroenterological cancers; involvement of differentiation-related genes in gastroenterological cancers; DNA methylation and cancer; the effect of environmental factors on gene expression and DNA methylation; and involvement of cancer stem cells and microRNA in gastric carcinogenesis.

Lecture Course: Genetic and Epigenetic Involvement in Gastric Carcinogenesis

Abstract

Gastric carcinoma (GC) is the second most frequent cause of death from cancer in both sexes in the world. To date, many genetic and epigenetic alterations have been reported in GCs. However, the molecular mechanism underlying gastric carcinogenesis remains unclear. GC can be histologically divided into two distinct groups, the intestinal (differentiated) and diffuse (undifferentiated) types.

Defects in E-cadherin, a calcium-dependent cell adhesion molecule, have been found to be associated specifically with the diffuse type of GC. To investigate how the loss of E-cadherin affects gastric epithelial cell growth and differentiation, we generated transgenic mice using the Cre-loxP system where E-cadherin is specifically knocked-out in parietal cells. In the mutant mice, expression of E-cadherin was lost or reduced in parietal cells, which became round in shape, possibly by decreased cell-to-cell adhesion. Moreover, undifferentiated round cells formed clusters in the gastric mucosa, which did not express E-cadherin and some of which were Ki-67 positive. These results suggest that these proliferating cells are derived from E-cadherin-knockout parietal cells. This mouse model would be useful for investigating the role of E-cadherin in gastric carcinogenesis.

Epigenetic silencing of genes by aberrant DNA methylation is recognized as a crucial component of the mechanism underlying tumorigenesis. However, the relationship between DNA methylation and the past lifestyle in cancer patients remains largely unknown. We examined the methylation statuses of six tumor-related genes, CDX2, BMP-2, p16-INK4A, CACNA2D3, GATA-5, and ER (estrogen receptor), in primary GCs and compared them with the past lifestyles of the patients. Significant association was found between a decreased intake of green tea and methylation of CDX2 and BMP-2. More physical activity was correlated with a lower methylation frequency of CACNA2D3. Thus, some epidemiological factors, such as green tea intake, could be important as to determination of the methylation statuses of selected genes and may influence the development of cancer, including that of the stomach.

Micro (mi)RNAs are non-coding small RNAs and aberrant expression of miRNA has been reported in various cancers. To clarify the role of miRNA in gastric carcinogenesis, we performed miRNA microarray analysis and investigated expressional changes of miRNAs in a 5-aza-2'-deoxycytidine (DAC)-treated GC cell line. On microarray analysis, miR-181c was found to be upregulated and miR-181c up-regulation was found in two more GC cell lines with DAC treatment. Decreased expression of miR-181c was observed in several primary GC cases. Hypermethylation signals in the upstream region of miR-181c were observed in some cultured and primary GC cells with low miR-181c expression. Transfection of the precursor miR-181c molecule induced decreased growth of GC cell lines. As for targets of miR-181c, oncogenic NOTCH4 and KRAS were identified. These results indicate that miR-181c may be silenced through methylation and play important roles in gastric carcinogenesis through its target genes, such as NOTCH4 and KRAS.

Dr. Masanobu Kitagawa
(Tokyo Medical and Dental University, Japan)

Biodata

Dr. Masanobu Kitagawa graduated from Tokyo Medical and Dental University (TMDU) in 1981 and was promoted to Professor in the Department of Comprehensive Pathology of TMDU in 2005. Dr. Kitagawa studies human/experimental pathology, especially in the field of hematopathology. The basic aims of his research are to clarify the mechanisms of host defensive reactions against carcinogenesis/tumor progression and to develop novel strategies for tumor therapy. Using animal models, several signaling molecules are identified as the targets for regulating tumor cell apoptosis/cell proliferation. Dr. Kitagawa also works as a clinical pathologist in the Pathology Division of the TMDU Medical Hospital. The Pathology Division investigates the clinicopathological aspects of various human diseases including myelodysplastic syndromes (MDS), other hematopoietic cell tumors and gastrointestinal tumors. Using fresh frozen samples as well as formalin-fixed samples, many kinds of molecules have been analyzed to characterize them in the network of cellular signaling in tumor cells.

Lecture Course: Pathological Approach for Cancer Research: Recent Advances in Morphological Analysis

Abstract

Recently, many kinds of technological methods for morphological and pathological analysis have been developed to detect various substances in the field of tumor biology. In the present lecture, recent advances in pathological approach for cancer research such as immunohiostochemistry, *in situ* hybridization, electron microscopy, tissue microarray, DNA microarray, and expression array for RNA and proteins will be introduced with a few examples of actual data. These technologies enabled us to clarify the i*n vivo* status of human tumors.

Pathological data of tumors would be of great importance not only as the tool for final diagnosis (histological typing) of tumors but also as information for interpreting the biological state of *in vivo* local tumors. To recognize the real signals or genetic alteration of the tumor cells, we have to exclude the influence of interstitial cells including vessels, fibroblasts, inflammatory cells, extracellular matrix and so on. However, in some situations, interactions of tumor cells with the interstitium would be extremely important for understanding the biological behavior of tumors. In that case we have to separately investigate the signals in the interstitial cells and the tumor cells. Therefore, to obtain the correct and appropriate information about tumors, localization of molecules should be realized in addition to the up- and down-regulation of their expression levels. Furthermore, analysis of early and small lesions from pre-cancerous or early-cancer state would have a significant impact on the studies of carcinogenesis.

Of course, the experimental approach should be added to the pathological analysis of clinical samples in order to confirm that the target molecules are really having a role on tumor cell biology. The experimental approach would include the *in vitro* works using cell line and animal model studies. At this stage also, pathological analysis methods are indispensable for understanding the correct state of tumors.

Implications of pathological analysis for cancer research will be discussed.

Dr. Minetta C. Liu

(Georgetown University Hospital, USA)

Biodata

Minetta C. Liu, MD, is the Director of Translational Breast Cancer Research and the Biomarker Section Chief of the Clinical Molecular Diagnostics Laboratory at Georgetown University's Lombardi Comprehensive Cancer Center in Washington, DC. An Associate Professor of Medicine and Oncology, her primary research focus is on the efficient development of reliable predictors of treatment response. Her clinical goals are to provide multidisciplinary breast cancer care and offer appropriate patients access to novel therapeutic agents and diagnostic tools. Toward that end, she serves as the principal investigator for several institutional, cooperative group, and industry sponsored clinical trials in breast cancer.

Dr. Liu received her medical degree from Jefferson Medical College in Philadelphia, Pennsylvania before completing a residency in Internal Medicine and a fellowship in Hematology/Oncology at Georgetown University Medical Center. Dr. Liu is a Diplomate of the American Board of Internal Medicine with certification in internal medicine and medical oncology. She serves on the Breast Committee, Solid Tumor Correlative Sciences Committee, and Executive Committee for the Cancer and Leukemia Group B, and she is an active member of the ASCO Cancer Education Committee. Her clinical and translational research efforts are currently supported by grants from the National Cancer Institute, the Department of Defense, and the Susan G. Komen for the Cure Foundation.

Lecture Course: Molecular Diagnostics and Staging of Breast Cancer

Abstract

We asked Dr. Liu to provide slides as an abstract for her lecture, and plan to have them available for participants at the ISP.

Dr. Yoshio Miki
(Tokyo Medical and Dental University, Japan)

Biodata

Dr. Yoshio Miki joined Tokyo Medical and Dental University (Tokyo, Japan) in 2002, as Professor of the Department of Molecular Genetics in the Medical Research Institute. The aims of his group are to promote basic biological research which clarifies the biological nature of cancer and establishes new diagnosis and medical treatment of the cancer based on the information acquired by the research. Concretely, Prof. Miki's team analyzes the roles of DNA damage repair and apoptosis in carcinogenesis, focusing on some kinases which bear this signal transduction, or BRCA1 and BRCA2. Prof. Miki's current research projects are
(1) The investigation of a mechanism in breast carcinogenesis—functional analysis of the gene responsible for hereditary breast cancer, BRCA2, and development of the personalized medicine for breast cancer applying genome science; (2) intracellular signaling transduction and cell death in DNA damage by analyzing the cell cycle control mechanism by protein kinase C delta, and the investigation of the mechanism of apoptosis induction by c-Abl.

Lecture Course: Large-scale Genomic Studies of Cancer Patients for Personalized Medicine

Abstract

The aim of the present investigation is to identify the genetic factors that can be used to optimize the development of highly efficacious, safe drugs for specific subpopulations of cancer patient. Paclitaxel and docetaxel are taxoid drugs, and are now the most active agents for breast cancer. They both work by interfering with mitosis, but they each do it a little differently and the sensitivity is heterogeneous. To avoid unnecessary treatment, identification of a predictive marker is desired to distinguish between patients who are likely to respond and those who are not. We report the discovery of a gene expression profile that predicts response to paclitaxel or docetaxel in breast cancer patients. We took core needle samples from patients with primary breast cancer before treatment and then assessed tumor response to neoadjuvant under IC. Patents were divided into five groups according to pathological responses (Grade 0, extremely resistant; Grade 1a, resistant; Grade 1b, moderate responder; Grade 2, responder; Grade 3, high responder). Approximately 50 genes were differentially expressed between responder (Grades 2 and 3) and extremely resistant (Grade 0) groups as selected by use of the Mann-Whitney U-test. Next, correlation between RNA expression measured by the arrays and quantitative RT-PCR was ascertained on the selected genes. Using the quantitative RT-PCR data of selected genes, we performed machine-learning method (AdaBoost) to determine the greatest estimated accuracy between responders (Grades 2 and 3) and non-responders (Grades 0, 1a and 1b), and high-scored predictive sets were selected.

Secondly, to predict the probability of adverse effects from the use of paclitaxel treatment, we conducted genotyping analysis on breast cancer patients enrolled onto neoadjuvant paclitaxel therapy. Adverse effects were evaluated according to NCI-CTC grading. To elucidate SNPs associated with granulocytopenia, genotypes of 3,144 SNPs over 507 genes on 54 participants were determined by Invader assay. Associations were examined by comparing genotypes of patients with and without granulocytopenia, and SNPs on two loci were found to be associated with granulocytopenia. Thus, we will demonstrate the application of large-scale genetic studies in breast cancer patients to molecular prediction of drug response and adverse effect to specific drug treatments.

Dr. Charlotte L. Bevan

(Imperial College London, UK)

Biodata

Dr. Charlotte Bevan joined Imperial College in 1999 as head of the Androgen Signalling Group in the Department of Oncology, SORA (Division of Surgery, Oncology, Reproductive Biology and Anaesthetics). The aims of the group are to investigate the mechanisms of signalling via the androgen receptor and how signalling is altered during prostate cancer progression. The group also investigates the biological causes of prostate cancer development and progression, with emphasis on research leading to the development of new therapies or improvement in the application of existing therapies. The mechanisms, how antiandrogens used in hormone therapy exert their effects, and the role of androgen receptor-interacting proteins (coactivators and corepressors) in these processes are studied as well. Dr. Bevan is also Non-Clinical Head of the Section of Molecular Cell Biology.

Lecture Course: Endocrine Approaches to Treating Prostate Cancer

Abstract

We asked Dr. Bevan to provide slides as an abstract for her lecture, and plan to have them available for participants at the ISP.

Dr. Yoshihiro Sasaki

(Tokyo Medical and Dental University, Japan)

Biodata

Yoshihiro Sasaki is currently an Associate Professor in the Organic Materials Laboratory of the Institute of Biomaterials and Bioengineering at Tokyo Medical and Dental University. Dr. Sasaki received a Ph.D. in 1999 from Kyoto University in polymer chemistry under the guidance of Prof. J. Sunamoto. After receiving his Ph.D., he worked as an assistant professor at Nara Institute of Science and Technology, and concentrated his research on artificial cell membranes and their application to nanobioscience. In 2003, Dr. Sasaki was a visiting scholar at the University of Notre Dame, USA. He then joined Prof Akiyoshi's group at Tokyo Medical and Dental University in 2008. His research covers a broad range of topics in bioinspired chemistry and nanobioscience centered around supramolecular chemistry, focusing on artificial cell (liposome), organic-inorganic nanohybrid, self-assembled nanogels, synthetic receptors, and molecular devices as well as the study of their biomedical applications including gene delivery and cancer chemotherapy.

Lecture Course: Drug Delivery for Cancer Therapy

Abstract

The induction of a specific immune response against tumor cells is a highly achievable goal in immune therapy for cancer. In this seminar, a novel nanogel/oncoprotein complex vaccine will be introduced. Nanogels have attracted growing interest with respect to their application in biomedical research including drug delivery systems (DDS). So far, we have been reported hydrophobized polysaccharides such as cholesterol-bearing pullulan (CHP) form stable amphiphilic nanogels in water by self-association of hydrophobic groups, which form physically crosslinked points. CHP nanogels trap various proteins and show molecular chaperone-like activity that is to prevent aggregation of denatured proteins and to release them as active forms. CHP nanogels are useful for protein delivery such as cancer vaccine and cytokine therapy. For example, CHP nanogels complexed with HER2 soluble protein has been demonstrated in mice model to elicit efficient $CD8^+$ and $CD4^+$ T cell responses and to produce higher titers of antibodies against HER2 protein. Clinical trial demonstrated that vaccination with the CHP-HER2 induced HER2-specific $CD8^+$ and/or $CD4^+$ T cell immune responses in five out of nine patients (Collaboration with Prof. H. Shiku in Mie University). For a valid cytokine immunotherapy of malignancies, a suitable delivery system that ensures slow-release of cytokines is required, because short half-life in vivo and causing severe systemic toxic effects. We applied the nanogel of CHP to administration in vivo of recombinant murine IL-12 (rmIL-12). Repetitive administrations of the CHP/rmIL-12, but not rmIL-12 alone, induced drastic growth retardation of pre-established subcutaneous fibrosarcoma without causing any serious toxic event (Collaboration with Prof. T. Mazda in Kyoto Prefectural University of Medicine). The present study proposes a novel therapeutic intervention technology, taking advantage of slow and sustained release of bioactive cytokines from the self-assembling biocompatible nanoparticles. Recent advances in drug delivery system will be also reviewed in the lecture.

