



Chiba University

Graduate School of Medicine

Founded 1874



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Greeting from the Dean



Haruaki Nakaya, M.D., Ph.D.
Dean :
Faculty of Medicine /
Graduate School of Medicine

The origin of Chiba University School of Medicine dates back to 1874 when Kyoritsu Hospital was established by donations from the people of Chiba town and surrounding villages. Many excellent clinicians and medical researchers have been educated in Chiba University School of Medicine for 135 years and they have greatly contributed to medical progress. Faculty members and students in our university have to follow the tradition of the great history of our university by dedicating ourselves to medicine and medical sciences.

Nowadays all hospitals including university hospital in Japan are facing many difficult problems. Even in such difficult environment our students in Chiba University School of Medicine have to think how they can contribute to enhancement of people's health and welfare as a physician in the future. The faculty members of Chiba University School of medicine are aiming to produce not only excellent clinicians but also physician scientists with strong motivation and capability for medical research. We have obtained several competitive research budgets including Global COE Program. We will promote translational research connecting basic medical science and clinical application.

We will educate young students in the hope that they will become leading medical doctors, physician scientists and life scientists. We will do our best to take into account society's wishes, opinions and criticisms, and to meet the expectations. We greatly appreciate your continuous support to our efforts.

Greeting from the Dean



Harigaya Kenichi, M.D., Ph.D.

Dean :

Graduate School of Medical and
Pharmaceutical Sciences

The 21st century promises more rapid advances in learning, culture, and science. As part of that society, the Graduate School of Medical and Pharmaceutical Sciences must foster medical personnel who can respond to the rapid advances in cutting-edge research and creative researchers with the ability to play a leading role in the international science community. Genome sequencing efforts have continued over the past few years, and the foundation has been laid to logically develop the in-depth results of basic research in every area of medicine and biology into clinical medicine and health promotion. Moreover, the area of translational research (TR) is expanding. Accordingly, medical care in the 21st century must do two things. First, it must provide a system of care that: (1) introduces medical research in areas like developmental and regenerative medicine, organ transplants, and allergies and immunology into medical settings, that (2) facilitates advances in molecular pharmacology, genomic pharmacology, and biopharmaceutical informatics, and that (3) accurately responds to changes in disease patterns as typified by the aging of society and the effects of environmental pollution on health. Second, medical care in the 21st century must foster medical personnel, medical and pharmaceutical specialists, and researchers in advanced biosciences by taking into account the individual as a whole. To thus meet society's needs, Chiba University established the Graduate School of Medical and Pharmaceutical Sciences in April 2001 to provide an interdisciplinary education based on new concepts.

This Institution features a Master's program and a Doctoral program. The Master's program consists of two specialties, one in Medical Sciences, a specialty consisting of subjects in medicine, and one in General Pharmaceutical Sciences, a specialty consisting of subjects in pharmacology. The Doctoral program consists of 2 specialties with fundamentally different course content. The specialties are: Advanced Life Sciences (medicine and pharmacology) and Pharmaceutical and Life Sciences (pharmacology), which

specifically deals with subjects in pharmacology. In addition to instructors from the Graduate School of Medicine, the Graduate School of Pharmaceutical Sciences, and the Medical Mycology Research Center, this Institution enjoys the cooperation of the National Institute of Radiological Sciences, the Chiba Cancer Center, the Kazusa DNA Research Institute, the National Institute for Environmental Studies, and the RIKEN Research Center for Allergy and Immunology. This Institution seeks to foster creative researchers who will conduct research in the biosciences, cultivate human resources with an eye toward drug research and development, and to foster research-minded physician-scientists who can respond to advances in medical care. About 70% of the students at this Institution are graduates of schools of medicine while the remaining 30% are graduates of other schools like pharmacology.

The recent tide of globalization has brought to mind the need to think of human actions beyond the dimensions of nation-states and East and West, and it has also significantly changed education norms. Amidst the surge of internationalization, Japanese society must cultivate human resources who can play a leading role in the international science community. Thus, this Institution has striven to cultivate human resources with the ability to play a leading role internationally. Along with financial support, this Institution arranges and encourages lectures, seminars, and presentations in English, active academic work overseas at universities in the US for 1–2 years, internships, or study-abroad programs. In addition, this Institution is also striving to incorporate exceptional personnel from other countries in this Institution's educational programs.

The Graduate School of Medical and Pharmaceutical Sciences seeks to provide a graduate school education in the combined disciplines of medicine and pharmacology rooted in this Institution's wide-ranging and extensive expertise; evidence of this can be found in this Institution's conferring of Ph.D. degrees (in Medicine or Pharmaceutical Sciences). Courses have been established in the combined disciplines of medicine and pharmacology, and students who complete them earn degrees and go on to work in drug development and at laboratories of pharmaceutical firms and in key hospitals and universities, research institutes, and graduate schools here in Japan and abroad. The educational program at this Institution is supported by MEXT via programs like its Global COE (Centers of Excellence) Program and Support Program to Improve Graduate School Education. The program has been hugely successful in crafting a new cross-disciplinary system that includes international exchanges and in helping the Graduate School fulfill its purpose.

Thus, many aspects of education at the Graduate School of Medical and Pharmaceutical Sciences are supported by faculty of the Graduate School of Medicine and seeks to enhance human happiness and development by utilizing this Institution's accumulated research results and experience and endeavoring to explore the advanced biosciences.

Preface

Chiba University was founded in 1949, unifying several regional former national colleges and schools. Currently, Chiba University consists of nine faculties, the university library, the university hospital and other educational and research facilities. With 12,000 students in the undergraduate program, it has long been one of the largest universities in Japan. As for the graduate school, there are about 2,100 students in six master's programs and 1,300 in six doctoral programs. Chiba University, with the support of the Japanese national government, is extending the frontiers of its international activities.

The Graduate School of Medicine is the one of the oldest and finest medical graduate schools in Japan. There are many domestically and internationally top-level researchers in basic and clinical research fields. The Graduate School of Medicine is establishing new cooperative relations with numerous overseas universities, and developing an even closer relationship with those with which it has already concluded cooperation agreements.

Facts and Figures

Dean of the Graduate School of Medicine;

Haruaki NAKAYA, M.D., Ph.D.

Dean of the Graduate School of Medical and Pharmaceutical Sciences;

Kenichi HARIGAYA, M.D., Ph.D.

1 7 7 full-time faculty members

4 7 1 Ph.D program students, 6 2 master's program students

Educational Organizations and their Objectives

Master Course; Medical Sciences

The objective of the Master Course is to cultivate human resources who have a wealth of diverse knowledge concerning new learning structures, including geriatrics in order to respond to the advanced aging of society that is predicted in the near future, environmental and health sciences to tackle environmental pollution on a global scale, and advanced genomics, regenerative medicine and advanced life sciences, who possess a rich degree of humanity enabling them to correctly understand the role of science in society and the responsibilities of science, and who can provide medical services in response to the needs of the people of the 21st century.

Doctor Course

Environmental and Health Sciences

The objective of the Doctor Course (4-Year Program) is to cultivate human resources who can establish systems of learning for scientific research and education into the impact that environmental factors can have on humans, based on their mutual interaction with genetic factors, establish new areas of learning related to the elderly, and put the results of research into practice.

Advanced Clinical Sciences

The objective of the Doctor Course (4-Year Program) is to cultivate human resources who can analyze the pathology of diseases, develop new methods of diagnosis and treatment, and put developed technologies into practice (highly advanced medical technology), and human resources who can understand diseases and pathology from the molecular level to the cellular level in order to enable the development and safe management of future medicines, such as genetic medicines, that are required in the field of highly advanced medical technology.

Life Sciences

The objective of the Doctor Course (4-Year Program) is to nurture broad knowledge in medical and pharmaceutical sciences, rich creativity and research abilities through advanced, interdisciplinary and international research that will serve to open up new areas of research, education and clinical science in the new area of structured life sciences, and to cultivate outstanding researchers and educators who can respond to the needs of the populace with a high degree of moral aptitude.

Environmental Biochemistry (A1)



◆ Overview

We aim to create evolutionary medicine based on the discovery of the SOS response. This will clarify the evolutionary capabilities of humans in the near future as well as the physiology involved in the control of gene mutations. We are also pursuing solutions for various environmental problems in the field of the life sciences targeting such stressors as gravity, radiation, chemical substances, forests, rivers, environmental water, food substances, and Chinese herbal medicines. At the same time, we are also aiming to establish a crisis-management life science for times of disasters.

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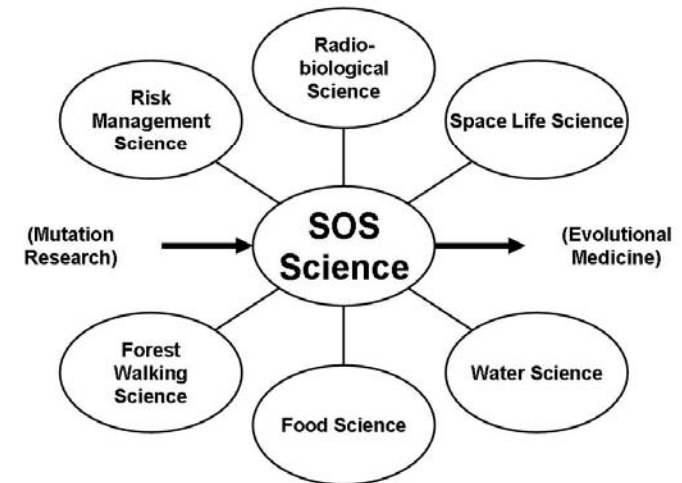
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◆ Research & Education

1. Research of mutability modulation
2. Analysis of stress-responsive genes
3. Research of protease-mediated signal transduction
4. Biological effects of environmental toxic compounds
5. Molecular mechanisms underlying accelerated aging diseases
6. Studies of space life science
7. Research on the relationship between health longevity and nutrition
8. Pathological analysis of neurodegenerative disease
9. Bioscience research of water
10. Bioscience research of crisis management



◆ Recent Publications

1. Guo W., Sugaya S., Satoh M., Tomonaga T., Nomura F., Hiwasa T., Kita K., Takiguchi M., Suzuki N. Nm23-H1 is responsible for SUMO-2-involved DNA synthesis induction after X-ray irradiation in human cells. *Arc. Biochem. Biophys.* 486, 81-87, 2009
2. Tong X., Kita K., Karata K., Zhu C., Sugaya S., Ichimura Y., Satoh M., Tomonaga T., Nomura F., Jin Y., Suzuki N. Annexin II, a novel HSP27-interacted protein, is involved in resistance to UVC-induced cell death in human AP⁺-1 cells. *Photochem. Photobiol.* 84, 1455-1461, 2008
3. Lu J., Suzuki T., Satoh M., Chen S., Tomonaga T., Nomura F., Suzuki N. Involvement of aldolase A in X-ray resistance of human HeLa and UV^r-1 cells *Biochem. Biophys. Res. Com.* 36, 948-952, 2008

Occupational and Environmental Medicine (A2)



◆ Overview

Regarding cadmium (Cd), we are continuously conducting epidemiological investigations such as a survey of the regional accumulation of health effects caused by exposure to Cd (see the figure), by applying new methods including estimation of the Cd tolerance level using the Benchmark dose method. Regarding occupational health, we are conducting additional investigations of such issues as the rotating shift system, long working hours, and occupational stress to examine their relationship with health indices. We are also working on molecular epidemiological research mainly concerning the relationship between genetic polymorphism and lifestyle-related diseases. In the field of preventive medicine, research themes have developed from fatal diseases caused by significant environmental pollution, to effects on health and diseases in the general population due to low-dose exposure. We also intend to continue research in residents of areas that are not polluted by Cd, as well as company workers.

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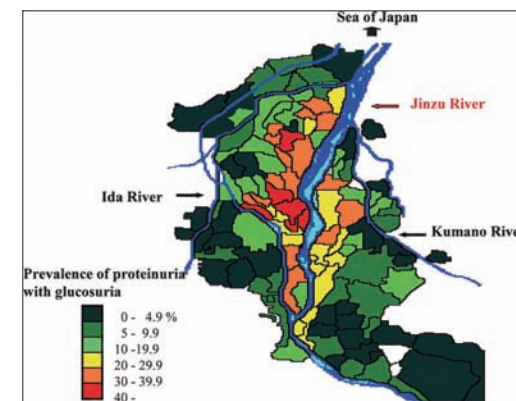
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◆ Research & Education

1. Management of working environment
2. Health management
3. Interaction between environment and human being
4. Public environmental hazard
5. Prevention of occupational disease
6. Work management
7. Mental health of workers

Geographical distribution of the prevalence of combined proteinuria and glucosuria among inhabitants aged 50 years and older.



(Uetani et al., 2007 PMID: 17479386)

◆ Recent Publications

Suwazono Y, Kido T, Nakagawa H, Nishijo M, Honda R, Kobayashi E, Dochi M, Nogawa K. Biological half-life of cadmium in the urine of inhabitants after cessation of cadmium exposure. *Biomarkers* 2009 14:77-81.

Suwazono Y, Dochi M, Sakata K, Okubo Y, Oishi M, Tanaka K, Kobayashi E, Nogawa K. Shift work is a risk factor for increased blood pressure in male Japanese: A 14-year historical cohort study. *Hypertension* 2008 52:581-6.

Suwazono Y, Sand S, Vahter M, Filipsson AF, Skerfving S, Lidfeldt J, Åkesson A. Benchmark dose for cadmium-induced renal effects in humans. *Environ Health Perspect.* 2006 114:1072-6.

Bioenvironmental Medicine (A3)

◆ Overview

In modern society, humans are exposed to uncountable man-made and natural environmental chemicals. Under the current toxicology, the target population in evaluating the health effect is “adults”. However, children before puberty, toddlers and fetuses sometimes show symptoms completely different from adults. When the health effect from human surrounding environment is considered, it is especially important to think of prevention rather than cure after diagnose. In the Department of Bioenvironmental Medicine, “environmental preventive medicine” to protect health of future generations is researched.



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◆ Research & Education

1. Effect of environmental chemical compounds on the reproductive system
2. Analysis of spermatogenesis
3. Study on the transfer of chemical compounds to fetus and its mechanism
4. Development of methods to reduce persistent lipophilic organic pollutants from human body
5. Detection of biomarkers for chemical exposure assessment
6. Risk assessment and risk management
7. Environmental education
8. Study on formaldehyde exposure
9. Study on the preventive medicine based on the improvement of living environment, using laboratory houses built with as few chemicals as possible in the Chemiless® Town
10. Human anatomy and embryology



Landscape of the Chemiless® Town

◆ Recent Publications

- “Establishment of sustainable health science for future generations: from a hundred years ago to a hundred years in the future.” Mori C, Todaka E. *Environ. Health Prev. Med.*, 2009; 14:1-6.
- “Polybrominated diphenyl ethers cause oxidative stress in human umbilical vein endothelial cells.” Kawashiro Y, Fukata H, Sato K, Aburatani H, Takigami H, Mori C. *Human & Experimental Toxicology*, 2009; in press.
- “Neonatal exposure to diethylstilbestrol alters expression of DNA methyltransferases and methylation of genomic DNA in the mouse uterus.” Sato K, Fukata H, Kogo Y, Ohgane J, Shiota K, Mori C. *Endocrine Journal*, 2009; 56:131-139.

Public Health(A4)



◆ Overview

Our initial goal is to identify genetic background of various disorders including multifactorial diseases like allergy, Kawasaki disease, and dysmorphic syndromes. We would like to explain the role of genetic factors together with environmental and social factors in the pathogenesis of target diseases. The final goal would be an establishment of personalized preventive medicine using knowledge obtained. To accomplish this goal, development of human resources is also essential to fit social needs properly. Thus, we are working on establishment of accreditation system for human resources in the personal genome era.

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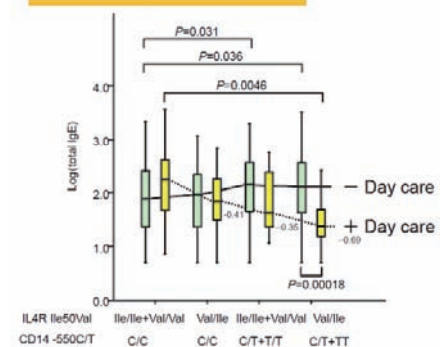
URL: <http://www.m.chiba-u.ac.jp/class/pubheal/>



◆ Research & Education

1. Genetic basis of allergic disorders
 - bronchial asthma
 - atopic dermatitis
 - allergic rhinitis
2. Kawasaki disease
 - Identification of susceptible genes for Kawasaki disease
 - Development of personalized medicine for Kawasaki disease
3. Genetic basis of inherited genetic diseases
 - Analysis of multiple congenital anomaly/mental retardation syndrome
4. Establishment of accreditation system of staffs for medical genetic service
5. Clinical genetics

Gene-gene and gene-environmental interactions for total IgE



Total IgE level in 4 groups of children classified by a combination of *IL4R* and *CD14* genotypes. Box plot of \log_{10} (total IgE) is shown for children who attended day care (+Day care) and for those who did not (-Day care).

◆ Recent Publications

- Suzuki Y, Hattori S, Mashimo Y, Funamizu M, Kohno Y, Okamoto Y, Hata A, Shimojo N. CD14 and IL4R gene polymorphisms modify the effect of day care attendance on serum IgE levels. *J Allergy Clin Immunol.* 123, 1408-1411, 2009
- Hata A, Onouchi Y. Susceptibility genes for Kawasaki disease: toward implementation of personalized medicine. *J Hum Genet.* 54, 67-73, 2009
- Onouchi Y, Gunji T, Burns JC, Shimizu C, Newburger JW, Yashiro M, Nakamura Y, Yanagawa H, Wakui K, Fukushima Y, Kishi F, Hamamoto K, Terai M, Sato Y, Ouchi K, Saji T, Akiyoshi Nariai A, Yoichi Kaburagi Y, Yoshikawa T, Suzuki K, Tanaka T, Nagai T, Cho H, Fujino A, Sekine A, Nakamichi R, Tsunoda T, Kawasaki T, Nakamura Y, Hata A. A functional polymorphism in *ITPKC* is associated with Kawasaki disease susceptibility and formation of coronary artery aneurysms. *Nature Genet.* 40, 35-42, 2008

Legal Medicine (A5)



◆Overview

We perform CT scan in all forensic cases before post-mortem autopsy. We also offer free CT scan in nonforensic cases of unnatural death if requested by the police and/or bereaved families. Through these activities, we compare CT scan findings and autopsy findings to identify the advantages and disadvantages of post-mortem CT examination, and then discuss the utility of CT-based screening in investigating the cause of death

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◆Research & Education

- (1) Utility of post-mortem CT scan in diagnosing the cause of death
- (2) Mechanism of cell death under the condition of hypoxia-reoxygenation
- (3) Estimation of the origins of unidentified cadavers based on DNA polymorphism in human-infecting bacteria and viruses
- (4) Drug screening by LC/MS/MS
- (5) Personal identification using dental findings and DNA testing



◆Recent Publications

- “Evaluation of the utility of CT as a screening test for death inquest.” Iwase H, Yajima D, Hayakawa M, Yamamoto S, Motani H, Sakuma A, Kasahara S, Ito H. J Forensic Sci. (in press).
- “The relationship between cell membrane damage and lipid peroxidation under the condition of hypoxia-reoxygenation: analysis of the mechanism using antioxidants and electron transport inhibitors.” Yajima D, Motani H, Hayakawa M, Sato Y, Sato K, Iwase H. Cell Biochem Funct. 2009 Aug;27(6):338-43.
- “Useful DNA typing using AmpFlSTR® Identifiler® Kit for formaldehyde-fixed paraffin-embedded (FFPE) tissues in early gastric cancer patient with lymph node metastasis.” Motani-Saitoh H, Inoue H, Tanizawa T, Nabeya Y, Yajima D, Hayakawa M, Sato Y, Nakatani Y, Matsubara H, Iwase H. Histol Histopathol. 2009 Sep;24(9):1139-45

Anesthesiology (B1)



◆ Overview

Anesthesiology includes an incredibly wide range of study fields. This is because anesthesiology is not only closely related to other clinical fields, but anesthesiology itself is deeply associated with basic medicine. In our department, we are conducting clinical research on the effect of anesthesia on respiration and circulation based on our motto to manage patients safely. At the same time we are conducting basic research concerning palliative medicine and pain relief.

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◆ Research & Education

1. Safe anesthesia for patients

Effects of anesthesia on cardiovascular function and organ flow

Control of breathing during anesthesia

Airway reflexes

Upper airway maintenance

2. Palliative care medicine

Assessment and evaluation of pain.

Mechanisms of chronic pain

Mechanism of dyspnea and its treatment

◆ Recent Publications

1. Nishino T, et al: Coughing induced by airway irritation modulates the sensation of air hunger. J Physiol,586.2: 649-658, 2008
2. Nishino T, et al: Sex differences in the effect of dyspnea on thermal pain threshold in young healthy subjects, Anesthesiology 109: 1100-1106, 2008
3. Nishino T, et al: THAM improves an experimentally-induced severe dyspnea. J Pain Symptom Manage 37:212-219, 2009

Respiratory Medicine (B2)



◆ Overview

In our department of respirology, we are conducting extensive research on diseases involving the respiratory organs such as pulmonary infection including pneumonia, which has recently been increasing in prevalence, allergic autoimmune diseases including bronchial asthma, chronic respiratory failure including chronic obstructive pulmonary disease, interstitial pneumonia including pulmonary fibrosis and hypersensitivity pneumonitis, diseases leading to pulmonary circulatory disorder including pulmonary hypertension, sleep apnea syndrome, and lung cancer.

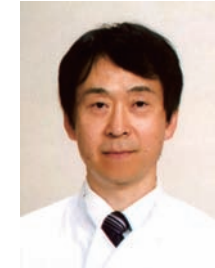
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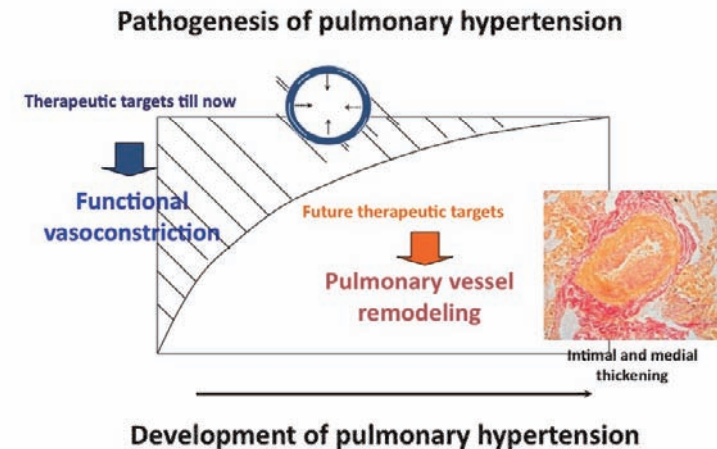
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◆ Research & Education

1. Remodeling of pulmonary artery in pulmonary arterial hypertension (PAH) and Therapy for PAH
2. Development and progression of chronic thromboembolic pulmonary hypertension (CTEPH) and Therapy for CTEPH
3. Pathophysiology, pathobiology and therapy for chronic obstructive pulmonary disease (COPD)
4. Cell death, remodeling and repair in pulmonary diseases
5. Pathophysiology and therapy for sleep apnea syndrome
6. Adaptation to hypoxia
7. Pathophysiology, pathobiology and therapy for interstitial lung diseases
8. New biomarkers including proteomics in respiratory diseases
9. Pathophysiology and therapy for pulmonary infectious diseases
10. Pathophysiology and therapy for pulmonary fungus diseases
11. Diagnosis and therapy for pulmonary malignant diseases
12. Herbal medicine for pulmonary diseases



◆ Recent Publications

Tatsumi K, Shinozuka N, Nakayama K, et al. Hochuekkito improves systemic inflammation and nutritional status in elderly patients with chronic obstructive pulmonary disease. *J Am Geriatr Soc* 57: 169-70, 2009.