Dr. Masahiko Miura

(Tokyo Medical and Dental University, Japan)

Biodata

Dr. Masahiko Miura was awarded a Ph. D. in Radiation Biology in 1991 and has been Professor of Oral Radiation Oncology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, since 2008. Dr. Miura has performed clinical research focused on radiotherapy for oral cancer treatment as well as basic research on the molecular mechanisms underlying tumor radioresistance and strategies for overcoming this resistance. Brachytherapy (BRT) for early oral cancer is regarded as a highly efficient modality associated with improved tumor control and QOL. At Dr. Miura's department, the local control rate in BRT-treated patients is approximately 90% and the five-year survival rate is approximately 80%. Dr. Miura and his collaborators recently discovered a natural compound, sulfoquinovosylacylglycerol (SQAG), that functions as an antiangiogenic radiosensitizer. Current research is aimed at further development of these compounds for clinical applications. Dr. Miura's research interests also extend to signal transduction pathways downstream of growth factor receptors and molecular imaging of tumor cells using the cell cycle- and tumor microenvironment-associated fluorescent probes.

Lecture Course: Radiation Oncology and Biology for Oral Cancer

Abstract

The oral cavity is involved in many basic life functions, such as speech, occlusion, swallowing, respiration, and social interactions. Therefore, when treating oral cancers, it is necessary to minimize the deterioration of the quality of life (QOL) and maximize tumor control. Low dose-rate brachytherapy (LDR-BRT) is thought to be one of the best modalities to treat early oral cancers. Unlike fractionated conventional radiotherapy (RT), which uses external beam radiation, LDR-BRT uses radioisotopes consisting of Cs-137 needles, Ir-192 hairpins, or Au-198 grains that are directly implanted into the tumor tissues. With this modality, the local control rate is approximately 90%, and the five-year survival rate is 80% for Stage I and II oral cancers at our institution, which is comparable to surgery results.

Conventional RT is unable to give a sufficient radiation dose that will cure the tumor because its irradiation fields include normal, radiosensitive tissues, such as the mandibular bones and salivary glands. Even state of the art techniques, notably intensity modulated radiotherapy (IMRT) or heavy ion beam therapy, are inferior to LDR-BRT in their ability to focus the dose on tumor tissues. This specificity of LDR-BRT is simply explained by the "inverse squares law". In addition to the physical advantages of dose distribution, LDR-BRT also has biological advantages. Low dose-rate irradiation efficiently induces G2 arrest in tumor cells. Because cells at this phase are radiosensitive, continuous irradiation readily kills these tumor cells. The repair of radiation damage in normal tissues, especially late-responding tissues like the mandibular bones, strongly depends on the dose-rate. Therefore, low dose-rate irradiation allows the mandibular bones to remarkably repair radiation damage, while the tumor cell killing effect is minimally affected. The use of spacers for tongue tumors, which are inserted between the lower gum and tongue, further reduces the radiation damage to the bones. Although the total treatment time for conventional RT is 6-7 weeks, the treatment time for LDR-BRT is 5-6 days, which minimizes the repopulation of cancer stem cells.

In this lecture, I would like to briefly show you the clinical practice of LDR-BRT and share some basic knowledge regarding radiation biology, which will help you understand why LDR-BRT is extremely useful for early oral cancers. I will also introduce some of our recent research on the radiosensitization of tumor tissues.

Dr. Michael S. O'Reilly

(M. D. Anderson Cancer Center, USA)

Biodata

Dr. Michael O'Reilly has focused his research efforts on the discovery and characterization of endogenous inhibitors of angiogenesis. By studying the phenomenon of the suppression of tumor growth by tumor mass, he discovered the angiogenesis inhibitors angiostatin and endostatin and an antiangiogenic form of antithrombin. Dr. O'Reilly is now studying the interaction of antiangiogenic agents with each other, radiation therapy, and chemotherapy in a series of projects designed to produce improved efficacy and diminished toxicity in the treatment of cancer. Dr. O'Reilly has characterized a novel type of tumor dormancy, study of which should allow for a better understanding of the dormant state and the patterns of growth of primary and metastatic cancer.

Lecture Course: Angiogenesis: From Discovery to Clinical Application

Abstract

We asked Dr. O'Reilly to provide slides as an abstract for his lecture, and plane to have them available for participants at the ISP.

Dr. Sumio Sugano

(The University of Tokyo, Japan)

Biodata

Dr. Sugano earned his B.M. from Tokyo Medical and Dental University in 1978, and his M.D. / Ph.D. from the University of Tokyo in 1982. Dr. Sugano has worked at the Institute of Medical Science of the University of Tokyo for 22 years, and is now a professor at the university's Department of Frontier Sciences.

The main emphasis of Dr. Sugano's research is to identify and collect genes of human en masse in the form of full-length cDNAs. He initiated the so-called FLJ project of collecting and determining the entire sequences of human full-length cDNAs. He also determined 5'-end one pass sequences of 1,145,855 cDNAs isolated from 134 full-length enriched cDNA libraries constructed by the oligo-capping method. As an example of his research findings was to find an unexpectedly large population of cDNAs which contained no obvious ORFs. Furthermore, an unexpectedly large number of alternative splice and alternative promoters seems to have been present. Dr. Sugano was a member of the council of HUGO from 2002-2008, and was the chairman of HUGO Asia-Pacific in the same period.

Lecture Course: High Throughput Identification of Transcriptional Start Sites Using Second Generation Sequencers

Abstract

Several methods have been developed for proper identification of transcriptional start sites (TSSs). We also have developed a method to selectively replace the cap structure of the mRNA with a synthetic oligo, which we named "oligo-capping". By sequencing 1.8 million cDNAs isolated from oligo-cap cDNA libraries from various kinds of human cells and tissues, we have collected the positional information of the TSS and analyzed upstream putative promoter regions. However, although an overview of the TSSs has been obtained from collective data from various cell types and tissues, for each of these data coverage still remains relatively scarce. Therefore, the current overview does not represent the actual transcriptional landscape in a particular cell type. Massively parallel sequencing technologies, brought about by second-generation sequencers, have provided the opportunity to further improve the throughput of TSS identification. For example, Illumina GA sequencers can provide approximately 40 to 100 million sequence tags per run. Although the read length which these sequencers can generate is short (36-50 bases), it is sufficient to uniquely determine the precise positions of TSSs. We have devised a simple method to enable extremely high-throughput sequencing of the 5'-ends of transcripts by combining our full-length cDNA method and the massively parallel sequencer. Using this method, we performed genome-wide analysis of TSS.

Profiles and Abstracts of the Symposium Presenters

Dr. Minetta C. Liu

(Georgetown University Hospital, USA)

Biodata

Minetta C. Liu, MD, is the Director of Translational Breast Cancer Research and the Biomarker Section Chief of the Clinical Molecular Diagnostics Laboratory at Georgetown University's Lombardi Comprehensive Cancer Center in Washington, DC. An Associate Professor of Medicine and Oncology, her primary research focus is on the efficient development of reliable predictors of treatment response. Her clinical goals are to provide multidisciplinary breast cancer care and offer appropriate patients access to novel therapeutic agents and diagnostic tools. Toward that end, she serves as the principal investigator for several institutional, cooperative group, and industry sponsored clinical trials in breast cancer.

Dr. Liu received her medical degree from Jefferson Medical College in Philadelphia, Pennsylvania before completing a residency in Internal Medicine and a fellowship in Hematology/Oncology at Georgetown University Medical Center. Dr. Liu is a Diplomate of the American Board of Internal Medicine with certification in internal medicine and medical oncology. She serves on the Breast Committee, Solid Tumor Correlative Sciences Committee, and Executive Committee for the Cancer and Leukemia Group B, and she is an active member of the ASCO Cancer Education Committee. Her clinical and translational research efforts are currently supported by grants from the National Cancer Institute, the Department of Defense, and the Susan G. Komen for the Cure Foundation.

Symposium Talk: Molecular Diagnostics and Staging of Breast Cancer

Abstract

Dr. Liu's abstroct will be available for participants of the ISP 2009.

Dr. Charlotte L. Bevan
(Imperial College London, UK)

Biodata

Dr. Charlotte Bevan joined Imperial College in 1999 as head of the Androgen Signalling Group in the Department of Oncology, SORA (Division of Surgery, Oncology, Reproductive Biology and Anaesthetics). The aims of the group are to investigate the mechanisms of signalling via the androgen receptor and how signalling is altered during prostate cancer progression. The group also investigates the biological causes of prostate cancer development and progression, with emphasis on research leading to the development of new therapies or improvement in the application of existing therapies. The mechanisms, how antiandrogens used in hormone therapy exert their effects, and the role of androgen receptor-interacting proteins (coactivators and corepressors) in these processes are studied as well. Dr. Bevan is also Non-Clinical Head of the Section of Molecular Cell Biology.

Symposium Talk: Inhibiting the Androgen Receptor in Prostate Cancer

Abstract

Growth of prostate tumours is initially dependent on androgens. Androgens exert their effects via the androgen receptor (AR), a ligand-activated transcription factor that recruits cofactor proteins (coactivators and corepressors) in response to ligand binding. Coactivators and corepressors alter the accessibility of chromatin to the transcriptional machinery and hence alter rates of transcription of target genes.

Current hormonal therapies for prostate cancer aim to reduce levels of circulating androgens by chemical castration and also to inhibit the AR directly by use of antiandrogens. These therapies are effective initially but inevitably tumours progress to an advanced, metastatic stage, often referred to as “androgen-independent” or hormone-refractory. However, the AR signalling pathway is still key for their growth. In some cases, the AR Is mutated allowing its activation by alternative ligands. IN others, it is speculated that tumours escape hormonal control via alterations in cofactor levels – increases in coactivators or reduction of corepressor proteins. Manipulating such proteins is thus a potential therapeutic strategy to halt or even reverse tumour progression.

We aimed to elucidate the effects of altering levels of one such factor - the AR corepressor and androgen target protein prohibitin - on prostate tumour growth. Prostate cancer cells incorporating an integrated androgen-responsive reporter gene and stably expressing vectors to inducibly overexpress or knockdown prohibitin were generated and used to assess effects on androgen signalling (by real time imaging and target gene expression) and cell/tumour growth (by FACs and tumour volume measurement) both in culture and in vivo in xenograft models. We found that prohibitin overexpression inhibited AR activity and PSA expression as well as androgen-dependent growth of cells, inducing rapid accumulation in G0/G1. Conversely, reduction of prohibitin increased AR activity, PSA expression, androgen-mediated growth and S-phase entry. In vivo, doxycycline-induced prohibitin regulation resulted in marked changes in AR activity, and showed significant effects upon tumour growth. Overexpression led to tumour growth arrest and protection from hormonal starvation, whereas RNAi knockdown resulted in accelerated tumour growth, even in castrated mice. Further, we also found preliminary evidence that reduction of prohibitin levels may promote tumour metastasis.

This study provides proof-of-principle that (i) reduction of prohibitin promotes both androgen-dependent and “androgen-independent” tumour growth and (ii) altering AR activity via increasing levels or activity of corepressors is a valid therapeutic strategy for advanced prostate cancer. However, most corepressors are relatively large proteins. To create a more viable therapeutic, we are designing and validating artificial corepressors with the potential to be synthesised as small molecule inhibitors of AR activity. These are designed to inhibit AR activity even under the conditions predicted to lead to androgen independence, including AR mutation and AR or coactivator overexpression.

Dr. Michael S. O'Reilly
(M. D. Anderson Cancer Center, USA)

Biodata

Dr. Michael O'Reilly has focused his research efforts on the discovery and characterization of endogenous inhibitors of angiogenesis. By studying the phenomenon of the suppression of tumor growth by tumor mass, he discovered the angiogenesis inhibitors angiostatin and endostatin and an antiangiogenic form of antithrombin. Dr. O'Reilly is now studying the interaction of antiangiogenic agents with each other, radiation therapy, and chemotherapy in a series of projects designed to produce improved efficacy and diminished toxicity in the treatment of cancer. Dr. O'Reilly has characterized a novel type of tumor dormancy, study of which should allow for a better understanding of the dormant state and the patterns of growth of primary and metastatic cancer.

Symposium Talk: Antiangiogenesis as Part of a Combined Modality Approach for the Treatment of Lung Cancer

Abstract

Angiogenesis is critical for a number of physiologic and pathophysiologic processes and several lines of direct evidence confirm that tumor growth is angiogenesis dependent. Although antiangiogenic agents show great promise, their clinical use, particularly when administered as monotherapy, may be associated with a number of potential limitations including a delayed onset of anti-tumor activity, the development of resistance, and the potential for persistent microscopic residual disease even after prolonged high dose administration. Further, the specific organ microenvironment of a given malignancy may influence response to antiangiogenic, anti-vascular, and other biologic therapies. For patients with advanced malignancy, the limitations of antiangiogenic monotherapy will necessitate a combined modality approach and surrogates of response to therapy need to be developed and validated. To overcome the limitations of antiangiogenic monotherapy, angiogenesis inhibitors can and should be combined with radiation therapy, chemotherapy, and other therapeutic modalities. In preclinical and clinical studies, antiangiogenic therapy enhances the effects of radiotherapy and chemotherapy although the degree of enhancement may be dependent upon the sequencing of each modality and upon the tumor microenvironment. A number of antiangiogenic agents have been described and several are currently in clinical trials in cancer patients in conjunction with chemotherapy and radiation therapy. Two of the most widely studied targets are epidermal growth factor (EGFR) and VEGFR and clinical trials of agents that target these and other pathways are currently underway. Bevacizumab (Avastin), an antibody that targets the proangiogenic molecule vascular endothelial growth factor (VEGF), is now approved for clinical use as part of combined modality therapy for patients with lung, colorectal, renal, and other cancers and has also shown efficacy when combined with chemotherapy in Phase III clinical trials for breast, colon, and lung cancer patients. Orally available small molecules can also be used to target VEGFR, EGFR, and other receptor tyrosine kinases involved in angiogenesis. To study the potential therapeutic efficacy of antiangiogenic therapies as part of a combined modality approach to the treatment of lung cancer, we have developed orthotopic and metastatic non-small cell and small cell lung cancer models that closely mimic clinical patterns of lung cancer growth and dissemination. By developing a rational basis for the combination of antiangiogenic agents with conventional therapies, improved efficacy and diminished toxicity in the treatment of lung and other cancers will be possible. The endothelial cell can now be considered as one gatekeeper capable of regulating tumor growth and it will be prudent to use angiogenesis inhibitors in combination with other modalities in order to overcome the limits of each. To accomplish this goal, a better understanding of the regulation of angiogenesis is needed and strategies for the use of antiangiogenic agents may need to be optimized on a site, disease, and perhaps patient specific basis. By doing so, cancer can potentially be transformed into a chronic and controllable disease.