Sakao S, Tatsumi K, Voelkel NF. Endothelial cells and pulmonary arterial hypertension : apoptosis, proliferation, interaction and transdifferentiation. *Respiratory Research* 10: 95-103, 2009.

Diagnostic Pathology (B3)



◆ Overview

Diagnostic pathology is attractive, because it aims to understand the mechanism of unidentifiable lesions in an integrated manner by making it possible to observe the lesions with the naked eye, extracting the characteristics of tissues by microscopy, and further clarifying genetic or molecular abnormalities in the background. As a result, we can contribute to medical treatment in clinical settings by providing useful information on diagnosis and treatment. At our department, we are advancing research and education mainly on pulmonary diseases by such an approach, as described below:

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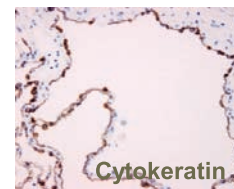
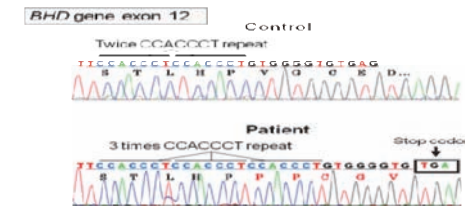
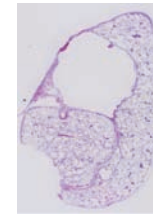
◆ Research & Education

1. Pathology of pulmonary and pleural Diseases

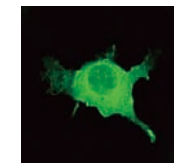
- ..Histopathological and molecular studies of large cell neuroendocrine carcinoma
- ..Histopathological and molecular studies of malignant mesothelioma
- ..Histopathological and molecular studies of pulmonary blastoma
- ..Diagnosis and pathogenesis of lung cysts in Birt-Hogg-Dube syndrome
- ..Proteomics of lung cancers
- ..Histopathological analysis of IgG4-related inflammatory pseudotumor
- ..Histopathological and molecular analysis of pulmonary adenocarcinomas
- ..Molecular pathogenesis of congenital cystic adenomatoid malformation
- .. Molecular pathogenesis of sclerosing hemangioma

2. Surgical pathology

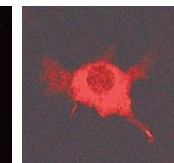
3. Cytology of lung diseases



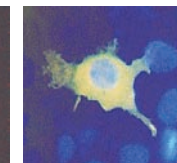
Lung cysts in Birt-Hogg-Dube syndrome



HAタグ



Folliculin



Merge

Folliculin cDNA transfection in Cos 7 cells

◆ Recent Publications

- “Lung cysts in Birt-Hogg-Dubé syndrome: histopathological characteristics and aberrant sequence repeats.” Koga S, Furuya M, Takahashi Y, Tanaka R, Yamaguchi A, Yasufuku K, Hiroshima K, Kurihara M, Yoshima I, Aoki I, Nakatani Y. *Pathol Int.* 2009;59:720-08.
- “Malignant pleural mesothelioma: Clinicopathology of 16 extrapleural pneumonectomy patients with special reference to early stage features.” Hiroshima K, Yusa T, Kameya T, Ito I, Kaneko K, Kadoyama C, Kishi H, Saitoh Y, Ozaki D, Itami M, Iwata T, Iyoda A, Kawai T, Yoshino I, Nakatani Y. *Pathol Int.* 2009;59:537-45.
- “Role of the PI3K/Akt, mTOR, and STK11/LKB1 pathways in the tumorigenesis of sclerosing hemangioma of the lung.” Amin RM, Hiroshima K, Miyagi Y, Kokubo T, Hoshi K, Fujisawa T, Nakatani Y. *Pathol Int.* 2008;58:38-44.

Japanese-Oriental "KAMPO" Medicine (B4)



◆ Overview

Kampo medicine (Japanese oriental medicine) is a system of medicine that originated in Chinese medicine and was introduced to Japan in the middle of the 6th century. Thereafter, it has been the main form of medical treatment in Japan for over a thousand years. In the Meiji era, however, it was regarded as old-fashioned medicine and was excluded from medical treatment applications. However, it was revitalized due to consistent support from people, since pathological conditions and defects that cannot be resolved by Western medicine, which regards human beings as an assembly of mechanical pieces, have emerged with the recent aging society. Our ultimate objective is to harmonize Kampo medicine and Western medicine. We firmly believe that the harmonization of these two different paradigms (schemes of thoughts) is one of the major directions in which medical science and medical treatment will be reformed in the future.

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◆ Research & Education

1. Integrating Kampo Medicine with Conventional Medicine

--Since Kampo (Japanese-Oriental) medicine and conventional (Western) medicine each have their own unique features, their complementary clinical application should ideally make up for defects in each respective approach.

2. Standardization of Kampo Diagnosis

--We are standardizing Kampo diagnosis for the prescribing clinicians in order to apply Kampo medicine in a safe and effective manner.

3. Clinical and Pharmacological Analysis of Kampo Formulae

--Controlled clinical trials and cell biological studies are planned to verify the effectiveness of each Kampo prescription.

◆ Recent Publications

1. Chino A, Okamoto H, Hirasaki Y, Terasawa K. A Case of Atopic Dermatitis Successfully Treated with Juzentaihoto. *Altern Ther Health Med.* (in press)
2. Kogure T, Tatsumi T, Niizawa A, Fujinaga H, Ito T, Shimada Y, Terasawa K. No correlation exists between disease activity and the expression of killer-cell immunoglobulin-like receptors in patients with rheumatoid arthritis. *Mediators Inflamm.* 2007;65179.
3. Kainuma M, Fujimoto M, Sekiya N, Tsuneyama K, Cheng C, Takano Y, Terasawa K, Shimada Y. Cholesterol-fed rabbit as a unique model of nonalcoholic, nonobese, non-insulin-resistant fatty liver disease with characteristic fibrosis. *J Gastroenterol.* 2006;41(10):971-80.

Neurobiology (C1)



◆ Overview

The goal of our research is to understand how neurons respond to ischemic stress in brain stroke. Cerebrovascular disease is the third most common cause of death and accounts for ~ 30% of adult disability in Japan. To develop a novel therapy for stroke patients in acute phase, we intend to clarify the mechanism in which neurons response to brain ischemia using *in vitro* system and animal stroke model. Regarding medical education, we are in charge of the lectures and practical training of neuroanatomy for second and third-year students. Our lectures are mainly intended to bridge clinical neurology and basic neuroscience.

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◆ Research & Education

Research

1, Molecular mechanism underlying neuronal death in acute brain ischemia/reperfusion

Our goal is develop a novel therapy to protect neuron in penumbra of acute brain ischemia/reperfusion.

2, Molecular mechanism underlying aging/longevity across species.

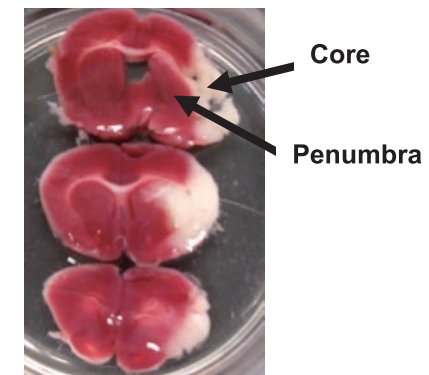
We are studying on aging/longevity using *C.elegans*, *Drosophila melanogaster* and mammalian cells. We focus on the molecular mechanism underlying dietary restriction, which extends lifespan across species.

Education

1, Basic Neuroscience in 2nd academic year.

2, Neuroanatomy in 3rd academic year.

Rat MCA-O Reperfusion model (TTC staining)



◆ Recent Publications

- 1, Fujita Y, Yamaguchi A, Hata K, Endo M, Yamaguchi N, Yamashita T. Zyxin is a novel interacting partner for SIRT1. BMC Cell Biol. (2009) Jan 27;10:6.
- 2, Tohyama D, Yamaguchi A, Yamashita T. Inhibition of a eukaryotic initiation factor (*eIF2Bδ/F11A3.2*) during adulthood extends lifespan in *Caenorhabditis elegans*. FASEB J(2008)2 2(12):4327-37

Cognitive Behavioral Physiology (C2)



◆ Overview

Cognitive behavior therapy is psychological therapy that has been shown by evidence to be equivalent to drug therapy for affective disorders such as anxiety and depression. With cognitive behavior therapy, the focus is on the detection of mechanisms to maintain patterns of vicious circles of cognition, behavior, and affects in the context of how people recognize things and take actions, as well as on the alteration of such patterns. We have great interest in how such changes in cognition and behavior affect the brain. We are conducting neuroscientific research to clarify the relationship between cognition, behavior, and affects by making extensive use of molecular analysis in animal models and non-invasive cerebrophysiological imaging tests targeting humans.

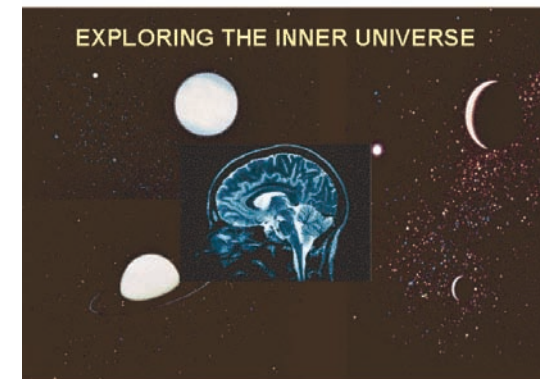
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◆ Research & Education

1. Molecular mechanisms of anxiety and fear
2. Effects and mechanisms of cognitive behavioral therapy
3. Non-invasive brain functional analyses in humans
4. Neural mechanism in larynx



◆ Recent Publications

Kurayama T, Nakazawa K, Matsuzawa D, Yoshida S, Nanbu M, Suto C, Shimizu E. Alterations of auditory p50 suppression in human fear conditioning and extinction. *Biol Psychiatry*. 2009 Mar 15;65(6):495-502.

Ohgake S, Shimizu E, Hashimoto K, Okamura N, Koike K, Koizumi H, Fujisaki M, Kanahara N, Matsuda S, Sutoh C, Matsuzawa D, Muramatsu H, Muramatsu T, Iyo M. Dopaminergic hypofunctions and prepulse inhibition deficits in mice lacking midkine. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009 Apr 30;33(3):541-6.

Kanahara N, Shimizu E, Ohgake S, Fujita Y, Kohno M, Hashimoto T, Matsuzawa D, Shirayama Y, Hashimoto K, Iyo M. Glycine and D: -serine, but not D: -cycloserine, attenuate prepulse inhibition deficits induced by NMDA receptor antagonist MK-801. *Psychopharmacology (Berl)*. 2008 Jun;198(3):363-74.

Medical Physiology (C3)



◆ Overview

In the department of medical physiology, we are currently conducting research on the regulatory mechanisms of glucose and energy metabolism, by using molecular biology and developmental engineering techniques. Our scientific interest covers a variety of metabolic disorders, including diabetes mellitus, obesity and eating disorders. We put a high value on unveiling the intra- and inter-cellular signaling pathways to maintain metabolic homeostasis in each hierarchy of molecules, cells, organs and individuals. We are also interested in research for a novel therapeutic strategies and/or agents by which the medical technology would greatly be improved.

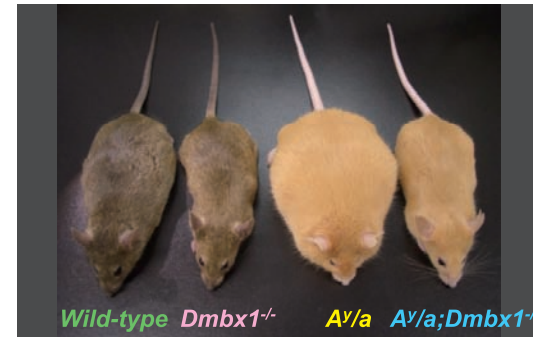
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◆ Research & Education

1. Regulation of glucose metabolism and energy homeostasis
2. Molecular dissection of exocytosis
3. Physiological analysis of insulin secretion and action using genetically engineered mouse models
4. Regulation of cell firing of electrically excitable cells
5. Metabolic regulation via signal crosstalk between brain and peripheral tissues
6. Pathogenesis of metabolic syndrome and diabetes mellitus
7. Search for novel therapeutic targets of diabetes mellitus



Dmbx1 is essential in agouti-related protein action.
Fujimoto et al. *Proc Natl Acad Sci USA* 104:15514, 2007

◆ Recent Publications

- “Niflumic acid-sensitive ion channels play an important role in the induction of glucose-stimulated insulin secretion by cyclic AMP in mice.” Fujimoto W, Miki T, Ogura T, Zhang M, Seino Y, Satin LS, Nakaya H, Seino S. (2009) *Diabetologia* 52(5):863-872.
- “The cAMP sensor Epac2 is a direct target of antidiabetic sulfonylurea drugs.” Zhang CL, Katoh M, Shibasaki T, Minami K, Sunaga Y, Takahashi H, Yokoi N, Iwasaki M, Miki T, Seino S. (2009) *Science* 325(5940):607-610.
- “LKB1 regulates pancreatic beta cell size, polarity, and function.” Granot Z, Swisa A, Magenheim J, Stolovich-Rain M, Fujimoto W, Manduchi E, Miki T, Lennerz JK, Stoeckert CJ Jr, Meyuhas O, Seino S, Permutt MA, Piwnicka-Worms H, Bardeesy N, Dor Y. (2009) *Cell Metab* 10:296-308.

Ophthalmology and Visual Science (D1)



◆ Overview

1. Research for pathogenesis and treatment of retinitis pigmentosa
2. Research for changes in retinal microstructure and retinal function after vitreoretinal surgery
3. Research for pathogenesis and treatment of age-related macular degeneration
4. Research for neuroprotection in diabetic retinopathy
5. Origins of photoreceptor responses in electroretinogram

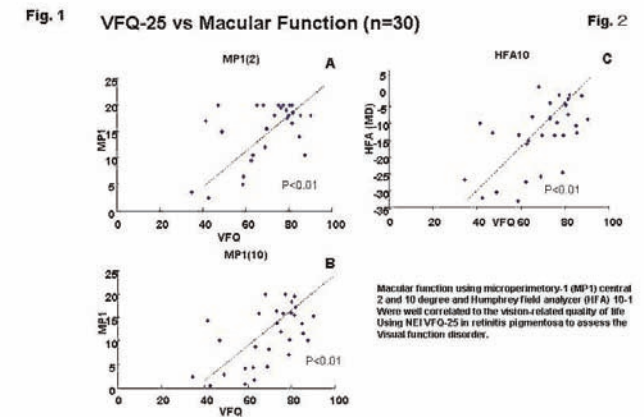
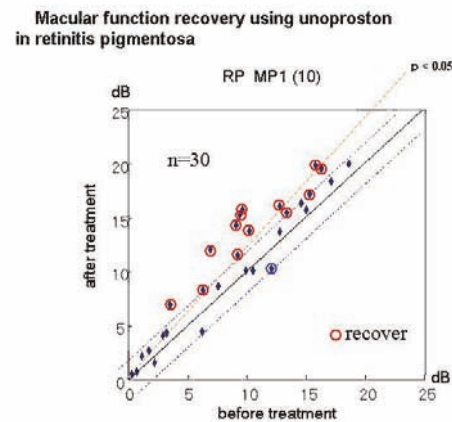
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◆ Research & Education

1. Research for processing of visual information
2. Electrophysiological study for vision abnormality
3. Molecular genetics for hereditary eye diseases
4. Research for pathogenesis of vitreoretinal diseases
5. Retinal transplantation
6. Regeneration and transplantation of optic nerve
7. Research for pathogenesis and treatment of glaucoma
8. Research for chorio-retinal degeneration
9. Immunological study of uveitis



◆ Recent Publications

- 1) Two-year comparison of photodynamic therapy and intravitreal bevacizumab for treatment of myopic choroidal neovascularization. Baba T, Kubota-Taniai M, Kitahashi M, Okada K, Mitamura Y, Yamamoto S: Br J Ophthalmol 2009. [Epub ahead of print]
- 2) The relationship between the NEI VFQ-25 and visual field defect with Goldmann perimetry in retinitis pigmentosa. Sugawara T, Hagiwara A, Hiramatsu A, Ogata K, Mitamura Y, Yamamoto S: Eye 2009 [Epub ahead of print]
- 3) Mitochondria- and caspase-dependent cell death pathway involved in neuronal degeneration in diabetic retinopathy. Oshitari T, Yamamoto S, Hata N and Roy S. Br J Ophthalmol;92:552-556, 2008

Neurological Surgery (D2)



◆ Overview

Department of Neurosurgical surgery maintains an active clinical service with ten staff neurosurgeons and residents. We provide leading-edge technologies for complex conditions in the following areas: sellar and parasellar lesions, skull base surgery, malignant brain tumors, spinal disorders and functional disorders. Our patients have access to less-invasive procedures and the most current therapies. We also offer excellent training program in neurosurgery for neurosurgical residents, in cooperation with other hospitals and medical centers in Chiba.

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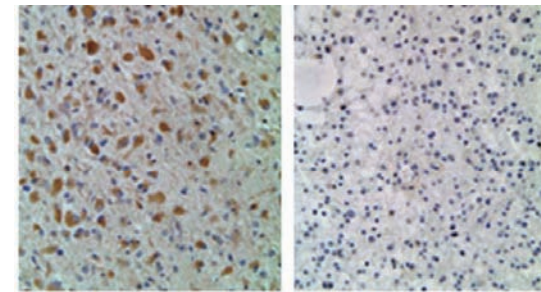
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◆ Research & Education

We focus on the following research area:

1. Diagnosis and treatment of sellar-parasellar lesions
2. Endoscopic surgery for intracranial lesions
3. Treatment strategy of skull base tumors
4. Diagnosis and treatment of malignant brain tumors
5. Gene therapy for brain tumors
6. Surgical and endovascular treatment for cerebral ischemia
7. Endovascular treatment for cerebral aneurysms
8. Mechanism of neurovascular compression syndrome
9. Treatment of spinal spondylosis and spinal cord tumor
10. Surgical treatment of syringomyelia
11. Flow dynamics of cerebrospinal fluid
12. Surgical treatment for movement disorders
13. Epilepsy surgery



Akt/PKB +

Akt/PKB -

Akt/PKB immunohistochemistry in diffuse astrocytoma. Overexpression of Akt/PKB predicts malignant progression and invasive regrowth and it can serve as a novel prognostic marker for diffuse astrocytoma.
(Matsutani T, 2009, *Acta Neurochir*)

◆ Recent Publications

Iwadate Y. Clinical proteomics in cancer research-promises and limitations of current two-dimensional gel electrophoreses. *Curr Med Chem*. 2008, 15: 2393-2400.

Matsutani T, Nagai Y, Mine S, Murai H, Saeki N, Iwadate Y: Akt/protein kinase B overexpression as an accurate prognostic marker in adult diffuse astrocytoma. *Acta Neurochir* 2009; 151:263-268

Yamakami I, Higuchi Y, Saeki N, Wada M, Oka N: Hearing preservation and intraoperative auditory brainstem response and cochlear nerve compound action potential monitoring in the removal of small acoustic neurinoma via the retrosigmoid approach. *J Neurol Neurosurg Psychiatry* 2009; 80:218-227

Higuchi Y, Serizawa T, Nagano O, Matsuda S, Ono J, Sato M, Iwadate Y, Saeki N: Three-staged stereotactic radiotherapy without whole brain irradiation for large metastatic brain tumors. *Int J Radiat Oncol Biol Phys* 2009; 74:1543-8

Neurology (D3)



◆ Overview

The 21st century is the century of neuroscience. Therefore, we adopt a multidisciplinary approach using various methods such as molecular cell biology, physiology, neuroimaging, and proteomics for each disease, to clarify the pathological conditions of nerve diseases on a molecular level and to develop new treatment drugs. Since this is a department of clinical medicine, we wish to conduct clinical and research activities while being strongly aware of treatment regimens. In our department, specialists in such fields involved in clinical medicine as neurosymptomatology, anatomy, electrophysiology, neuroimaging, pathology, molecular biology, and immunology are gathered, and all staff members are striving towards medical treatment, research, education, and a social contribution in the field of nerve diseases by cultivating excellent neurologists.

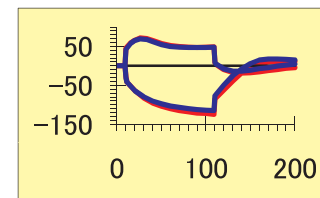
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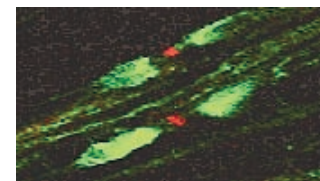
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◆ Research & Education

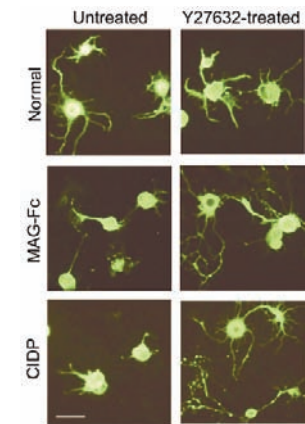
1. Neuronal/axonal ion channel physiology
2. Pathogenesis of neuro-immunological diseases
3. Peripheral nerve regeneration: promotion of axonal growth
4. Brain functional-molecular imaging
5. Molecular biology of neurological disorders
6. Development of new treatments for motor neuron diseases.
7. Pathogenesis and treatment of neuropathic pain syndrome
8. Clinical neurophysiology: EMG/NCS, evoked potentials



Threshold electrotonus in ALS



Immunohistochemistry
of ion channels



Axonal growth assay in
rat DRG neurons

◆ Recent Publications

- 1) CIDP sera inhibit axonal growth of mouse DRG neurons by activation of Rho kinase Taniguchi J, Sawai S, Mori M, Kubo T, Kanai K, Misawa S, Iose S, Yamashita T, Kuwabara, S. **Annals of Neurology** 2009 (in press).
- 2) "Cloud-like enhancement" is a magnetic resonance imaging abnormality specific to neuromyelitis optica. Ito S, Mori M, Makino T, Hayakawa S, Kuwabara S. **Annals of Neurology** 2009 ;66Sep;66(3):425-8.
- 3) Prediction of prognosis in Guillain-Barre syndrome. Hiraga A, Kuwabara S, **Lancet Neurology** 2007;6:572-573.