Dr. David Hawkins

(Ludwig Institute for Cancer Research, UCSD, USA)

Biodata

2005–present Postdoctoral Fellow, Ludwig Institute for Cancer Research, San Diego
Supervisor: Bing Ren, Ph.D., Head, Laboratory of Gene Regulation

1999–2005 UTSW graduate student, Washington University School of Medicine in St. Louis
Supervisor: Michael Lovett, Ph.D., Professor, Co-director Division of Human Genetics, Washington University School of Medicine

1997–1999 University of Texas, Southwestern Medical Center, Dallas
Graduate Student in Genetics & Development program

Symposium Talk: Global Analysis of the Human Stem Cell Epigenome

Abstract

Embryonic stem cells (ESCs) are defined by their ability to self-renew and their pluripotency. While gene expression studies and regulatory networks for a few select transcription factors have begun to elucidate the regulatory mechanisms that underlie these properties, our scope of transcriptional regulation in ESCs remains predominantly incomplete. To better understand the role of various cis-regulatory elements in the regulation of gene expression, we determined the genome-wide location of enhancers, based on chromatin modifications, and CTCF bound insulator sites in human ESCs. Collectively, they constitute the cis-regulatory blocks necessary for the coordinated control of gene expression with cell type-specific enhancers enriched in blocks with cell type-specific gene expression. Furthermore, the construction of genome-wide maps for several histone modifications in both human ESCs and differentiated cells allowed us to ascertain how one genome gives rise to separate epigenomes to control gene expression, and more specifically identify human ESC specific enhancers, many of which contain pluripotent transcription factor binding motifs. Additionally, we describe a dynamic chromatin modification switch at lysine 27 of histone H3 (H3K27) at gene promoters following differentiation. This epigenetic switch suggests genes important for maintaining ESC traits, as these genes are held in a repressed state following differentiation.

In addition, as a concerted effort to ascertain the epigenome, we have generated genome-wide maps for eleven histone modifications using high-throughput sequencing, ChIP-Seq, and begun a comparative analysis with DNA methylation in human embryonic stem cells and normal fetal fibroblasts. We find that the chromatin architecture is distinctly different between pluripotent and differentiated cells, specifically related to the use and size of the H3K27me3 and H3K9me3 domains. Additionally, these domain structures contrast with H3K4 methylation domains as well as acetylation domains. Significant proportions of the genome fall into large domains of H3K27me3, H3K9me3 or H3K36me3. Collectively, all histone modifications surveyed occupy 64% of the genome, each with a different correlation to DNA methylation. Surprisingly, while many modifications have predictive correlations with DNA methylation, the reciprocal is not true. Furthermore, we show that while H3K36me3 and DNA methylation are present in gene bodies, the chromatin structure is more highly correlated with gene expression levels. In conclusion, we provide a high resolution genome-wide view of two unique cellular epigenomes.

Dr. Hidehito Kuroyanagi

(Tokyo Medical and Dental University, japan)

Biodata

Educational History

B.S. Faculty of Science, University of Tokyo (Prof. Y. Inoue), 1994

M.S. Graduate School of Science, University of Tokyo (Prof. M. Oishi), 1996

Ph.D. Graduate School of Science, University of Tokyo (Prof. A. Miyajima), 1999

Research History

1999–2000	Postdoctoral Research Fellow, Yamanouchi Pharmaceutical Company
2000–2003	Assistant Professor, Graduate School, Tokyo Medical and Dental University
2003–2008	Lecturer, School of Biomedical Science, TMDU
2008–Present	Associate Professor, School of Biomedical Science, TMDU
2008–Present	PRESTO Researcher, Japan Science and Technology Agency (JST).

Symposium Talk: A Transgenic Reporter System Reveals Expression Profiles and Regulation Mechanisms of Alternative Splicing in vivo

Abstract

Alternative splicing of pre-mRNAs in metazoans is one of the most important mechanisms that confer a spatiotemporal diversity in gene expression. Recent global analyses of mRNAs from various tissues and cell lines revealed that as many as 90% of multi-exon genes generate alternative mRNA isoforms. Regulation mechanisms of alternative splicing have been studied mostly in vitro or in cultured cells, and many cis-elements and trans-factors have been characterized to date. However, molecular mechanisms underlying complex spatiotemporal patterns of alternative splicing in living organisms, or "splicing codes," are largely uncharacterized due to difficulties in analyzing splicing regulation in vivo.

We have recently developed a transgenic alternative splicing reporter system that visualizes expression profiles of alternative exons at a single cell resolution in vivo with multiple fluorescent proteins by utilizing Caenorhabditis elegans as a model organism. With the in-vivo monitoring system, we isolated several splicing mutants and identified trans-acting regulators and cis-elements. These studies also demonstrated that regulation mechanisms of alternative splicing have been evolutionarily conserved among metazoans. In this symposium, regulation mechanisms of some of the alternatively spliced genes will be described, and the advantages of the visualization system will be summarized.

The egl-15 gene, encoding the sole homolog of the FGF receptors, has mutually exclusive exons 5A and 5B, which confer ligand-specificity to the receptor. We showed that exon 5A is selected in a muscle-specific manner by visualizing the alternative splicing patterns in vivo. We demonstrated that Fox-1 family RNA-binding proteins, ASD-1 (for Alternative Splicing Defective-1) and FOX-1, and a muscle-specific RNA-binding protein SUP-12 cooperatively regulate the mutually exclusive alternative splicing by repressing the upstream exon 5B to allow inclusion of the downstream exon 5A in muscles.

The let-2 gene, encoding α2 (IV) collagen, has a unique property that usage of its mutually exclusive exons 9 and 10 in body wall muscles undergoes dramatic switching during larval development. We succeeded in visualizing the developmental switching of the let-2 alternative splicing in vivo. We demonstrated that removal of either of the introns downstream from the mutually exclusive exons occurs prior to the excision of the upstream introns, and that an evolutionarily conserved GSG/STAR family RNA binding protein ASD-2 promotes exon 10-inclusion in later stages by enhancing biased excision of the intron 10.

Ohno et al, *Genes & Development* 22: 360, 2008.

Kuroyanagi, et al, *Molecular and Cellular Biology* 27: 8612-8621, 2007.

Kuroyanagi et al, *Nature Methods* 3: 909-915, 2006.

Dr. Yoshihito Niimura

(Tokyo Medical and Dental University, Japan)

Biodata

1999	Ph.D., physics, University of Tokyo, Japan
1999-2002	Postdoctoral Fellow, National Institute of Genetics, Mishima
2002-2004	Postdoctoral Fellow, Pennsylvania State University, Pemsylvania, USA
2004-Present	Associate Professor, Tokyo Medical and Dental University
2009-Present	Associate Editor, Genome Biology and Evolution

Symposium Talk: ***Evolution of Olfactory Receptor Genes in Vertebrates: From the Viewpoint of Comparative Genomics***

Abstract

Olfaction is essential for the survival of animals. Versatile odor molecules in the environments are received by olfactory receptors (Ores), which form the largest multigene family in vertebrates. Identification of the entire repertories of OR genes using bioinformatic methods from the whole genome sequences of diverse organisms revealed that the numbers of OR genes vary enormously, ranging from ~1,200 in rats and ~400 in humans to ~150 in zebrafish and ~15 in pufferfish. Most species have a considerable fraction of pseudogenes. Extensive phylogenetic analyses suggested that the numbers of gene gains and losses are extremely large in the OR gene family, which is a striking example of the birth-and-death evolution. It appears that OR gene repertoires dynamically changed depending on each organism's living environment. For example, higher primates equipped with a well-developed vision system have lost a large number of OR genes. Moreover, two groups of OR genes for detecting airborne odorants have greatly expanded after the time of terrestrial adaption in the tetrapod lineage, whereas fishes retain diverse repertoires of genes that were present in aquatic ancestral species. The origin of vertebrate OR genes can be traced back to the common ancestor of all chordate species, but insects, nematodes, or echinoderms utilize distinctive families of chemoreceptors, suggesting that chemoreceptor genes had evolved many times independently in animal evolution.

References:

1. Yoshihito Niimura (2009) On the origin and evolution of vertebrate olfactory receptor genes: Comparative genome analysis among 23 chordate species. *Genome Biol. Evol.* 1: 34-44.
2. Masatoshi Nei, Yoshihito Niimura, Masafumi Nozawa (2008) The evolution of animal chemosensory receptor gene repertoires: roles of chance and necessity. *Nat. Rev. Genet.* 9: 951-963.
3. Yasuhiro Go, Yoshihito Niimura (2008) Similar numbers but different repertoires of olfactory receptor genes in humans and chimpanzees. *Mol. Biol. Evol.* 25: 1897-1907.
4. Yoshihito Niimura, Masatoshi Nei (2007) Extensive gains and losses of olfactory receptor genes in mammalian evolution. *PLoS ONE* 2: e708.
5. Yoshihito Niimura, Masatoshi Nei (2005) Evolutionary dynamics of olfactory receptor genes in fishes and tetrapods. *Proc. Natl. Acad. Sci. U.S.A.* 102: 6039-6044.

Dr. Yong Zhang
(Beijing Genomics Institute, China)

Biodata

Dr. Yong Zhang received his Ph.D. degree from Peking University in China. He has been working in genomics since 2001 and published several papers in Nature, Science, PNAS, PLoS Biology, NAR, and other such journals. He returned to BGI Shenzhen last summer after completing a postdoctoral fellowship in proteomics at the Max Planck Institute in Munich. As a project director at BGI Shenzhen, Dr. Zhang is supervising several cancer genomics projects using next-generation sequencing technology. He is mainly working on genomics relevant research, including: de novo genome, proteomics, genome resequencing, transcriptome, micro RNA and epigenome.

Symposium Talk: ***Application of Next-Generation Sequencing Technology on Cancer Genomics and Personal Genomics***

Abstract

In the past, traditional disease research focused only on a single gene or a small group of genes. The methodology was hypothesis driven. In the past two years, functional genomics research has taken advantage of newly available genome sequences and high-throughput genome technologies to study genes and/or proteins to inform the perspective of the entire biological processes. Next generation sequencing technology has sped up the entire research process. Disease research has thus become data-driven. We can use the next-generation of sequencing in many areas: 1) Whole genome resequencing, 2) Exome-capture sequencing, 3) Transcriptome, 4) Digital gene expression profiling, 5) MicroRNA, 6) Epigenome, 7) Pathogen, 8) Definition of structural rearrangements and CNV, 9) Definition of coding sequence mutations, 10) Definition of alteration in expression levels, aberrant splicing and fusion transcripts, 11) Definition of the relation with the virus.

Decreasing costs have also enabled the sequencing of individual human genomes to become feasible. Genome data of the human population will rapidly be accumulated and will result in the identification of new gene-disease associations and wide applications of genomics in clinics.

Dr. Masaaki Muramatsu
(Tokyo Medical and Dental University, Japan)

Biodata

Masaaki Muramatsu studied medicine at Chiba University (1976~1982) and molecular biology at the Graduate School of Science at Tokyo University (1986~1990). He was a postdoctoral fellow at DNAX Research Institute (Palo Alto, CA), and than an Assistant Professor at the Institute of Medical Science of the University of Tokyo. He was a Principal Scientist at Helix Research Institute (1996~2000) and then moved to HuBit Genomix Inc as CSO. He has been Professor of Molecular Epidemiology, Medical Research Institute, Tokyo Medical and Dental University since 2002. He also holds a board membership of HuBit Genomix. Masaaki Muramatsu has been working in the field of signal transduction, functional genomics and most recently molecular epidemiology. He is interested in gene-environment interaction of multifactorial diseases.

Symposium Talk: Gene Environment Interactions in Metabolic Diseases and Atherosclerosis

Abstract

Common metabolic disorders such as hyperglycemia, hypertension, hyperlipidemia and obesity accelerate atherosclerosis, which is the major risk factor for myocardial and cerebral infarctions. All of these disorders are the consequence of the interaction between genetic and environmental factors. Multiple genes and polymorphisms that underlie these common diseases have recently been revealed through genome wide association studies (GWAS) employing large number of cases and controls. However, the impact of individual gene is small and the relation with environmental factors still need to be clarified. This is especially important if such genetic information is to be applied for personal preventive medicine. We are studying the effect of these genetic factors in general population by taking environmental factors into account. We demonstrate that gene-environmental interaction is essential for these genetic factors to exert their effect. Without environmental exposure, the effect of the genetic factors remains mute, indicating that such information may be useful under a clinical setting. We also present our resent data of GWAS conducted for systemic atherosclerosis, which identified a novel candidate gene/polymorphism for atherosclerosis.

References:

1. Oda K., et al, *Hum. Mol Genet.*16: 592-599, 2007.
2. Song Y., et al. *Metabolism* 56:925-930, 2007
3. Zhang L., et al. *Metabolism* 57:502-505, 2008

Dr. Issei Imoto

(Tokyo Medical and Dental University, Japan)

Biodata

1987	Kyoto Prefectural University of Medicine, Japan, M.D.
1995–1999	Research Fellow, Mayo Clinic, U.S.A.
2000–2002	Assistant Professor, Dept. of Molecular Cytogenetics, Medical Research Institute, Tokyo Medical and Dental University, Japan
2002– Present	Associate Professor, Dept. of Molecular Cytogenetics, Medical Research Institute, Tokyo Medical and Dental University, Japan

Specialty and Present Interests: Molecular cytogenetics, Epigenetics, array-CGH

Symposium Talk: Integrative Genomics and Epigenomics in Cancer

Abstract

Although many genetic/epigenetic alterations were reported in human cancer, their precise molecular mechanisms remain unclear. We have focused on those alterations as landmarks to identify genes involved in the cancer development/progression.

Remarkable genomic copy-number aberrations, i.e. high-level amplifications and homozygous losses, detected by conventional or array-based CGH in cancer, are useful to identify putative oncogenes and tumor-suppressor genes, respectively, although most of tumor suppressors were silenced through promoter hypermethylation. Genome-wide methods to detect abnormally methylated sequences, including BAC array-based methylated CpG island amplification (BAMCA), have accelerated the identification of epigenetically silenced tumor suppressors. Since some of those genes seem to be useful as prognosticators and/or therapeutic targets, genome-wide surveys of genetic and epigenetic abnormalities interpreting them in the context of broader knowledge of cancers facilitates the identification of crucial genes/pathways involved in the carcinogenesis, resulting in the development of new diagnostic methods and molecular targeting therapies for personalized medicine.