Biochemistry and Genetics (E1)



◆ Overview

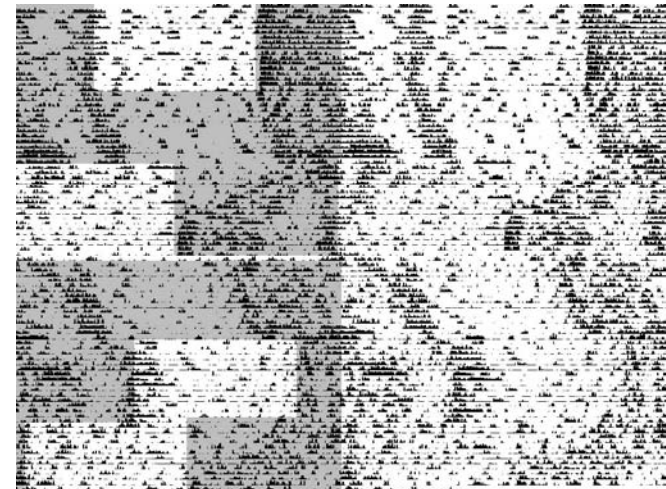
In our laboratory, we are investigating regulation of genes critical for daily behavioral and metabolic rhythms, neural plasticity and cell proliferation, from the point of views how the genes are regulated in systemic, cellular and molecular levels, and what are biological consequences of the altered gene expression.

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◆ Research & Education

1. Regulation of daily behavioral and metabolic rhythms by light stimuli and nutrients (Dr. Masaki TAKIGUCHI, Professor)
2. Gene regulation of neural plasticity exemplified by fear conditioning (Dr. Katsuro IWASE, Assistant Professor)
3. Gene regulation of cell proliferation and oncogenesis (Dr. Takaki HIWASA, Associate Professor)



◆ Recent Publications

- Activation of NFAT signal by p53-K120R mutant. Shinmen, N., Koshida, T., Kumazawa, T., Sato, K., Shimada, H., Matsutani, T., Iwadata, Y., Takiguchi, M., and Hiwasa, T. *FEBS Lett.* **583**, 1916-1922 (2009)
- Multifactorial regulation of daily rhythms in expression of the metabolically responsive gene Spot14 in the mouse liver. Ishihara, A., Matsumoto, E., Horikawa, K., Kudo, T., Sakao, E., Nemoto, A., Iwase, K., Sugiyama, H., Tamura, Y., Shibata, S., and Takiguchi, M. *J. Biol. Rhythms* **22**, 324-334 (2007)

Molecular Virology (E2)



◆ Overview

Tumor virus study has contributed to the clarification of carcinogenic mechanisms. In our department, we have been conducting research on carcinogenic mechanisms of the tumor virus, papillomavirus. Carcinogenic mechanism study of viruses also provides clues to clarify characteristics of human cancers that are not caused by viruses. Furthermore, tumor virus study has also provided the basic technology and knowledge to develop viruses that kill cancer (oncolytic viruses). In our department, we are conducting research on viruses to cure cancer based on achievements in this tumor virus study.

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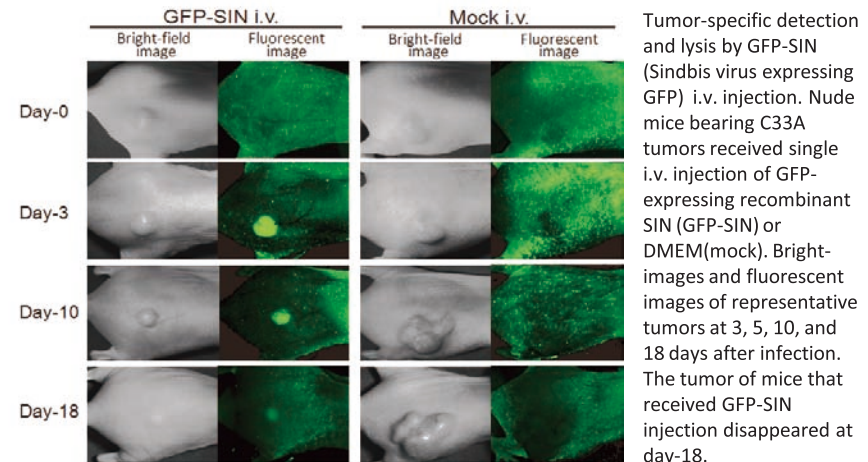
◆ Research & Education

Research

1. Sindbis virus as an oncolytic virus
 - Oncolytic activity of Sindbis virus (SIN) structural proteins
 - Oncolytic activity of Sindbis virus (SIN) replicon
 - Preclinical study of oncolytic viruses
2. Papillomaviruses
 - Functions of HPV-16 E6 protein
 - Functions of bovine papillomavirus (BPV) E5 proteins
3. Cellular genes involving in oncogenesis
4. Analyses of coronaviruses in the environment as a surveillance model

Education

1. Virology for medical students
2. Literacy of information processing for medical students



◆ Recent Publications

- "Oncolytic activity of Sindbis virus in human oral squamous carcinoma cells." Saito K, Uzawa K, Kasamatsu A, Shinozuka K, Sakuma K, Yamatoji M, Shiiba M, Shino Y, Shirasawa H, Tanzawa H., Br. J. Cancer. 2009;101:684-890.
- "TP53 codon 72 polymorphism and cervical cancer: pooled analysis of individual data of 15 834 women from 49 studies." Stefanie J. Klug et al., Lancet Oncology, 10, 772-784, 2009.
- "Human papillomavirus vaccine." Hiroshi Shirasawa, Virus Report, 5, 40-48, 2008.
- "Oncolytic viral therapy for cervical and Ovarian cells by sindbis virus AR339 strain." Unno, Y., Shino, Y., Kondo, F., Igarashi, N., Wang, G., Shimura, R., Yamaguchi, T., Asano, T., Saisho, H., Sekiya, S., Shirasawa, H. Clin Cancer Res 11, 4553-4560, 2005.

Molecular Pathology (E3)



◆ Overview

In Department of Molecular Pathology, we are studying pathogenesis and pathophysiology of the diseases, especially in digestive and gynecological organs. In addition to the basic research, we also take part in clinical practice as clinical pathologists in Chiba University Hospital.

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◆ Research & Education

1. Tumor metastasis

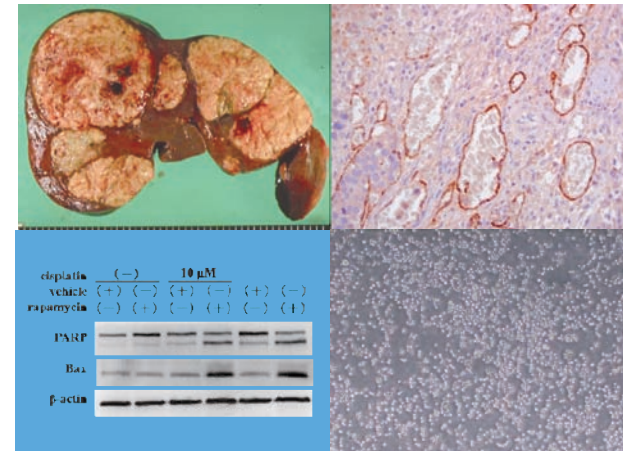
---Anoikis, a special form of apoptosis that is induced by loss of cell-cell or cell-extracellular matrix (ECM) interaction
---Signal transduction including PI3K/Akt, mTOR, and MAPK

2. Tumor transdifferentiation

---Epigenetics in tumor transdifferentiation

3. Histopathological analysis

---Gynecological pathology
---AFP-producing tumors and hepatoid adenocarcinoma



◆ Recent Publications

1. Kishimoto T, Yano T, Hiroshima K, Inayama Y, Kawachi K, Nakatani Y. A case of a-fetoprotein-producing pulmonary carcinoma with restricted expression of hepatocyte nuclear factor-4a in hepatoid foci: a case report with studies of previous cases. *Hum Pathol* 2008; 39: 1115-20.
2. Kamata S, Kishimoto T, Kobayashi S, Miyazak M. Expression and localization of ATP binding cassette (ABC) family of drug transporters in gastric hepatoid adenocarcinomas. *Histopathology* 2008; 52: 747-54.
3. Mikami Y, Kiyokawa T, Sasajima Y, Teramoto N, Wakasa T, Wakasa K, Hata S. Reappraisal of synchronous and multifocal mucinous lesions of the female genital tract: a close association with gastric metaplasia. *Histopathology* 2009, 54:184-91.

Molecular & Tumor Pathology (E4)

◆ Overview

In the department of pathology, definite diagnoses of lesions are made in the clinical medicine setting. Pathologists also play an important role to bridge basic medicine and clinical medicine in modern medical diagnosis and treatment with extensive knowledge in both fields. Therefore, in our department of molecular and tumor pathology, we are performing pathological diagnosis as well as aiming to analyze the nature of lesions by using methods of molecular biology and cellular biology, and to deepen pathological diagnosis by an understanding of the molecular background of lesions. In such a setting, we, in this department, are analyzing the mechanisms of invasion and metastasis of cancer, using methods of molecular and cellular biology and morphology, including molecular imaging, paying attention to interactions between cancer cells and substrates or cancer cells and surrounding interstitial cells.



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◆ Research & Education

1. Tumor cell biology

- Molecular mechanism of invasion and metastasis of colorectal and breast carcinomas
- Molecular interaction between fragmented hyaluronan and CD44
- Hyaluronan-induced cell motility (activation of RhoGTPases and assembly of cytoskeletons)
- Molecular mechanism of epithelial-mesenchymal transition

2. Stem cell biology

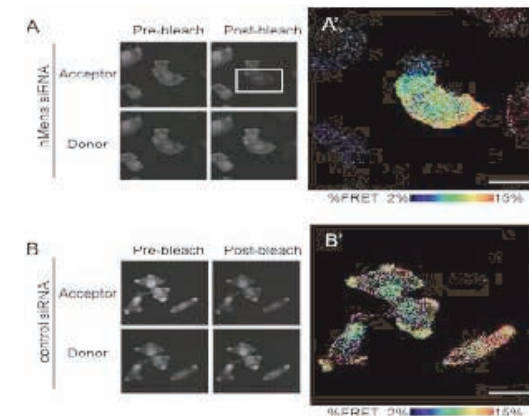
- Cell-cell and cell-matrix interaction of stem cell (Notch signaling and function of CD44)

3. Signal transduction

- Hyaluronan-induced signaling
- Notch signaling: function of mastermind (knockout mice)

4. Live cell imaging

5. Human pathology



◆ Recent Publications

- “Nemo-like kinase suppresses Notch signalling by interfering with formation of the Notch active transcriptional complex.” Ishitani T, Hirao T, Suzuki M, Isoda M, Ishitani S, Harigaya K, Kitagawa M, Matsumoto K, Itoh M. *Nat Cell Biol.* 12, 278-285, 2010.
- “Human Mena associates with Rac1 small GTPase in glioblastoma cell lines.” Higashi M, Ishikawa C, Yu J, Toyoda A, Kawana H, Kurokawa K, Matsuda M, Kitagawa M, Harigaya K. *PLoS One.* 4(3):e4765, 2009.
- “CD44 suppresses TLR-mediated inflammation.” Kawana H, Karaki H, Higashi M, Miyazaki M, Hilberg F, Kitagawa M, Harigaya K. *J Immunol.* 180(6):4235-45, 2008 .
- “Mastermind-1 is required for Notch signal-dependent steps in lymphocyte development in vivo.” Oyama T, Harigaya K, Muradil A, Hozumi K, Habu S, Oguro H, Iwama A, Matsuno K, Sakamoto R, Sato M, Yoshida N, Kitagawa M. *Proc Natl Acad Sci U S A.* 104(23):9764-9, 2007 .