Dr. Jan P. Dumanski
(Uppsala University, Sweden)

Biodata

Jan Dumanski is a professor of experimental pathology at the Department of Genetics and Pathology, Uppsala University, in Sweden. Jan Dumanski was born in 1960 in Krakow (Cracow, Poland) and studied medicine at the Medical Academy of Krakow, from 1979 to 1984. In 1985 he entered the Ph.D. program at Karolinska Institutet in Stockholm and graduated, in 1990, from the Department of Clinical Genetics and Ludwig Institute for Cancer Research, Stockholm branch. In 1994 Dr. Dumanski received an associate professorship at Karolinska Institutet, in medical molecular genetics. Dr. Dumanski assumed his present position at Uppsala University in February, 2000. Between May 2006 and May 2008, Dr. Dumanski was active as Professor of Genetics at the University of Alabama at Birmingham, Department of Genetics, and Director of the Howell and Elizabeth Heflin Center for Human Genetics.

Dr. Dumanski has published papers in human and mouse genetics as well as in cancer research. Since 1986 he has been participating in the characterization of human chromosome 22, which has led to the cloning of several disease-causing genes. His is currently involved in projects related to genetic mechanisms behind metastasis of cancer and cancer predisposition. He is also studying genetic and epigenetic differences between monozygotic twins as new model towards characterization of disease biomarkers.

Symposium Talk: How Common is Somatic Mosaicism for DNA Copy Number Variations (CNVs)?

Abstract

DNA Copy Number Variation (CNV) has emerged as the most common form of human inter-individual genetic differences and this is important for basic research in biology/genetics as well as for disease-oriented translational science. When comparing unrelated subjects, the amount of sequence variation involving CNVs is considerably higher than that for single-nucleotide polymorphisms (SNPs). Furthermore, the mutation rate for CNVs has been suggested to be two to four orders of magnitude greater than the corresponding number for SNPs. We have recently discovered that monozygotic (MZ) twins frequently display within-pair differences in CNV profiles, which indicates the feasibility of studying MZ twins, discordant for established phenotypes in search for disease-causing aberrations. In addition, recent analysis of differentiated human tissues of normal deceased subjects supports the notion that somatic CNV mosaicism is underestimated. We tested multiple tissues from three people for differences in CNV profiles and observed changes, affecting a single organ or one or more tissues of the same person. Our above mentioned results from MZ twins and CNV differences between normal differentiated human tissues of the same person suggest that humans are commonly affected by mosaicism for stochastic CNVs, which occur in a substantial fraction of normal cells and are detectable by available array-based methods. However, the somatic variation for CNV is not well studied.

The work in the group focuses on establishment of "baseline CNV" (the normal frequency and genomic distribution of CNVs) in phenotypically unselected, healthy, concordant MZ twins. We also study differences in the CNV distribution and/or frequency in MZ twins discordant for various disease phenotypes in search for new disease-related biomarkers.

Another line of research in the group concentrates on breast cancer-related metastasis research. Breast cancer is a major cause of morbidity and mortality in women and its metastatic spread is the principal reason behind the fatal outcome. Metastasis research of breast cancer is, however, underdeveloped, in contrast to the abundant literature on primary tumors. We compared at high resolution the global genomic CNV profiles of primary tumors and synchronous axillary lymph node metastases from patients with breast cancer and observed numerous genetic differences between matched primary and metastatic tumors. Overall, primary tumors displayed 20% higher number of aberrations than metastases. We observed differences that can be linked to metastatic disease and there was also an overlapping pattern of changes between different patients. Many of the differences have been previously linked to poor patient survival, based on extensive analysis of primary tumors. This provides a proof of concept that this approach towards finding biomarkers for disease progression is correct. By analogy, the novel genetic aberrations acquired in metastases and not yet linked to patient survival might also lead to description of breast cancer progression-related genes, which forms the basis for development of new anti-cancer drugs.

Abstracts of the
ISP 2009 Poster Presenters

Poster
#1

Qian Zhang
(Dalian Medical University, China)

Title: Research on the Migration of Adenoid Cystic Carcinoma Cells in 3D Matrix Using a Microfluidic Device

Abstract
Qian Zhang, Tingjiao Liu

Objectives: The purpose of this study is to develop a microfluidic device for studying tumor cell migration in a 3-dimensional (3D) matrix. Furthermore, the mechanism of growth factor-induced migration of adenoid cystic carcinoma (ACC) cells will be investigated using this platform.

Materials and methods: This device consists of a PDMS layer and a glass layer. The PDMS layer was fabricated by replicate molding on the master, which was prepared by spin coating SU8 negative photoresist onto a glass wafer and patterned by photolithography. The piece of PDMS was bonded to a glass slide irreversibly. Two ACC cell lines were cultured in RPMI 1640 medium. To mimic extracellular matrix (ECM), Cultrex Basement Membrane Extract (BME) was used in our study. Epidermoid growth factor (EGF) was used to induce tumor cell migration.

Results: This device consists of two parallel perfusion channels, which are connected by nine cell culture chambers. Gelled BME supported 3D distribution of ACC cells. The viability of ACC cells in the 3D matrix could be maintained up to 7 days. The morphology of ACC cells was shifted from the flat cells seen on surface cultures to spherical cells in the 3D matrix. ACC cells formed cellular protrusions under EGF stimulation and migrated toward high concentration of EGF.

Conclusions: In this work, we developed a microfluidic-based 3D model that allows cancer cells to form protrusions before initiating migration. This device will be served as a useful platform to investigate the biological mechanism of ACC cells migration in a 3D matrix.

Section of Oral Pathology, College of Stomatology, Dalian Medical University, China

Poster
#2

Na-kyung Han
(Korea University, Korea)

Title: Cathepsin D and Eukaryotic Translation Elongation Factor 1 as Promising Markers of Cellular Senescence

Abstract

Na-Kyung Han[1,3], Hae-Ok Byun[1], Hae-June Lee[2], Ki-Bum Kim[3], Young-Gyu Ko[3], Gyesoon Yoon[4], Yun-Sil Lee[2], Seok-Il Hong[5], and Jae-Seon Lee[1]

To identify biomarkers for cancer treatment, we performed comparative proteomic analysis of MCF7 cells undergoing cellular senescence in response to ionizing radiation (IR). IR-induced senescence was associated with up-regulation of cathepsin D (CD) and down-regulation of eukaryotic translation elongation factor 1 beta 2 (eEF1B2). These findings demonstrate that CD and eEF1 are promising markers for the detection of cellular senescence induced by a variety of treatments.

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Poster
#3

Na-Young Song
(Seoul National University, Korea)

Title: 15d-PGJ$_2$-induced GCL and MRP1 Expression

Abstract

Na-Young Song, Eun-Hee Kim, Do-Hee Kim, Hye-Kyung Na and Young-Joon Surh

Nrf$_2$-driven up-regulation of glutamate cysteine ligase and multidrug-resistance protein 1 by 15-deoxy-D^{12,14}-prostaglandin J$_2$ confers resistance to doxorubicin-induced apoptosis in human breast cancer cells

15-Deoxy-D^{12,14}-prostaglandin J$_2$ (15d-PGJ$_2$), a representative J-series cyclopentenone prostaglandin, is one of the terminal products of the cyclooxygenase-2 pathway, and may act as a lynchpin in inflammation-associated cancer. In the present study, we have found that human breast cancer (MCF-7) cells pretreated with 15d-PGJ$_2$ are less prone to undergo doxorubicin-induced apoptosis. An elevated level of glutathione (GSH) in cancer cells has been associated with resistance to certain chemotherapeutics. Treatment of MCF-7 cells with 15d-PGJ$_2$ (10 mM) caused upregulation of glutamate cystein ligase catalytic (GCLC) subunit, the rate-limiting enzyme in the GSH synthesis. Nrf2 is a redox-sensitive transcription factor involved in the transactivation of many genes encoding phase 2 detoxifying/antioxidant enzymes including GCLC. 15d-PGJ$_2$ resulted in nuclear translocation and transactivation of Nrf2. siRNA knockdown of Nrf2 abrogated 15d-PGJ$_2$-induced GCLC expression. Following 15d-PGJ$_2$ treatment, the intracellular GSH level was initially diminished, but eventually enhanced. 15d-PGJ$_2$ contains an electrophilic a,b-unsaturated carbonyl moiety and readily forms adducts with GSH. It is likely that the formation of a 15d-PGJ$_2$-GSH conjugate can result in a transient decrease in the GSH level, which triggers the accumulation of ROS, provoking Nrf2 activation. This, in turn, induced expression of GCLC and subsequent enhancement of GSH levels in MCF-7 cells. Multidrug-resistance protein 1 (MRP1) is involved in GSH homeostasis via efflux of GSH conjugated with many electrophiles out of the cell. 15d-PGJ$_2$ up-regulated the expression of MRP1 in a Nrf2-dependent manner as well. Interestingly, 15d-PGJ$_2$-induced GCLC expression was attenuated by inhibiting MRP1. In conclusion, the coordinated up-regulation of GCLC and MRP1 induced by 15d-PGJ$_2$ via the Nrf2-ARE signaling may confer resistance to doxorubicin-induced MCF-7 cell death.

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Poster
#4

Jung-Min Oh
(Seoul National University, Korea)

Title: Human Papillomavirus Type 16 E5 Protein Inhibits Hydrogen Peroxide-induced Apoptosis by Stimulating Ubiquitin/Proasome-Mediated Degradation of Bax in Human Cervical Cancer Cells

Abstract

To investigate the mechanism by which the human papillomavirus (HPV) E5 protein contributes to the carcinogenesis of uterine cervical cancer, we studied the effect of HPV E5 on apoptosis of cervical cancer cells and its underlying mechanism. Expression of HPV16 E5 protein inhibited hydrogen peroxide-induced apoptosis in C-33A cervical cancer cells. E5 decreased the expression of Bax protein, and exogenous expression of Bax abolished the anti-apoptotic effect of E5. E5 also inhibited hydrogen peroxide-induced apoptosis with concurrent decrease in Bax expression in Cask cervical cancer cells and RHEK keratinocytes. Transient expression of E5 significantly increased the degradation rate of Bax protein by inducing the ubiquitination. The E5-induced decrease in Bax expression was inhibited by a cyclooxygenase-2 (COX-2) inhibitor, prostaglandin E2 (PGE2) receptor antagonists, and cAMP-dependent protein kinase (PKA) inhibitor. Treatment with PGE2 decreased the expression of Bax and inhibited hydrogen peroxide-induced apoptosis of C-33A cells. We concluded that HPV16 E5 protein inhibits hydrogen peroxide-induced apoptosis of cervical cancer cells by stimulating the ubiquitin/proteasome-mediated degradation of Bax protein, and the pathway involves COX-2, PGE2, and PKA. This finding suggests the possibility that HPV 16 E5 protein contributes to cervical carcinogenesis by inhibiting apoptosis of transformed cervical epithelial cells.

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Poster
#5

Mehru Nisha Muhamad Haneef
(Universiti Sains Malaysia Health Campus, Malaysia)

Title: Virulence Assay of apy Mutant of Shigella Flexneri 2a Using HeLa cells

Abstract

Mehru Nisha[1], Mohd Zaki Salleh[3], Lau Hut Yee[2], Manickam Ravichandran[4], Kirnpal-Kaur B.S.[1]

Introduction: The mechanism of pathogenicity of Shigella flexneri is based on the capacity of this strain to ingest colonic mucosa, to invade colonic epithelial cells, intracellular multiplication, spreading to adjacent cell and eventually cell death. The pINV-carried apy gene which codes for apyrase enzyme, decreases dNTP levels in host cells during intracellular multiplication and is considered possibly involved in host cell death. Thus, the mutation of apy gene seems to be a promising method of producing a live-attenuated vaccine candidate.

Objective: To study the virulence characteristic of apy mutant on HeLa cells by determining the plaque formation post-infection.

Methods: The apy mutant was constructed by mutating the apy gene using a kanamycin resistant gene cassette (aphA). By homologous recombination and sucrose selection methods, the wild apy gene was knocked off from the parental bacteria strain. HeLa cells were grown routinely on DMEM medium with 10% fetal calf serum. The HeLa cell was seeded on 6 well culture dish and was grown to 85% confluency. Next, 0.2 ml of diluted bacterial suspension, $2.0x10^8$cfu, as added to the cells and it was incubated for 90 minutes. The reaction was stopped by adding DMEM with gentamicin (50 ug/ml). Agarose (0.5%) was added to the wells and the plates were examined daily up to 7 days for plaque formation. To enhance plaques visualization, 0.01% neutral red was added on day 3.

Results The apy gene was successfully cloned and mutated using a kanamycin resistant gene cassette. Evaluation on HeLa cells showed, SF/USM1 (Shigella flexneri 2a apy mutant) facilitated moderate cell death and smaller plaque formation compared to the wild strain.

Discussions and Conclusion: SF/USM1 demonstrated its attenuation in virulence compared to its parental wild strain. Future work is currently being conducted on SF/USM1 in the laboratory to evaluate the functionality of the apyrase enzyme. SF/USM1 is an important approach towards the development of a potential vaccine strain for Shigella, as apy gene has been demonstrated as potential virulence gene candidate.

[1]Department of Medical Microbiology and Parasitology, [2]Reconstructive Sciences Unit School of Medical Sciences, Universiti Sains Malaysia Health Campus, Kubang Kerian 16150 Kelantan, Malaysia [3]Faculty of Pharmacy, Universiti Teknologi Mara (UiTM), 40450 Shah Alam, Selangor, Malaysia [4] Faculty of Applied Sciences, AIMST University, Semeling, 08100 Bedong, Kedah, Malaysia

Poster
#6

Giang Do Thuy Nguyen
(The University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam)

Title: Breast Conserving Therapy for Early Invasive Breast Cancer at Ho Chi Minh City Oncological Hospital: Oncological Results

Abstract

Nguyen Do Thuy Giang, Nguyen Chan Hung, Cung Thi Tuyet Anh, Truong Van Truong, Tran Viet The Phuong, Huynh Hong Hanh, Le Hoang Chuong, Tran Thi Thu Hien

Introduction: Breast conservation therapy (BCT) nowadays is a standard choice and widely used in treatment of early stage breast cancer because of its oncologic and cosmetic effects.