Urology (E5)



◆ Overview

Major interests of Department of Urology are basic and clinical biology of prostate cancer and minimally invasive therapy for genitourinary cancers. Research interests focused on development and testing of new and existing methods for predicting the aggressiveness of prostate cancers. Clinical interests are focused on development of nomograms to help patients and their physicians decide among the major treatment choices for prostate cancers and non-malignant conditions. Surgical interests are focused on development of the new devices assisting laparoscopic surgery.

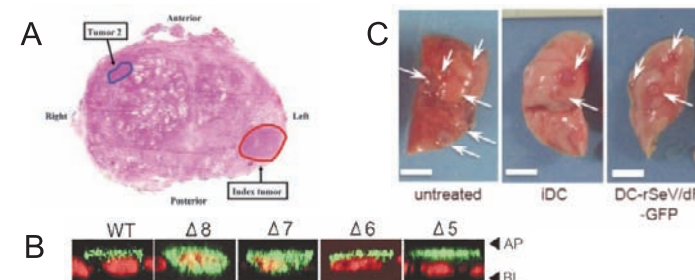
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◆ Research & Education

1. Laparoscopic surgery for adrenal tumor, renal and urothelial cancers, and prostate cancer
2. Cause and prevention of urolithiasis
3. Genetic diagnosis of renal and urothelial cancers
4. Tumor immunity in advanced renal cancer
5. Pathogenesis of neurogenic bladder
6. Tumor-suppressor genes and metastasis-suppressor genes for prostate cancer
7. Mechanism of development of hormone-refractory prostate cancer
8. New treatment for advanced prostate cancer
9. Male infertility and sexual dysfunction



- A. Whole-mount section of radical prostatectomy specimen showing two outlined tumor foci. (Kobayashi M, et al. *Prostate* 2008)
- B. Confocal-microscopic images of MDCKII cells expressing GFP-b0,+AT and its C-terminus deletion mutants. (Sakamoto S, et al. *Biochem J* 2009)
- C. Prevention of lung metastasis of RM-9 prostate cancer by DC therapy. (Komaru A, et al. *J Immunol* 2009)

◆ Recent Publications

- "Molecular analysis of multifocal prostate cancer by comparative genomic hybridization." Kobayashi M, Ishida H, Shindo T, Niwa S, Kino M, Kawamura K, Kamiya N, Imamoto T, Suzuki H, Hirokawa Y, Shiraishi T, Tanizawa T, Nakatani Y, Ichikawa T. *Prostate*. 2008 Dec 1;68(16):1715-24.
- "A novel role of the C-terminus of b0,+AT in the ER-Golgi trafficking of the rBAT-b0,+AT heterodimeric amino acid transporter." Sakamoto S, Chairoungdua A, Nagamori S, Wiriyasermkul P, Promchan K, Tanaka H, Kimura T, Ueda T, Fujimura M, Shigeta Y, Naya Y, Akakura K, Ito H, Endou H, Ichikawa T, Kanai Y. *Biochem J*. 2009 Jan 15;417(2):441-8.
- "Sustained and NK/CD4+ T cell-dependent efficient prevention of lung metastasis induced by dendritic cells harboring recombinant sendai virus." Komaru A, Ueda Y, Furuya A, Tanaka S, Yoshida K, Kato T, Kinoh H, Harada Y, Suzuki H, Inoue M, Hasegawa M, Ichikawa T, Yonemitsu Y. *J Immunol*. 2009 Oct 1;183(7):4211-9.

Pediatric Surgery (E6)



◆ Overview

The Department of Pediatric Surgery treats a wide variety of clinical problems in neonatology, pediatric gastroenterology, oncology, urology, thoracic surgery, and several other specialty areas. Our pediatric surgery team is sensitive to the concerns and care of each child and treats the family as a whole.

The Department provides educational and training opportunities for medical students and residents. In addition to the clinical programs and education, the Department has an active program in the pediatric surgical research.

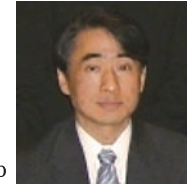
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◆ Research & Education

1. Elucidation of the molecular mechanisms in the development and progression of childhood malignant solid tumors
2. Investigation of oncolytic virus therapy and gene therapy for advanced neuroblastoma
3. Embryological study of congenital anomalies
4. Strategy based on the prenatal assessment in congenital anomalies
5. Pathophysiology and therapy of hepatobiliary tract diseases
6. Management of short bowel syndrome
7. Pathogenesis and treatments of inflammatory bowel diseases
8. Abdominal imaging diagnosis
9. Development of novel surgical procedures and surgical instruments
10. Management and issues of the home medical care
11. Provide a comprehensive training program, conference schedule and clinic experience to medical students and residents in the Pediatric Surgery Program.



This picture is the cover of *Developmental Biology* in which Dr Sato collaborated with Dr Heuckeroth at Washington University described the effect of retinoid on the development of enteric nervous system.

Yoshiharu Sato M.D., Ph.D.

◆ Recent Publications

- Induction of Wnt5a-expressing mesenchymal cells adjacent to the cloacal plate is an essential process for its proximodistal elongation and subsequent development. Nakata M, Takada Y, Hisiki T, Saito T, Turui K, Sato Y, Koseki H, Yoshida H. *Pediatr Res*. 66, 149-154, 2009
- Plk1 regulates liver tumor cell death by phosphorylation of TAp63. Komatsu S, Takenobu H, Ozaki T, Ando K, Koida N, Suenaga Y, Ichikawa T, Hishiki T, Chiba T, Iwama A, Yoshida H, Ohnuma N, Nakagawara A, Kamijo T. *Oncogene*. 15, 3631-3641, 2009.
- Retinoic acid regulates murine enteric nervous system precursor proliferation, enhances neuronal precursor differentiation, and reduces neurite growth in vitro. Sato, Y., Heuckeroth, RO. *Dev Biol*. 320, 185-198, 2008.

Molecular Infectiology (F1)



◆ Overview

In our department, we intend to clarify the molecular mechanism of bacterial infection and its onset as well as biological defense and adjusting mechanisms and to apply them to the control and prophylaxis of various diseases associated with bacterial infection. At present, our department is characterized by extensive research into issues including pathological molecules produced by pathological bacteria (such as toxins), pathological changes in target cells attacked by them, and the consequent conditions of infected individuals, without inclining to a one-sided aspect of either pathogens or hosts. While our department has made a number of achievements by vigorously conducting cooperative studies with domestic and overseas universities and national research institutes, we are aggressively promoting cooperative studies with pharmaceutical-related companies and clinicians aiming to develop new technologies and drugs that apply the above knowledge to the prophylaxis and treatment of bacterial infections. With the recent emergence of new and reemerging infections, studies on pathological organisms, immunity against infection, infectious genetics, and genome-based drug discovery are again recognized as being important. However, there are only a few researchers in this field in Japan. Therefore, we consider the promotion of international research exchange activities in pathogenic microbiology and bacterial infectionology as well as the cultivation of excellent next-generation researchers, educators, and physicians as our important missions.

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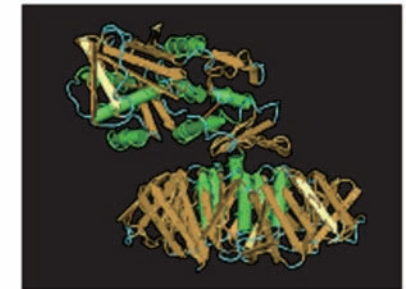


◆ Research & Education

1. The study on the mode of action of Shiga-like toxin produced by EHEC
--Molecular mechanism of toxin production and secretion
2. The study on the mode of action of subtilase cytotoxin produced by Shiga-toxin producing *E. coli*
--Molecular mechanism of cytotoxicity *in vitro* and *in vivo*
3. The study on the mode of action of bacterial ADP-ribosylating toxins
4. The study on the mode of action of new bacterial toxins
5. The study on the inhibitor of new bacterial toxins
--Effects of plant polyphenols on bacterial toxins
6. The study on the detection system of new bacterial toxins



Enterohaemorrhagic *Escherichia coli*
(EHEC)



Shiga toxin

◆ Recent Publications

- Shimizu, T., Y. Ohta, and M. Noda. 2009. Shiga toxin 2 is specifically released from bacterial cells by two different mechanisms. *Infect Immun* **77**:2813-2823.
- Matsuura, G., N. Morinaga, K. Yahiro, R. Komine, J. Moss, H. Yoshida, and M. Noda. 2009. Novel subtilase cytotoxin produced by Shiga-toxigenic *Escherichia coli* induces apoptosis in vero cells via mitochondrial membrane damage. *Infect Immun* **77**:2919-2924.
- Morinaga, N., K. Yahiro, G. Matsuura, J. Moss, and M. Noda. 2008. Subtilase cytotoxin, produced by Shiga-toxigenic *Escherichia coli*, transiently inhibits protein synthesis of Vero cells via degradation of BiP and induces cell cycle arrest at G1 by downregulation of cyclin D1. *Cell Microbiol* **10**:921-929.

Pharmacology (F2)

◆ Overview

Pharmacotherapy occupies a very important part of medicine. In order to find innovative and appropriate pharmacological strategies it is important to analyze and understand the pathophysiology of various diseases. In the department of pharmacology, we are conducting a variety of research to clarify the pathophysiology of cardiovascular diseases such as arrhythmia, ischemic heart disease, and heart failure using the patch-clamp method and other functional experiments in various kinds of genetically-engineered animals and disease models. We also conduct a research to clarify the regulatory mechanism of intercellular signaling through nitric oxide (NO) in relation to functional alteration in physiology and pathophysiology with use of biochemical and molecular biological techniques.



Professor:
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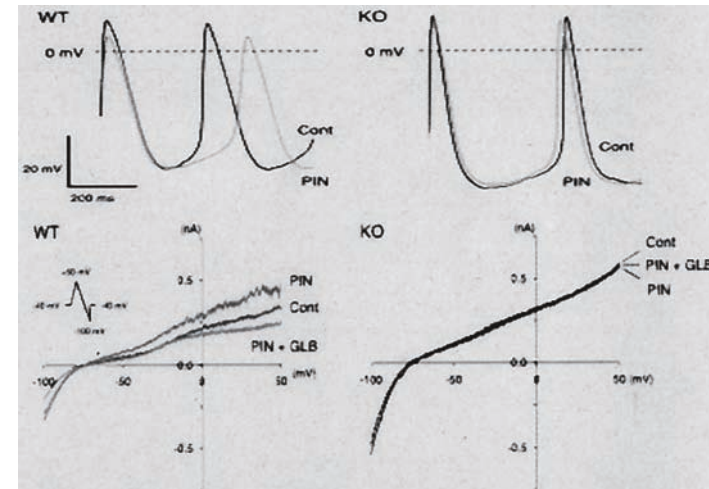
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◆ Research & Education

1. Functional role of ion channels clarified by use of genetically engineered mice.
2. Development of novel antiarrhythmic agents for the treatment of atrial fibrillation.
3. Molecular mechanism of cardioprotection by preconditioning and postconditioning during myocardial ischemia and reperfusion.
4. Regulatory role of nitric oxide (NO) in cellular signaling through S-nitrosylation.
5. Mechanisms of inter-cellular signaling by NO.



Pinacidil (PIN), a K_{ATP} channel opener, activated glibenclamide (GLB)-sensitive outward current and inhibited the automaticity in sinoatrial node cells of wild-type (WT) but not Kir6.2-deficient (KO) mice.

◆ Recent Publications

- “Role of sarcolemmal ATP-sensitive K⁺ channels in the regulation of sinoatrial node automaticity: an evaluation using Kir6.2-deficient mice.” Fukuzaki K, Sato T, Miki T, Seino S, Nakaya H. *J Physiol (Lond)* 2008; 586(11): 2767-2778.
- “Infarct size limitation by adrenomedullin; protein kinase A but not PI3-kinase is linked to mitochondrial K_{Ca} channels.” Nishida H, Sato T, Miyazaki M, Nakaya H. *Cardiovasc Res* 2008; 77(2): 398-405.