Methods: Between 09/2002 to 12/2007, we conducted 102 cases early invasive breast cancer were treated with conservative surgery (lumpectomy/quadrandectomy and axillary dissection group I-II). Radiation "total breast and boost" was given at 58-60Gy/24-30 fractions and/or axillary/clavicle lymph node irradiation. Adjuvant chemo/hormonal therapy if indicated. Locoregional recurrence rate was correlated with clinical-pathological factors and analysis. Survival results were calculated by Kaplan-Meier methods and Log-rank test to found out some prognostic factors.

Results: Mean age: 43.1; mean size of tumor: 1.8 cm and 5.1 cm interval from nipple. Lumpectomy plus radiation was 80.4%. Positive surgical margin was 7.8%. Mean follow-up: 50 months. Local recurrence rate was 2.9% and had no to find out factors correlated with recurrence. The 5-year DFS and 5-year OS were 92.4% and 95.7%, respectively.

Conclusion: Although the follow-up period was too short to draw definite conclusion about long-term outcome, this results was acceptable and fully promise in treatment breast cancer by conservative surgery in the future.

Poster
#7

Yue Zhao
(China Medical University, China)

Title: Dishevelled-1 and -3 Affect Lung Cancer Cell Invasion Through β-catenin and p120ctn, Which is Associated With Poor Prognosis

Abstract
Yue Zhao, Zhi-Qiang Yang, Yang Han, Yuan Miao, Yang Liu, Shun-Dong Dai, Hong-Tao Xu, En-Hua Wang

Background: Dishevelled family proteins are over-expressed in non-small cell lung cancer (NSCLC), but the correlations between Dvls, β-catenin and p120ctn, as well as prognosis are not clear.

Methods: Dvl-1, Dvl-3, β-catenin and p120ctn in 80 NSCLC tissues were detected by immunohistochemistry. Effects of Dvl-1 and Dvl-3 on Tcf-dependent transcriptional activity, β-catenin and p120ctn expression, as well as invasiveness of two lung cancer cells were also assessed.

Results: Dvl-1 was expressed in 52.5% (42/80), and Dvl-3 in 51.3% (41/80), of primary tumors. Their expressions were associated with poor tumor differentiation, high TNM stage and lymph node metastasis. Dvl-1 correlated to abnormal expression of β-catenin, while Dvl-3 correlated to p120ctn. Dvl-3 was related to poor patient prognosis. Exogenous expression of Dvl-1 and Dvl-3 enhanced the expression of p120ctn in A549 and LTEP-α-2 cells. Interestingly, Dvl-1 over-expression increased Tcf transcriptional activity, while Dvl-3 over-expression inhibited Tcf transcriptional activity, which was accompanied by increased p120ctn mRNA. The invasiveness of Dvl-1 and Dvl-3-enhanced cells was inhibited by β-catenin and p120ctn antibodies, respectively.

Conclusions: Dvls are over-expressed in NSCLC, in a manner related to the tumor histological type, differentiation, clinical stage and lymph node metastasis. Dvl-1 expression is related to abnormal β-catenin expression in NSCLC, and Dvl-3 to abnormal expression of p120ctn and poor prognosis. Dvl-1 may affect the biological behavior of lung cancer cells through β-catenin, while Dvl-3 may act through p120ctn. Dvl-3 expression could be a useful indicator of NSCLC prognosis.

Department of Pathology, College of Basic Medical Sciences, China Medical University and Department of Pathology, the First Affiliated Hospital of China Medical University, Shenyang 110001, P. R. China

Poster
#8

Nonglak Yoonim
(Naresuan University, Thailand)

Title: Preliminary Study of Proteomic Analyses of Serum from Breast Cancer Patients for Possible Diagnostic Protein Markers

Abstract

[1]Nonglak Yoonim, [3]Sittiruk Roytrakul, [1,2]Sukkid Yasothornsrikul

Breast cancer is the most common form of cancer among women and also is a major public health problem. Because of the mechanism of breast cancer in human is very complicated and there are many factors such as biological, physiological and genetics that involved in such complex mechanism. In addition, genetic alterations and modifications in gene expression are found during different steps of tumor progression. These changes are translated at the protein level where quantitative and qualitative modifications are found in tumor compared to normal samples. Therefore, the aim of this study is to identify type and quantities of protein molecules involved in breast cancer using proteomics technology and then apply these results for using as the biomarkers and index that specific for breast cancer. For the study, one hundred breast cancer sera and ninety-five normal sera were analyzed on SDS-PAGE. From the SDS-PAGE, protein bands of differences were excised, digested and then analyzed by LC-MS/MS. The serum protein profiles by SDS-PAGE of breast cancer group showed the same pattern as was observed in normal group; however, all of the sera from patients with breast cancer showed much higher levels of a protein band at approximately 16 kDa compared to the sera from normal controls. Then, this protein band was excised, digested and analyzed by LC-MS/MS. The results were compared with available databases in order to identify the proteins. Our data showed that proteomics can be applied in identification of serum proteins or biomarkers useful for the early detection, diagnosis, prognosis and management of cancer.

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Poster
#9

Nirmal Panthee
(Tribhuvan University Teaching Hospital, Nepal)

Title: Evaluation of Cardiovascular System in Cancer

Abstract

Heart disease and cancer both are more common in the elderly. There is high chance that a patient diagnosed with cancer could be concomitantly having some heart problem. Heart itself is a very rare organ to have primary tumor, however secondaries to pericardium presenting as pericardial effusion are not so uncommon. Cardiotoxicity of some of commonly used anticancer agents is well established, with anthracyclines and transtuzumab being at the top of the list. Avoiding these drugs as far as possible, reducing the cumulative dose by using different treatment schedule, and early detection of subclinical cardiotoxic effects, followed by reduction of the dose of offending drug are the strategies during cardiotoxic chemotherapy institution. Baseline echocardiography at the beginning of chemotherapy and during and/or after chemotherapy is hence recommended. Symptoms of heart failure are often confused with the primary effects of the malignancy or the effects of chemotherapy. So serial echocardiography with measurement of LVEF (Left Ventricular Ejection Fraction) is of great importance to diagnose cardiac failure at early stage in any cancer patient may it be cancer related or cardiotoxicity of anticancer treatment.

Chemotherapy and radiotherapy both pose a significant risk to the heart. Arrhythmias, dilated cardiomyopathy, heart failure, vasospasm resulting in angina or myocardial infarction are potentially serious complications related to cancer chemotherapy. Risk increases even more if the patient has history of heart disease. Radiotherapy commonly instituted for lymphoma and other radiosensitive tumors most commonly affects pericardium causing pericarditis. For now, it is important for the medical field to develop least cardiotoxic and at the same time as potent or even more potent new chemotherapeutic agents. Clinicians and basic scientists should work together for the development of good anticancer agent.

Poster
#10

Mohammad Safiqul Islam
(Noakhali Science and Technology University, Bangladesh)

Title: Evaluation of Diclofenac Loaded Alginate Beads Prepared by Ionotropic Gelation Method

Abstract

[1]Mohammad Safiqul Islam, [2]Jakir Ahmed Chowdhury

Cross-linked alginate beads of Diclofenac Sodium were prepared by ionotropic gelation method. Drug was blended with Sodium alginate in 1:1, 1:2, 1:3 and 1:4 ratios. The blended mass was then dissolved in water. Beads were prepared by dropping the hot aqueous solution into a beaker of different percentages of chilled CaCl2 solution (5%, 7.5%, 10%, 12.5% and 15%) followed by decantation of the solution and drying at room temperature. The initial drug and alginate ratios (1:1, 1:2, 1:3 and 1:4) ultimately resulted 33.33%, 20%, 14.28% and 11.11% drug loading into beads due to the formation of cross linked Calcium alginate instead of Sodium alginate. The viscosity of Sodium alginate solution was maintained properly to control the size of beads as well as ensuring pouring of solution through syringe. The entrapment efficiency of drug into the beads depends on the degree of cross-linking. The cross linking greatly depends on the amount of drug and polymer ratio as well as Calcium Chloride concentration. The percent entrapment is highest when the ratio of drug and Sodium alginate was 1:4 and the concentration of Calcium Chloride is 5%. The efficiency of entrapment decreases with increase in Calcium Chloride concentration. In Vitro dissolution studies were carried out in phosphate buffer of pH 7.2 in a thermal shaker with a shaking speed of 50 rpm at 37±0.5oC for 5 hours. The drug release was measured by UV-spectrophotometric method at a λ_{max} 277nm. It can be concluded that with the increasing polymer concentration, the release rate of Diclofenac Sodium was decreased and swelling index was increased and with the increasing electrolyte concentration, the release rate was increased and swelling index was decreased.

[1]Noakhali Science and Technology University, [2]University of Dhaka

Poster
#11

Marie Chiew Shia Loh
(National University of Singapore)

Title: Pharmacogenetic Differences Between Race and Chemotherapy Outcomes in Colorectal Cancer Patients

Abstract

Marie Loh[1,2], Darren Chua[1], Ross Soo[3], Barry Iacopetta[2], Richie Soong[1,4]

Fluoropyrimidines are currently the most commonly used chemotherapy agents in the treatment of colorectal cancer (CRC). Polymorphisms in thymidylate synthase (TYMS), dihydropyrimidine dehydrogenase (DPD) and methylene tetrahydrofolate reductase (MTHFR) are among the most well-studied with respect to their role in the chemotherapy outcomes. These polymorphisms had been associated with differences in clinical outcomes of chemotherapy such as toxicity, survival and response. As chemotherapy regimens are typically developed in Caucasians and followed only by small equivalence studies to establish adequate safety in Asian populations, it is hypothesized that by investigating these outcome-related polymorphisms, one may be able to optimize the chemotherapy regimens for Asians. From our meta-analysis of published studies, significant differences were found between the genotype distributions of these polymorphisms in Asians and Caucasians. It is the aim of this study to establish and compare the genotype frequencies of above-stated polymorphisms in Asian and Caucasian colorectal patients, as well as to study the association between the above-stated polymorphisms with fluoropyrimidine-based chemotherapy outcomes (toxicity, survival and response) in Asian and Caucasian colorectal patients.

[1]Cancer Science Institute of Singapore, National University of Singapore [2]School of Surgery, The University of Western Australia [3]Department of Haematology Oncology, National University Hospital [4]Department of Pathology, National University of Singapore

Poster
#12

Nutchapon Chamusri
(Chiang Mai University, Thailand)

Title: Overexpression of Akt and Its Activated Form, p-Akt in Oral Squamous Cell Carcinoma

Abstract
Nutchapon Chamusri, Suttichai Krisanaprakornkit, Anak Iamaroon

Aberration of signal transducers in PI3K/Akt pathway has been found in many human cancers and may play a role in carcinogenesis of those cancers.

Objectives: The objectives of the present study were (1) to investigate protein expression of pan-Akt and its phosphorylated form, p-Akt, in oral squamous cell carcinoma (OSCC) tissues of 15 Thai patients and (2) to analyze mRNA expression of three isoforms of Akt; Akt-1, -2, and -3 and protein expression of pan-Akt in five OSCC cell lines and human oral keratinocytes (HOK).

Methods: The expression of pan-Akt and p-Akt in OSCC tissues was studied by immunohistochemistry. The mRNA expression of Akt-1, -2, and -3 in OSCC cell lines and HOK was analyzed by RT-PCR and the protein expression of pan-Akt was studied by Western blot assay.

Results: The results showed that pan-Akt and p-Akt were overexpressed in 80% and 100% of OSCC cases, respectively. We observed more intense expression of pan-Akt and p-Akt at the invasive fronts of some OSCC tissues. Pan-Akt protein was also overexpressed in all OSCC cell lines in comparison with HOK. Interestingly, Akt-1 and -2 mRNA of OSCC cell lines were only constitutively expressed in comparison with HOK. Akt-3 mRNA appeared to be minimally expressed in OSCC cell lines and HOK.

Conclusions: These findings suggested that overexpression of pan-Akt and p-Akt may be involved with OSCC carcinogenesis and post-transcriptional modification of the expression of Akt isoforms in OSCC may occur. Studies on protein expression of Akt isoforms particularly Akt-1 and -2 and the mechanism of post-transcriptional regulation of Akt isoforms in OSCC are now undertaken.

This study was supported by an Intramural Research Grant, Faculty of Dentistry, Chiang Mai University, Thailand.

Department of Oral Biology and Diagnostic Sciences, Faculty of Dentistry, Chiang Mai University, Chiang Mai, Thailand

Poster
#13

Karen Ng Lee Peng
(University of Malaya, Malaysia)

Title: Single Nucleotide Polymorphisms (SNPs) Discovery in Oral Squamous Cell Carcinoma (OSCC)

Abstract

Karen-Ng L.P.[1], Rahman Z.A.A.[1], Prepagaran N.[3], Hercus R.[2], Anwar A.[2], Aisyah N.[2], Saidin A.[2], Ismail S.M.[1], Merican A.F.[4], Abraham M.T.[5], Tay K.K.[5], Mustaffa W.M.W.[5], Norain A.T.[5], Cheong S.C.[6] and Zain R.B.[1]

It is well established that mutation-induced sequence variations plays an important role in the development of cancer. Whole genome sequencing using second generation sequencers coupled with bioinformatics analysis, affords an opportunity to systematically identify somatic mutations that are implicated in cancer. Five oral squamous cell carcinoma tumours including 2 matched samples, obtained from smokers and 8 control tissues from non-cancer patients who had their wisdom tooth removed were used in this study. The socio-demographic information of the patients was obtained from the Malaysian Oral Cancer Data and Tumour Bank System (MOCDTBS) at the OCRCC. All of the patients were male and the mean age among the cancer and non-cancer patients was 48.8 years (range 34 - 56 years) and 28.5 years (range 21 - 35 years) respectively. Samples were homogenised by utilisation of a modified micro-dissection protocol. An average of 1Gbp of sequence data as single reads was generated with the Illumina Genome Analyzer for each sample. All reads were mapped to the Human reference genome and gene databases (Human Genome NCBI v36.1, and Human Transcriptome Database RefSeq mRNA release 28). A powerful and detailed bioinformatics analysis pipeline was utilized and was successful in identifying mutations (SNPs and Indels) and differentially expressed genes. Discovery of SNPs can be performed by alignment to publicly available sequence data. Between tumour and normal samples, 25,504 known SNPs were detected at 2 minimum supporting reads. Upon further filtering, 36 SNPs were observed to be common in all tumour samples but not in normal samples. Of the total 36 SNPs, 13 SNPs were found to be novel. Whole transcriptome sequencing is a comprehensive method in identifying SNVs that may be important in oral carcinogenesis.