Infection and Host defense (F3)



◆ Overview

Defense mechanisms of hosts against intracellular parasites such as *Plasmodium* and *Toxoplasma* mainly consist of cell-mediated immunological reaction, which is induced and controlled by antigen presenting cells (APC) that act like a control tower. In our department, we have found that *Toxoplasma gondii*-derived heat shock protein 70 (*T.g.HSP70*) induces maturation and differentiation of professional APC, dendritic cells, and activates naïve T cells. Thus we are conducting research aiming to clarify the induction mechanism of innate and cell-mediated acquired immunity to develop gene vaccines.

We are also advancing analyses of the molecular biological mechanisms associated with the pathogenesis of congenital and acquired toxoplasmosis.

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◆ Research & Education

1. Protective immunity against parasite infection and vaccine development

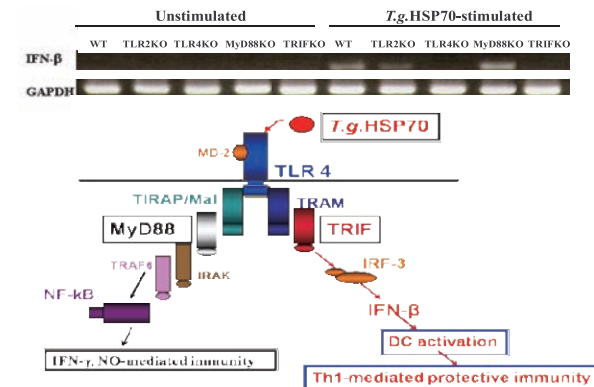
- Mechanisms of antigen presentation by antigen presenting cells (APC) infected with intracellular parasitic protozoan *Toxoplasma gondii* (*T. gondii*)
- T cell activation by professional APC
- Roles of *T. gondii* HSP70, a virulent pathogenic molecule specific for tachyzoites, and DNA vaccination with *T. gondii* HSP70 gene
- Mechanisms of host death and innate immunity
- Regulation of autoimmunity by *T. gondii* infection

2. Pathogenesis of toxoplasmosis, especially ocular toxoplasmosis

- Adhesion molecules, cytokine and chemokine networks that regulate the protective and pathological immune responses after *T. gondii* infection

3. Research for clinical parasitology

- Congenital and acquired toxoplasmosis in Japan



Signal pathway stimulated with *T.g.HSP70*

◆ Recent Publications

- Kikumura A, Fang H, Mun HS, Uemura N, Makino M, Sayama Y, Norose K, Aosai F. Protective immunity against lethal anaphylactic reaction in *Toxoplasma gondii*-infected mice by DNA vaccination with *T. gondii*-derived heat shock protein 70 gene. *Parasitol Int.* 2010; in press.
- Aosai F, Sayama Y, Uemura N, Kikumura A, Akira S. Innate immunity in *Toxoplasma gondii* heat shock protein 70-stimulated dendritic cell maturation and Th1 polarization. *Curr. Res. in Immunology* 2009; 3: 1-15.
- Norose K, Aosai F, Mun HS, and Yano A. Effects of sulfamethoxazole on murine ocular toxoplasmosis using interferon- γ knockout mice. *Invest Ophthalmol Vis Sci.* 2006; 47(1): 265-271.

Biochemistry & Molecular Pharmacology (F4)



◆ Overview

1. G protein-coupled receptors (GPCRs) are receptors on the cell membrane that receive various extracellular signals from hormones and neurotransmitters, as well as photo stimulation, and play roles in conversion of extracellular signals to intracellular signals. We are (1) searching for new bioactive peptides as orphan GPCR ligands, and (2) researching on roles of regulator of G-protein signaling (RGS) proteins (which are intracellular regulatory factors of GPCR signaling) in physiological and pathological conditions of the cardiovascular system.
2. The p38 mitogen-activated protein kinases (p38MAPK) are deeply involved in the production and control of inflammatory cytokines and chemokines, and are attracting attention as a drug target for inflammatory diseases. We are searching how p38 is involved in various inflammatory diseases and are conducting research to seek new treatment methods for diseases for which a complete cure has not been found.
3. We are conducting research into the involvement of N-type voltage-dependent calcium channels in nerve cell death in case of neurodegenerative disease and in the function of neural stem cells and precursor cells in case of nervous tissue regeneration.

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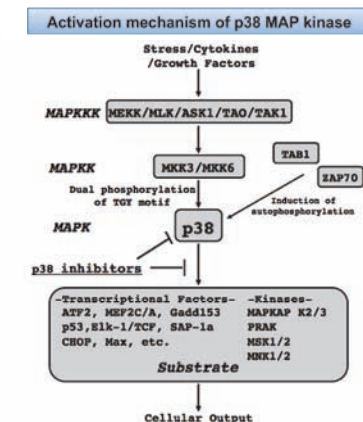
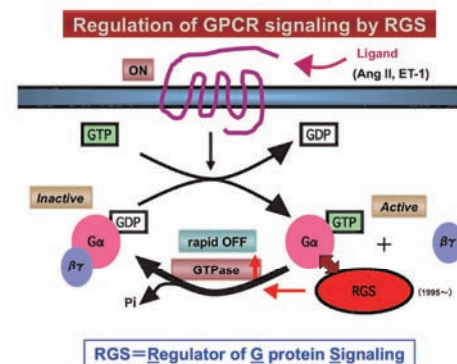
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◆ Research & Education

1. Systematic search of novel bioactive peptides for orphan G-protein coupled receptors (GPCRs)
 - bioinformatic approaches and reverse pharmacology
2. Regulation of GPCR signaling in hypertension by RGSs
 - Cellular mechanism of GPCR-selectivity by RGS
 - Regulation of RGS functions by scaffold proteins
3. Pathophysiological roles of p38 mitogen-activated protein kinase in inflammatory diseases
 - Analysis using p38 MAP kinase KO and TG mice
4. Participation of N type voltage-dependent calcium channels in neuronal apoptosis and tissue regeneration processes in CNS damage and diseases
 - Roles of voltage-dependent calcium channels in neural stem and progenitor cells
 - Analysis using N-type calcium channel-deficient mice



◆ Recent Publications

- “The utilization of gene targeting models during in preclinical study of drug discovery process? -Example of phenotypic and functional analysis of Cacna1b gene product-” Miyamoto N, Namiki K, Tokuhara N, Uesugi M, Takahashi E, Kuromitsu J, Kasuya Y. *Curr Pharmaceut Biotech*. 2009;10(2):261-267.
- “Phosphorylation of Ser166 in RGS5 by protein kinase C causes loss of RGS function.” Moroi K, Nishiyama M, Kawabata S, Ichiba H, Yajima T, Kimura S. *Life Sciences*. 2007;81(1):40-45.
- “Involvement of p38alpha mitogen-activated protein kinase in lung metastasis of tumor cells.” Matsuo Y, Amano S, Furuya M, Namiki K, Sakurai K, Nishiyama M, Sudo T, Tatsumi K, Kuriyama T, Kimura S, Kasuya Y. *J. Biol. Chem*. 2006;281(48):36767-36775.

Clinical Cell Biology and Medicine (F5)



◆ Overview

The Department of Clinical Cell Biology and Medicine, formerly called the Second Department of Internal Medicine, has a long history of major contributions in basic and clinical research, fellow-training for academic and clinical careers, as well as a commitment to providing specialized care for patients with complex endocrine and hematological diseases. The basic science and clinical studies that are carried out at Chiba University cover a broad range of areas in diabetes, metabolism, endocrinology, gerontology and hematology. Through our integrated research, education, patient and community outreach programs, we are dedicated to maintaining the highest standards of academic medicine and patient care.

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◆ Research & Education

Diabetes, Metabolism, Endocrinology and Gerontology

1. Pathogenesis and treatment of type 2 diabetes
2. New diabetic model mice: with emphasis on mutant insulin receptor knock-in mice.
3. Molecular mechanism of diabetic complications: the role of new podocyte genes in nephropathy.
4. Obesity research: molecular mechanisms involved in white and brown fat function.
5. Molecular mechanism of atherosclerosis.
6. Intracellular signaling in regulation of proliferation, differentiation, and apoptosis of endocrine cells.
7. New roles of oncogene p53 and its related genes in metabolic diseases.
8. Advanced research for osteoporosis and bone metabolism.
9. Molecular neuro-endocrinology and neuroscience.
10. Molecular mechanism of aging: Pathogenesis and treatment of progeric Werner syndrome.

Hematology

1. Mechanism of leukemogenesis by *MLL-ELL* fusion gene.
2. Mechanism of chronic myeloproliferative disorders (CMPD) development.
 - Analysis of newly-identified *TEL-Lyn* fusion gene in idiopathic myelofibrosis.
3. POEMS (Crow-Fukase) syndrome.
 - Pathogenesis of POEMS syndrome.
 - Clinical trial with autologous peripheral blood transplantation.
4. Clinical trials in hematopoietic stem cell transplantation.

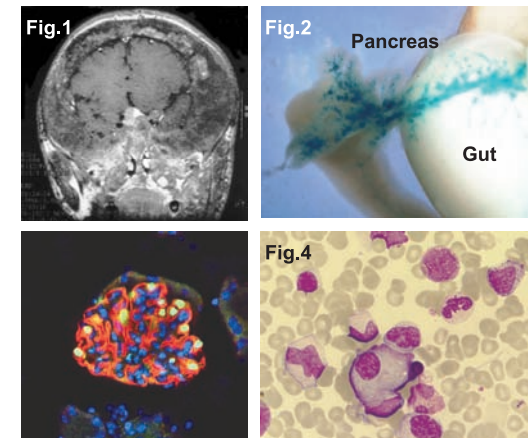


Fig.1. GH-producing pituitary adenoma in McCune-Albright syndrome.
Fig.2. Newly identified pancreatic islet gene.
Fig.3. Identification and characterization of a novel podocyte gene.
Fig.4. Bone marrow plasma cell in POEMS syndrome.

◆ Recent Publications

1. Shimoyama T et al. CCN3 Inhibits Neointimal Hyperplasia Through Modulation of Smooth Muscle Cell Growth and Migration. *Arterioscler. Thromb. Vasc. Biol.* 2010, *in press*.
2. Suzuki S et al. Phosphate-activated glutaminase (GLS2), a p53-inducible regulator of glutamine metabolism and reactive oxygen species. *Proc. Natl. Acad. Sci. USA.* 2010, *in press*.
3. Honjo S et al. Clinical outcome and mechanism of soft tissue calcification in Werner syndrome. *Rejuvenation Res.* 2008;11:809-819.
4. Abe D et al. Restrictive usage of monoclonal immunoglobulin λ light chain germline in POEMS syndrome. *Blood* 2008; 112:836-839.

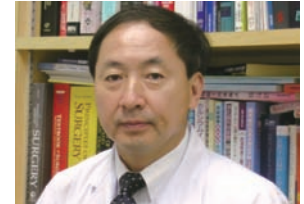
General Surgery (F6)



◆ Overview

An advance in the procedures for hepatobiliary-pancreatic surgery and breast surgery is a specific interest and goal in our department. Aggressive surgical treatment such as combination with vascular resection and reconstruction increases a chance in better prognosis. In addition, we perform living-donor liver transplantation in a patient with severely diseased liver. An induction or downstaging chemotherapy is undertaken for patients with breast cancer or metastatic colorectal liver metastases. We also are interested in a basic research to improve a better prognosis.