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Poster
#14

Yan Pan
(Peking University, China)

Title: Effects of Low Molecular Weight Heparin on Tumor-endothelium Interactions and Protein Profile of Cultured HUVECs

Abstract

Yan PAN [a], Ji-hong LIU [b], Jun-hua WANG [a], He-ming YU [c], Xue-jun LI [a]

Aim: The endothelium is involved in the generation and regulation of multiple physiological and pathological processes, including cancer metastasis. Low molecular weight heparin (LMWH) has been used in cancer patients with venous thromboembolic complications, resulting in a higher survival rate. In the present study, we sought to determine the effects of LMWH on tumor cell adhesion and migration through endothelial monolayers in vitro and to uncover mechanisms governing these processes.

Methods: Morphology of cultured human umbilical vein endothelial cells (HUVECs) was studied after stimulation with human prostate cancer cells (PC-3M). A comprehensive proteomic analysis of HUVECs before and after treatment with LMWH (0.05 mg/ml for 24 h) was carried out using two dimensional high-resolution electrophoresis (2-DE) and mass spectrometry (MS). Protein changes in HUVECs were confirmed by indirect immunofluorescence and HUVECs intracellular calcium ([Ca2+]i) detection.

Results: LMWH inhibited significantly 1) the adhesion of PC-3M cells to HUVECs ($P < 0.05$) and 2) the migration of PC-3M cells through HUVECs in a dose-dependent manner. Note that LMWH was not cytotoxic to HUVECs ($P > 0.05$). Additionally, LMWH protected HUVECs from morphological damage caused by PC-3M cells. 2-DE analysis revealed that one of the significantly down-regulated proteins was cytoskeletal vimentin intermediate filament, which accumulated in bundles to the perinuclear area. When PC-3M cells stimulated HUVECs, LMWH reduced $[Ca2^{+}]i$ levels.

Conclusion: LMWH has potential anti-metastasis effects on PC-3M cells and that the underlying mechanism may be related to LMWH's regulation on numerous proteins of HUVECs and vimentin rearrangement in the HUVECs.

[a]Department of Pharmacology, School of Basic Medical Sciences and State Key Laboratory of Natural & Biomimetic Drugs, Peking University, Beijing 100083, [b]Center of Biomedical Analysis, Peking University, Beijing, 100083, China, [c]National Research Institute for Family Planning, Beijing 100081, China

Poster
#15

Jianbo An
(Tokyo Medical and Dental University, Japan)

Title: Locating Inhibits LPS-Induced Inflammatory Signaling by PPAR-Gamma Dependent and Independent Mechanisms in Human Macrophage

Abstract

Jianbo An[1,2], Toshiaki Nakajima[1,2], Keiji Kuba[3], Akinori Kimura[1,2]

Renin-angiotensin system (RAS), besides its canonical effects in regulation of cardiovascular function and renal metabolism, participates in inflammatory signals among various cells and tissues. In pathological conditions, enhanced signaling of RAS by its main component angiotensin II (AngII) contributes to pathogenesis of cardiovascular diseases, such as myocardial infarction, cardiomyopathy, atherosclerosis, and hypertension. Losartan, widely known as a member of AngII type I receptor blocker (ARB), specifically antagonizes the effect of AngII and is frequently used on clinical treatment for cardiovascular diseases. In recent years, it has been demonstrated that some ARBs exert unexpected function in the absence of AngII and other RAS components. For example, another ARB Telmisartan is structurally similar to peroxisome proliferator–activated receptor-gamma (PPARγ) agonist and suppresses lipid inflammatory signals. On the other hand, innate immune system plays a crucial role in bio-defence against harmful organism including microbial and virus. Macrophages response to these external pathogens by using Toll-like receptors (TLRs) and induce inflammatory reaction via expressing and secreting inflammatory cytokines. Losartan was reported to play a role in monocyte/macrophage inflammatory signals. However, the molecular mechanism linking Losartan function and innate immune system is poorly understood. In this research, we have demonstrated that Losartan had an ability to inhibit LPS-induced inflammatory signals in human macrophage by two different mechanisms. One mechanism was that Losartan down-regulated the expression of certain groups of inflammatory cytokines as a PPARγ agonist. The other was, to our surprise, Losartan prevented IkB from degradation by inhibiting IkB phosphorylation and attenuated inflammatory signals in the IKK-IkB-NF-kB step.

[1]Laboratory of Genome Diversity, Graduate School of Biomedical Science, [2]Department of Molecular Pathogenesis [3]MTT Program, Medical Research Institute, Tokyo Medical and Dental University

Poster
#16

Pichayanoot Rotkrua
(Tokyo Medical and Dental University, Japan)

Title: MiR-9 Down-regulates CDX2 Expression in Gastric Cancer Cells

Abstract
Pichayanoot Rotkrua, Yoshimitsu Akiyama, Yutaka Hashimoto, Takeshi Otsubo, Yasuhito Yuasa.

Ectopic expression of CDX2, a caudal-related homeobox transcription factor, is associated with development of intestinal metaplasia in the stomach. Intestinal metaplasia is thought to be pre-cancerous lesions of intestinal type gastric cancers. We have previously published that DNA methylation was partly responsible for CDX2 silencing in gastric cancers. However, the mechanism underlying aberrant expression of CDX2 during malignant progression has been unclear yet. MicroRNAs are small non-coding RNAs that negatively control gene expression at a post-transcriptional level. Here, we examined the role of miRNAs in CDX2 down-regulation in gastric cancer cells. The interaction between miR-9 and CDX2 3´-UTR was computationally predicted. After exogenous Pre-miR-9 precursor transfection, the luciferase activity of the reporter vector containing a part of 3´-UTR of CDX2 was down-regulated in HEK-293T cells. Using miR-9 over-expression and knock-down techniques, the expression levels of CDX2 protein and its downstream target genes (p21 and MUC2) were responsively altered in MKN45, AGS and NUGC-3 cells. The transfection of anti-miR-9 molecules significantly inhibited cell growth in MKN45 cells. Finally, we performed real-time RT-PCR to quantify the endogenous miR-9 levels and immunohistochemistry to score the CDX2 protein levels in primary gastric cancer tissues. The results showed the inverse correlation between miR-9 and CDX2 protein levels in those gastric cancer tissues. Therefore, the regulatory miR-9 might account for CDX2 reduction in gastric carcinogenesis by targeting its binding-site in the CDX2 3´-UTR.

Department of Molecular Oncology, Tokyo Medical and Dental University

Poster
#17

Hua Bai
(Tokyo Medical and Dental University, Japan)

Title: Significance of Frequently Reduced Expression for LC3A Variant-1 in Human Cancers

Abstract
Bai Hua[1,2], Jun Inoue[1,3], Issei Imoto[1], Johji Inazawa[1,2,3]

Microtubule-associated protein 1 light chain 3 (LC3) is closely associated with formation of autophagosome during induced autophagy. Human LC3 family consists of four genes, LC3A, LC3B, LC3B2, and LC3C. Among them, LC3A has two transcriptional variants, LC3Av1 and LC3Av2. Here we investigated physiological roles in these genes in human cancers and results have been obtained as following; 1) the localization of GFP tagged-LC3Av1 and -LC3B proteins were frequently changed to dotted pattern during induced autophagy, 2) the expression level of LC3Av1, not LC3B, was frequently decreased in various human cancer cell lines (37/113 cell lines from 6 tumor tissue; 32.7%) and primary tumors. 3) the overexpression of GFP-LC3Av1 into LC3Av1-silenced cell line enhanced MPP+ (1-methyl-4-phenyl-pyridinium)-induced cell death.

These findings suggest that the loss of function of LC3Av1 may contribute to tumorigenesis due to resistance to cellular stress in human cancer cells.

[1]Department of Molecular Cytogenetics, Medical Research Institute and Graduate School of Biomedical Science, Tokyo Medical and Dental University [2]Global Center of Excellence (GCOE) Program, "International Research Center for Molecular Science in Tooth and Bone Diseases", Tokyo Medical and Dental University, [3]Hard Tissue Genome Research Center, Tokyo Medical and Dental University

Poster
#18

Asma Begum
(Tokyo Medical and Dental University, Japan)

Title: Identification of a Novel Amplification-target Gene in Oral Squamous Cell Carcinoma (OSCC) Using Array-CGH-assisted Strategy

Abstract

Asma Begum[1,2,5,6], Emina Suzuki[1,2], Erina Nakamura[1,2], Issei Imoto[1,3,5,6], Ken-ichi Kozaki[1,3,5,6], Hitoshi Tsuda[3,5,6,7], Teruo Amagasa[2], Johji Inazawa[1,3,4,5,6]

Remarkable genomic copy-number changes, such as amplifications and homozygous losses, can be landmarks for oncogenes and tumor suppressor genes, respectively. In order to identify novel cancer-related genes involved in the progression of oral squamous cell carcinoma (OSCC), we performed genome–wide analysis for DNA copy-number aberrations in 18 OSCC cell lines using in-house bacterial artificial chromosome (BAC) array-based comparative genomic hybridization (CGH). Through this program, we detected several remarkably amplified chromosomal regions. Among them, we constructed a refined map of 19q amplification by FISH and determined the smallest region of the amplicon. Searching of the expression database and performing quantitative mRNA expression analysis of selected genes revealed four putative genes within this amplicon, which frequently overexpressed in a panel of OSCC cell lines. Cross-examination of these four genes by growth analyses, we determined that Gene14 (lab. name) might be a novel amplification target within this amplicon, because the knockdown by gene-specific siRNA showed clear growth suppressive effect on cell lines with its amplification and overexpression. Immunohistochemical analysis using 105 primary head and neck squamous cell carcinoma (HNSCC) including 50 OSCCs demonstrated that this gene was frequently expressed in primary HNSCC tumors, and notably patients with positive Gene14 immunoreactivity showed poor prognosis compared with those exhibiting negative Gene14 immunoreactivity. Those results suggest that Gene14 may contribute to the pathogenesis of OSCC through overexpression at least in part by promoting cell growth, and might be a good candidate for therapeutic target.

[1]Department of Molecular Cytogenetics, Medical Research Institute, Tokyo Medical and Dental University [2]Department of Maxillofacial Surgery, Tokyo Medical and Dental University [3]Hard Tissue Genome Research Center, Tokyo Medical and Dental University [4]Center of Excellence, Tokyo Medical and Dental University (COE). [5]Core Research for Evolutional Science and Technology, Japan Science and Technology Agency (CREST. JST) [6]New Energy and Industrial Technology Development Organization (NEDO) [7]Department of Pathology, National Defense Medical College

Poster
#19

Talati Gulibaha
(Tokyo Medical and Dental University, Japan)

Title: Effect of Angiotensin II (AngII) on WNK-OSR1/SPAK-NCC Phosphorylation Cascade in Mouse Kidney

Abstract
Gulibaha Talati, Akihito Ohta, Tatemitsu Rai, Eisei Sohara, Shotaro Naito, Sei Sasaki, Shinichi Uchida

We recently identified using WNK4 (D561A) knock-in mice that WNK-OSR1/SPAK-NaCl cotransporter (NCC) phosphorylation cascade is important for regulating NCC function in vivo. Phosphorylation of NCC was shown to be necessary for its functional activation and also important for its apical membrane localization. Previously, AngII infusion was reported to increase apical membrane expression of NCC in rats. Accordingly, we investigated in this study whether AngII was an upstream regulator for WNK-OSR1/SPAK-NCC cascade in mouse kidney. Chronic administration of AngII for 10days by using osmotic minipump (20ng/kg/min) also increased total and phosphorylated NCC in the mouse kidney. This increase was inhibited not only by angiontensin receptor1 blocker (varsartan, 3mg/kg/day), but by aldosterone receptor blocker (eplerenone, 400mg/kg/day).

Thus, AngII was identified as an upstream regulator for WNK-OSR1/SPAK-NCC phosphorylation cascade. However, the effect may be transient due to the downregulation of AngII receptor, and the increased NCC phosphorylation in kidney by chronic treatment of AngII was not the direct effect of AngII to this cascade but was mediated by aldosterone action induced by AngII.

Supervisor: Akihito Ohta

About
Tokyo Medical and Dental University

Historical Sketch

Apr. 1899 ● Hospital associated with Tokyo Medical License Exam (Eiraku Hospital)

Aug. 1,1917 ● Hospital associated with Tokyo Dental License Exam

Jun. 1918 ● Hospital associated with Tokyo Dental License Exam

Jan. 1922 ● Hospital of Dentistry

Apr.1, 1934

● Oct. 12,1928
Tokyo National School of Dentistry

● Dec. 1930
Tokyo National School of Dentistry

● Apr. 1944 (～ Mar. 1950)
Tokyo Medical and Dental College
(Established the School of Medicine)

Aug. 1946
Tokyo Medical and Dental University (The Former System)

Established Apr. 2004
National University Corporation Tokyo Medical and Dental University

Apr. 1951
Tokyo Medical and Dental University (The New System)

Apr. 1929 ● Hospital associated with Tokyo National School of Dentistry

● Dec. 1946
Kasumigaura Branch, University Hospital, Faculty of Medicine

● Nov. 1947
Kounodai Branch, University Hospital, Faculty of Medicine

● Oct. 1946 (～ 1950)
Established the Premedical Course

● Aug. 1946
University Library

Apr. 1958
Branch Library
(Kounodai Branch School)

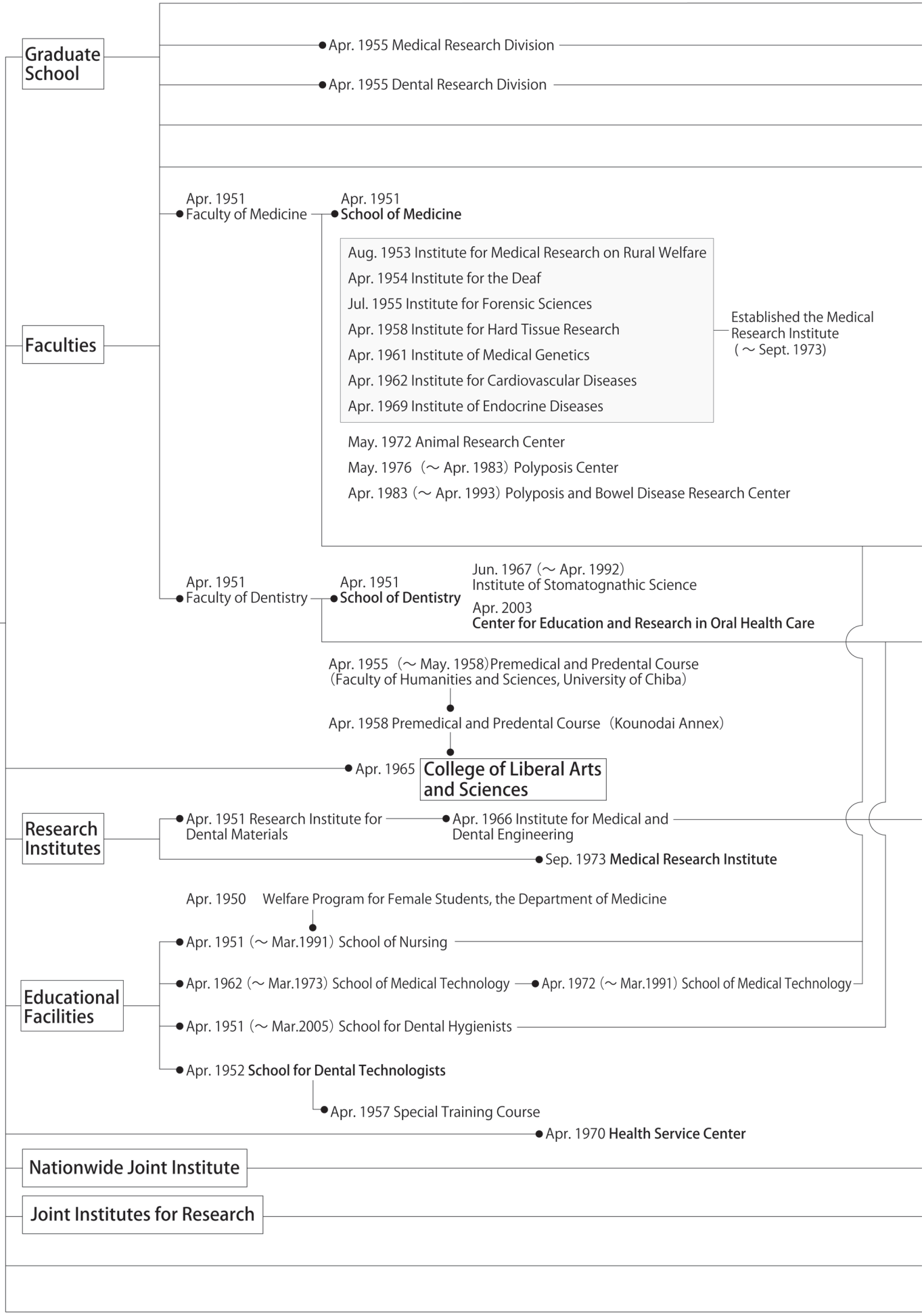
Apr. 1964
Kounodai Branch Library
(formerly the Branch Library)

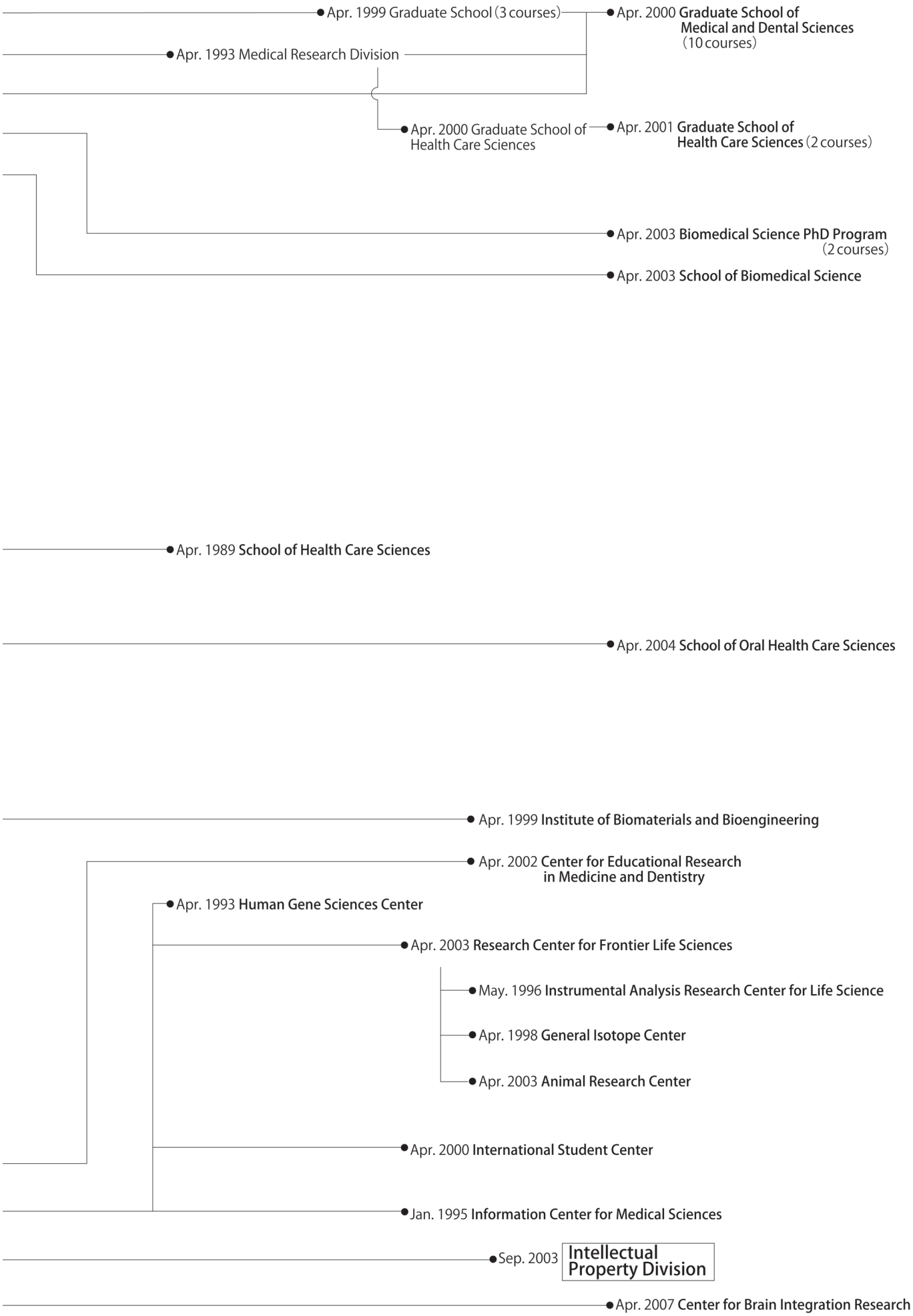
Jun. 1949
University Hospital of Medicine

Kasumigaura Branch
(～ Apr. 1997)

Kounodai Branch
(～ Apr. 1965)

Jun. 1949
University Hospital of Dentistry


Graduate School
Apr. 1955 Medical Research Division
Apr. 1955 Dental Research Division
Faculties
Apr. 1951
Faculty of Medicine
Apr. 1951
School of Medicine
Aug. 1953 Institute for Medical Research on Rural Welfare
Apr. 1954 Institute for the Deaf
Jul. 1955 Institute for Forensic Sciences
Apr. 1958 Institute for Hard Tissue Research
Apr. 1961 Institute of Medical Genetics
Apr. 1962 Institute for Cardiovascular Diseases
Apr. 1969 Institute of Endocrine Diseases
Established the Medical Research Institute
(～ Sept. 1973)
May. 1972 Animal Research Center
May. 1976 （～ Apr. 1983）Polyposis Center
Apr. 1983（～ Apr. 1993）Polyposis and Bowel Disease Research Center
Apr. 1951
Faculty of Dentistry
Apr. 1951
School of Dentistry
Jun. 1967（～ Apr. 1992）
Institute of Stomatognathic Science
Apr. 2003
Center for Education and Research in Oral Health Care
Apr. 1955 （～ May. 1958）Premedical and Predental Course
（Faculty of Humanities and Sciences, University of Chiba）
Apr. 1958 Premedical and Predental Course （Kounodai Annex）
Apr. 1965
College of Liberal Arts and Sciences
Research Institutes
Apr. 1951 Research Institute for Dental Materials
Apr. 1966 Institute for Medical and Dental Engineering
Sep. 1973 Medical Research Institute
Apr. 1950 Welfare Program for Female Students, the Department of Medicine
Educational Facilities
Apr. 1951（～ Mar.1991）School of Nursing
Apr. 1962（～ Mar.1973）School of Medical Technology
Apr. 1972（～ Mar.1991）School of Medical Technology
Apr. 1951（～ Mar.2005）School for Dental Hygienists
Apr. 1952 School for Dental Technologists
Apr. 1957 Special Training Course
Apr. 1970 Health Service Center
Nationwide Joint Institute
Joint Institutes for Research


Apr. 1999 Graduate School (3 courses)
Apr. 2000 Graduate School of Medical and Dental Sciences (10 courses)
Apr. 1993 Medical Research Division
Apr. 2000 Graduate School of Health Care Sciences
Apr. 2001 Graduate School of Health Care Sciences (2 courses)
Apr. 2003 Biomedical Science PhD Program (2 courses)
Apr. 2003 School of Biomedical Science
Apr. 1989 School of Health Care Sciences
Apr. 2004 School of Oral Health Care Sciences
Apr. 1999 Institute of Biomaterials and Bioengineering
Apr. 2002 Center for Educational Research in Medicine and Dentistry
Apr. 1993 Human Gene Sciences Center
Apr. 2003 Research Center for Frontier Life Sciences
May. 1996 Instrumental Analysis Research Center for Life Science
Apr. 1998 General Isotope Center
Apr. 2003 Animal Research Center
Apr. 2000 International Student Center
Jan. 1995 Information Center for Medical Sciences
Sep. 2003 Intellectual Property Division
Apr. 2007 Center for Brain Integration Research

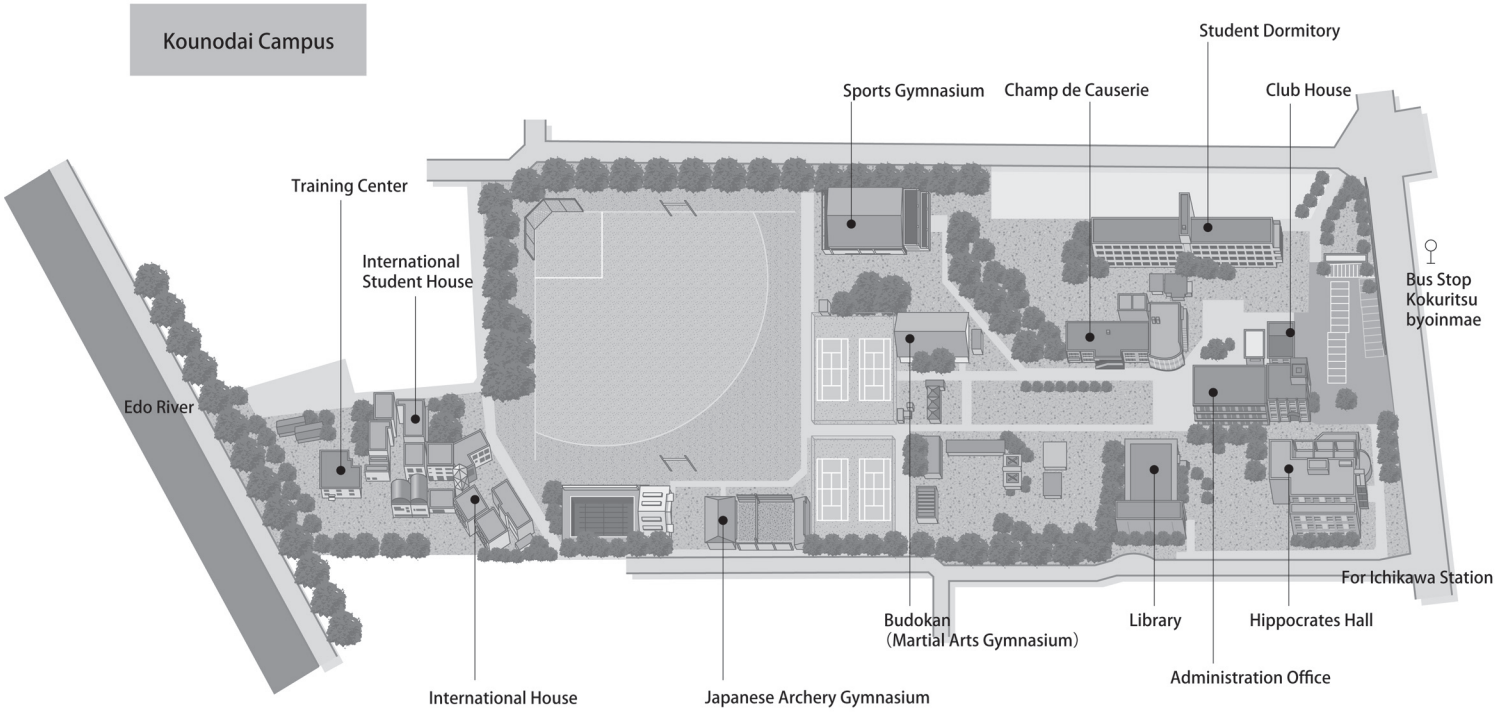
TMDU Campuses

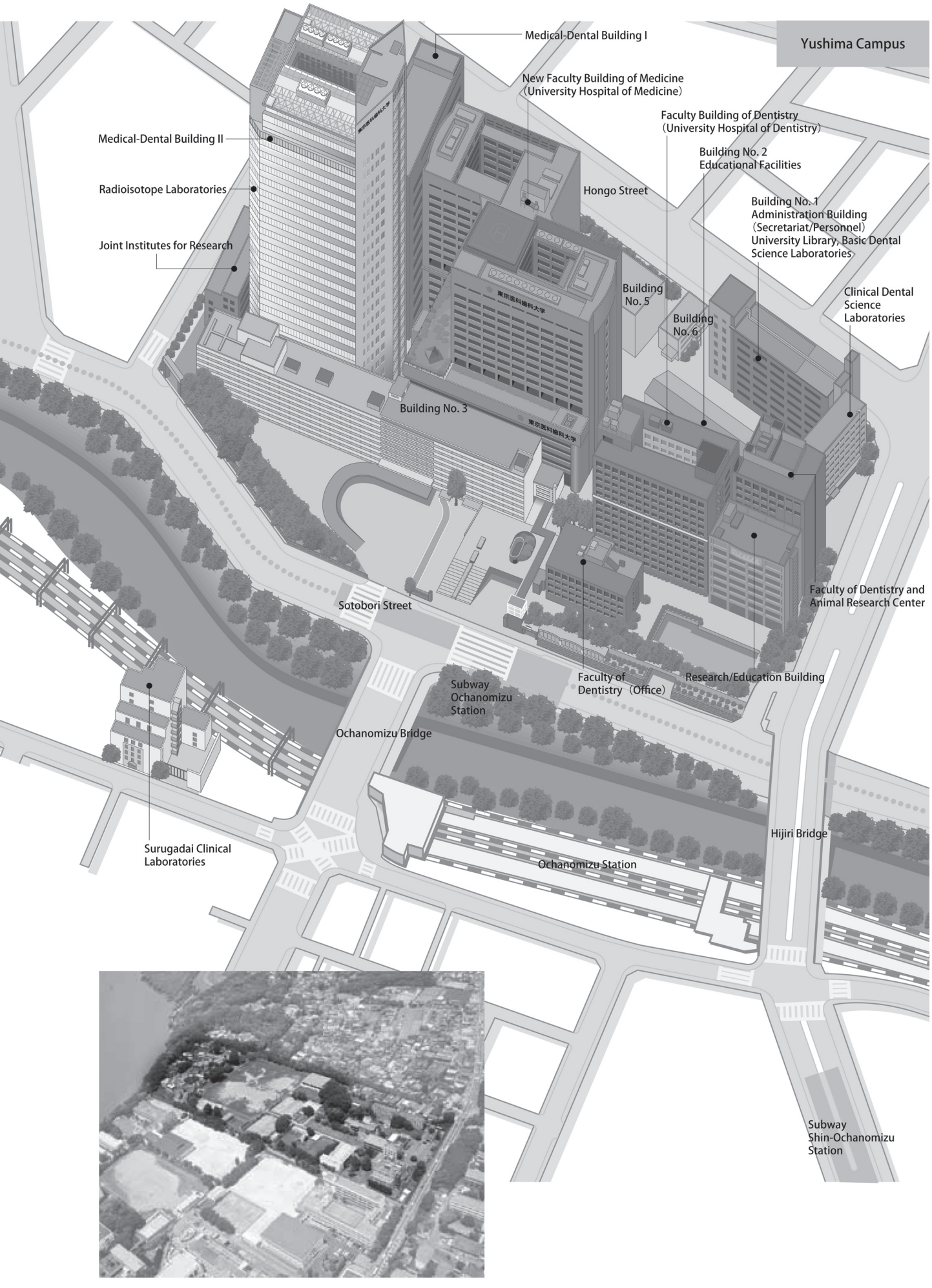
Medical-Dental Building II

Medical-Dental Building II

To foster academic doctors and world-class researchers who will meet the needs of the 21st century, a new building is under construction on Yushima campus. This building is to become a core facility of TMDU by providing space for communal use, versatile research and laboratory zones, open labs for education and research projects, and common labs for the TMDU community.

Building No. 2
Educational Facilities




Yushima Campus
Medical-Dental Building I
New Faculty Building of Medicine
(University Hospital of Medicine)
Faculty Building of Dentistry
(University Hospital of Dentistry)
Building No. 2
Educational Facilities
Medical-Dental Building II
Radioisotope Laboratories
Hongo Street
Building No. 1
Administration Building
(Secretariat/Personnel)
University Library, Basic Dental
Science Laboratories
Joint Institutes for Research
Building
No. 5
Clinical Dental
Science
Laboratories
Building
No. 6
Building No. 3
Faculty of Dentistry and
Animal Research Center
Sotobori Street
Subway
Ochanomizu
Station
Faculty of
Dentistry (Office)
Research/Education Building
Ochanomizu Bridge
Hijiri Bridge
Surugadai Clinical
Laboratories
Ochanomizu Station
Subway
Shin-Ochanomizu
Station

Location of University Campuses, Buildings and Addresses

(May 1, 2008)

Yushima Campus

■ Grounds (sq. Metre) : 45,192 ㎡ ■ Buildings (sq. Metre) : 237,832 ㎡

Name	Address • Zip code • Telephone
Administration Bureau / Graduate School of Medical and Dental Sciences Graduate School of Health Care Sciences Biomedical Science PhD Program School of Biomedical Science	5-45, Yushima 1 chome, Bunkyo-ku, Tokyo 〒113-8510 03-3813-6111
Faculty of Medicine University Hospital of Medicine	5-45, Yushima 1 chome, Bunkyo-ku, Tokyo 〒113-8519 03-3813-6111
Faculty of Dentistry University Hospital of Dentistry	5-45, Yushima 1 chome, Bunkyo-ku, Tokyo 〒113-8549 03-3813-6111
University Library / Health Service Center Human Gene Sciences Center Research Center for Frontier Life Sciences Instrumental Analysis Research Center for Life Science General Isotope Center / Animal Research Center Information Center for Medical Sciences Center for Education Research in Medicine and Dentistry	5-45, Yushima 1 chome, Bunkyo-ku, Tokyo 〒113-8510 03-3813-6111
School for Dental Technologists	5-45, Yushima 1 chome, Bunkyo-ku, Tokyo 〒113-8549 03-3813-6111

Surugadai Campus (1)

■ Grounds (sq. Metre) : 5,047 ㎡ ■ Buildings (sq. Metre) : 17,946 ㎡

Institute of Biomaterials and Bioengineering	3-10, Kanda Surugadai 2 chome, Chiyoda-ku, Tokyo 〒101-0062 03-5280-8000
Medical Research Institute	3-10, Kanda Surugadai 2 chome, Chiyoda-ku, Tokyo 〒101-0062 03-5280-8050

Surugadai Campus (2)

■ Grounds (sq. Metre) : 532 ㎡ ■ Buildings (sq. Metre) : 2,156 ㎡

International Exchange Center	3-21, Kanda Surugadai 2 chome, Chiyoda-ku, Tokyo 〒101-0062 03-5283-5855

Kounodai Campus

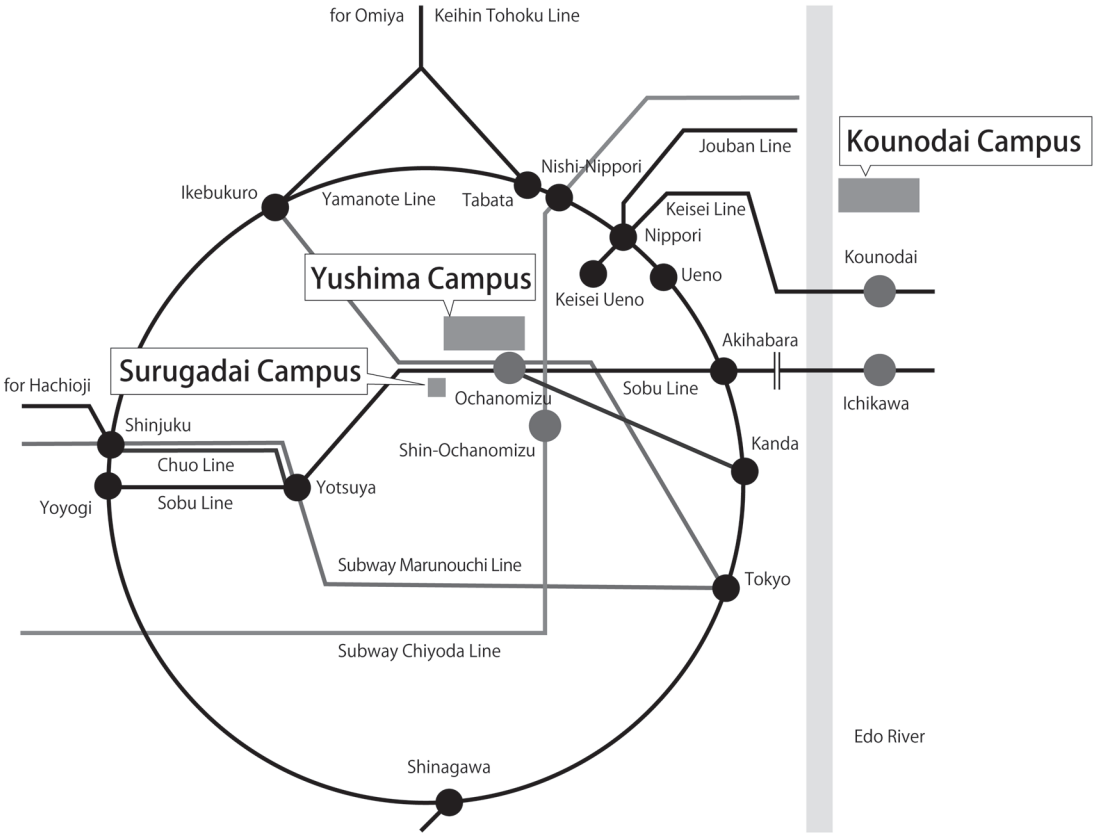
■ Grounds (sq. Metre) : 60,938 ㎡ ■ Buildings (sq. Metre) : 13,993 ㎡

College of Liberal Arts and Sciences / Kounodai Branch Library Health Service Center, Kounodai Branch	8-30, Kounodai 2 chome, Ichikawa-city, Chiba Prefecture 〒272-0827 047-300-7103
International House International Student House	8-1, Kounodai 2 chome, Ichikawa-city, Chiba Prefecture 〒272-0827 047-371-7936

Name	Address	Grounds (sq. Metre)	Buildings (sq. Metre)
Toda Boat-House	60, Todakoen 1 chome, Toda-city, Saitama Prefecture	691 ㎡	478 ㎡
Akakura Resort House	Akakura-Onsen, Myoko-city, Niigata Prefecture	1,655 ㎡	334 ㎡
Tateyama. Oga-Resort House	Oga, Tateyama-city, Chiba Prefecture	4,334 ㎡	839 ㎡
Hakusan Residence Housing	36-3, Hakusan 2 chome, Bunkyo-ku, Tokyo	495 ㎡	96 ㎡
Wakamiyacho Residence Housing	26, Wakamiya-cho, Shinjuku-ku, Tokyo	995 ㎡	
Tonoyama Residence Housing	50-3, Chuo 1 chome, Nakano-ku, Tokyo	1,960 ㎡	1,815 ㎡
Etchujima Residence Housing	3, Etchujima 1 chome, Koto-ku, Tokyo	18,136 ㎡	28,492 ㎡
The Ossuary (Nokotsu-do)	10-1, Kounodai 3 chome, Ichikawa-city, Chiba Prefecture	(115)	
Total		139,975 ㎡ (115)	268,393 ㎡

* Surugadai Campus (1) indicates the Institute of Biomaterials and Bioengineering and Medical Research Institute and Nurses Dormitory.
* Surugadai Campus (2) indicates Surugadai Clinical Laboratories.
* The numbers in parentheses independently show temporary or long-term rental grounds and buildings.

Location



Yushima Campus
Surugadai Campus

JR Line Ochanomizu Sta.
Subway Marunouchi Line Ochanomizu Sta.
Subway Chiyoda Line Shin-Ochanomizu Sta.

Kounodai Campus

Keisei Line Kounodai Sta.
Sobu Line Ichikawa Sta.

Symbol of Tokyo Medical and Dental University

This is the symbol of Tokyo Ikashika Daigaku (Tokyo Medical and Dental University), which has the following meaning:
1. This symbol is designed to show the history of development of Tokyo Medical and Dental University. This shape represents the plum blossom ; it is the symbol of Yushima Tenjin (Yushima Shrine) which exists in the same location as the University. Tenjin is the God of Knowledge.
2. The center circle of this symbol, the core of the flower, was the emblem of the former Tokyo Koto Shikaigakko (Tokyo National School of Dentistry) and the 5 petals around the core show the present University which has developed from that school.
3. The 5 petals express the Faculty of Medicine, Faculty of Dentistry, College of Liberal Arts and Sciences, Institute of Biomaterials and Bioengineering , and Medical Research Institute, and these 5 petals, which join together to make the flower bloom, represent the activity of the University.
4. The bold outline of these 5 petals suggests further development and progress in the future.

ISP2009

Participants

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KAREN NG LEE PENG	◎	University of Malaya
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RUISHAN ZHANG		China Medical University
KWAN LEUNG CHIA		The University of Hong Kong
RACHAI JUENGSOMJIT		Mahidol University
PUCHONG TANGNORAKUL		Prince of Songkla University
THANATHORN ARIYAWATCHARIN		Prince of Songkla University
MEI LING CHONG		National University of Singapore
YAGYA PRASAD TIWARI		Tribhuvan University Teaching Hospital
WEN GU		Peking University
BAKHTOVAR KARIM-ZADE		Tajik State Medical University
HANSINIE SEWWANDIMA WEERAWARDHANA THENANDALU MUDALIGE		The University of Peradeniya
NA-KYUNG HAN	◎	Korea University
TOUNGTHONG POBSOOK		Chulalongkorn University
NA-YOUNG SONG	◎	Seoul National University
SUHYEON KIM		Seoul National University
THANIT PRASITSAK		Naresuan University
WARAYUT CHOTPRAKAIKIAT		Naresuan University
JUNG-MIN OH	◎	Seoul National University
NANFANG XU		Peking University
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TAN KA LIONG		Universiti Sains Malaysia
MEHRU NISHA MUHAMAD HANEEF	◎	Universiti Sains Malaysia
JIANBO AN	◎	Tokyo Medical and Dental University
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HUA BAI	◎	Tokyo Medical and Dental University
ASMA BEGUM	◎	Tokyo Medical and Dental University
TALATI GULIBAHA	◎	Tokyo Medical and Dental University
HUI CHIANG LAU		Nanyang Technological University
SURESH PANTHEE		Tokyo Medical and Dental University
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JEA JUNG LEE		Korea University
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GOVINDEN KUGHAN		Nizhny Novgorod State Medical Academy
ALEXANDER ZABORONOK		University of Tsukuba