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◆ Research & Education

1, Hepatobiliarypancreatic Surgery

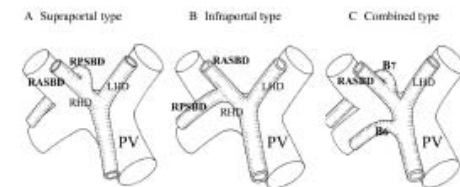
Medical & surgical treatment of hepatobiliarypancreatic malignancy
 Mechanism of hepatic metastases and local invasion of gastroenterological carcinoma
 Surgical treatment for duodenum tumors
 Surgical stress after hepatobiliarypancreatic surgery
 Nutritional changes after hepatobiliarypancreatic surgery
 Surgical treatment for portal hypertension

2, Organ transplantation

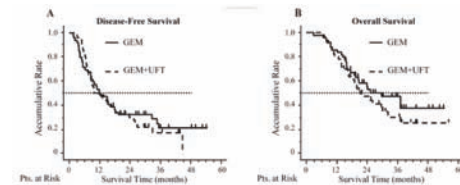
living donor liver transplantation
 xenograft organ transplantation
 cellular and organ regeneration after transplantation

3, Breast and thyroid surgery

Diagnostic strategy for breast and thyroid tumors
 Surgical strategy for breast and thyroid tumors



Confluence patterns of the right posterior sectional bile duct



Randomized control trial of adjuvant chemotherapy for patients with resected pancreatic cancer

◆ Recent Publications

- Clinical significance of biliary vascular anatomy of the right liver for hilar cholangiocarcinoma applied to left hemihepatectomy. Shimizu H, Sawada S, Kimura F, Yoshidome H, Ohtsuka M, Kato A, Miyazaki M. *Ann Surg* 2009; 249(3):435-9
- A randomized phase II trial of adjuvant chemotherapy with uracil/tegafur and gemcitabine versus gemcitabine alone in patients with resected pancreatic cancer. Yoshitomi H, Togawa A, Kimura F, Ito H, Shimizu H, Yoshidome H, Otsuka M, Kato A, Nozawa S, Furukawa K, Miyazaki M. *Cancer* 2008;113(9):2448-56
- Combined vascular resection in operative resection for hilar cholangiocarcinoma: dose it work or not? Miyazaki M, Kato A, Ito H, Kimura F, Shimizu H, Ohtsuka M, Yoshidome H, Yoshitomi H, Furukawa K, Nozawa S. *Surgery* 2007;141(5):581-8
- Clinical significance of axillary microresiduals after neoadjuvant chemotherapy in breast cancer patients with cytologically proven metastases. Sakakibara M, Nagashima T, Kadowaki M, Onai Y, Fujimori T, Yokomizo J, Suzuki H, Fushimi K, Nakatani Y, Miyazaki M. *Ann Surg Oncol* 2009;16(9):2470-8

Dermatology (F7)



◆ Overview

The mission of the department of dermatology in Chiba university is to provide a better environment and methods to achieve the following three objectives:

1. To provide the most appropriate medical treatment for patients who visit our department
2. To cultivate dermatologists with high ethical standards and a sense of responsibility who are also able to communicate well, and always aim to improve diagnostic and treatment techniques.
3. To deepen a scientific comprehension of normal and abnormal skin and to use of it for better treatment.

Professor:
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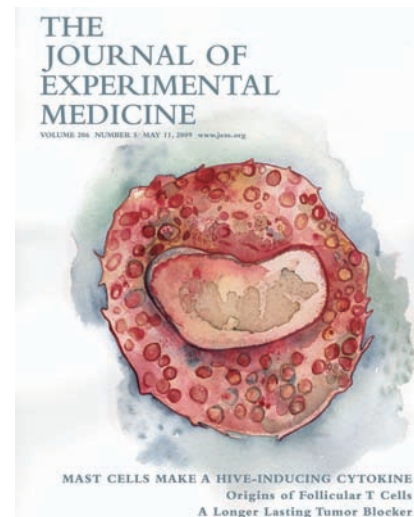
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◆ Research & Education

Our research interests are to understand pathophysiological roles played by dendritic cells and/or mast cells in (skin) diseases and to develop new therapeutic interventions by manipulating dendritic cell and/or mast cell functions.

1. Development of dendritic cell (DC)-based immunoregulation
2. DC-based cancer immunotherapy
3. Development of new screening systems to discover new immunosuppressants
4. Development of new topical anti-inflammatory drugs
5. Roles of mast cells in autoinflammatory diseases
6. Roles of mast cells in innate immunity
7. Roles of mast cells in acquired immunity



ON THE COVER

Watercolor by New York artist Emilie Clark. Mast cells secrete the rash-inducing cytokine IL-18 in patients with CAPS. Related article by Nakamura and Kambe et al.

◆ Recent Publications

- “Mast cells mediate neutrophil recruitment and vascular leakage through the NLRP3 inflammasome in histamine-independent urticaria.” Nakamura Y, Kambe N, Saito M, Nishikomori R, Kim YG, Murakami M, Nunez G, Matsue H. *J Exp Med*. 2009; 206:1037-46.
- “Murine fetal skin-derived cultured mast cells: A useful tool for discovering functions of skin mast cells.” Matsue H, Kambe N, Shimada S. *J Invest Dermatol*. 2009; 129:1120-5.
- “Osteopontin is produced by mast cells and affects IgE-mediated degranulation and migration of mast cells.” Nagasaka A, Matsue H, Matsushima H, Aoki R, Nakamura Y, Kambe N, Kon S, Uede T, Shimada S. *Eur J Immunol*. 2008; 38: 489-99.

Molecular Diagnosis (F8)

◆ Overview

21st century is the so-called post-genomic era and a variety of *post-genomic technologies* have been applied to clinical medicine. **Proteomic and genomic approach** to clinical medicine have been rapidly progressing; so our field of **Molecular Diagnosis & Division of Clinical Genetics and Proteomics** is pretty attractive and is necessary for present and future medicine. The information of pharmacogenomics, biomarkers for cancer detection and monitoring, indicators of the difference among individual genetic background, pre-onset or pre-neonatal diagnosis, all these are essential for medical doctors. Again, technologies, background of molecular biology that closely related to genetic and proteomic analysis is eagerly required for medical students. *Minimum essential training and lectures* to accomplish these purposes are prepared in our course.

Professor:
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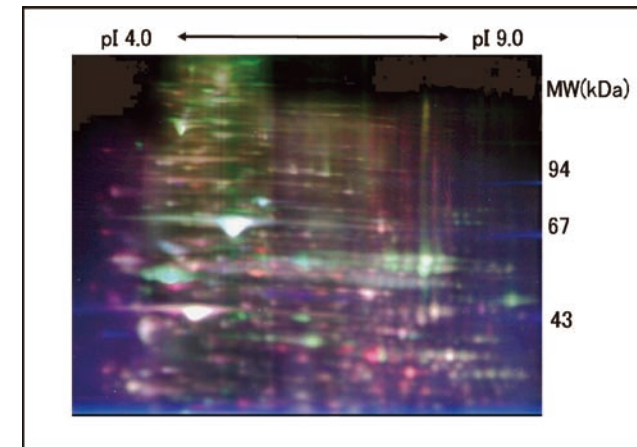


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◆ Research & Education

1. Application of gel-based- and gel-free proteomic technologies to discover and identify novel biomarkers for a variety of human disorders
2. Genetic testing and genetic counseling: establishment of individualized medicine based on genomics, transcriptomics and proteomics
 - Genetic risk assessment for cancers and other common polygenic diseases
 - Predictive testing for late onset hereditary diseases
3. Pathogenesis of alcoholic liver diseases and drug-induced liver diseases
4. Clinical perspectives of *c-myc* gene regulation and splicing regulation
5. Pathophysiology and non-invasive diagnosis of NASH (non-alcoholic steatohepatitis)
6. Cost effectiveness of medical tests and decision analysis

Two-dimensional DIGE analysis detecting protein/peptide biomarkers of a variety of human disorders



◆ Recent Publications

1. Umemura H, Nezu M, Kodera Y, Satoh M, Kimura A, Tomonaga T, Nomura F. Effects of the time intervals between venipuncture and serum preparation for serum peptidome analysis by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. *Clin Chim Acta*. 2009 Aug;406(1-2):179-80
2. Matsushita K, Tomonaga T, Kajiwara T, Shimada H, Itoga S, Hiwasa T, Kubo S, Ochiai T, Matsubara H, Nomura F. *c-myc* suppressor FBP-interacting repressor for cancer diagnosis and therapy. *Front Biosci*. 2009 Jan 1;14:3401-8.
3. Seimiya M, Tomonaga T, Matsushita K, Sunaga M, Oh-Ishi M, Kodera Y, Maeda T, Takano S, Togawa A, Yoshitomi H, Otsuka M, Yamamoto M, Nakano M, Miyazaki M, Nomura F. Identification of novel immunohistochemical tumor markers for primary hepatocellular carcinoma: clathrin heavy chain and formiminotransferase cyclodeaminase. *Hepatology*. 2008 Aug;48(2):519-30.

Anatomy and Developmental Biology (G1)



◆ Overview

Our major interests are 1) male germ cell differentiation, 2) fertilization, 3) early embryonal development, 4) oocyte differentiation leading to fertilization, 5) factors leading to infertility, 6) imaging of these reproductive events and production of human germ cells from ES and iPS cells. Our final goal is to understand the biology of reproductive events on male and female organs, tissues and cells focusing on the topics described in the Research section.

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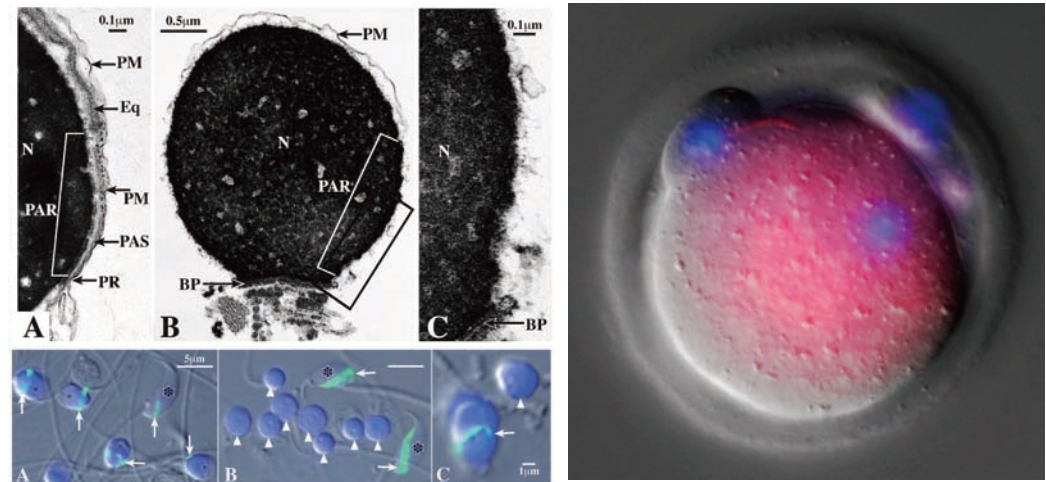
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◆ Research & Education

1. Molecular mechanisms of reproductive germ cell differentiation.
2. Gene and protein expressions in testis.
3. Communication between developing germ cells and Sertoli cells.
4. Oocyte development leading to fertilization.
5. Sperm-egg interaction.
6. Failure leading to infertility.
7. Imaging of germ cell differentiation, fertilization and infertility.
8. Testis-brain genes.
9. Production of human germ cells from ES and iPS cells.



◆ Recent Publications

- 1) Toshimori K. Dynamics of the mammalian sperm head: modifications and maturation events from spermatogenesis to egg activation. *Anatomy, Embryology, Development and Cell Biology* 204:1-94.2009. Review.
- 2) Ito C, Akutsu H, Yao R, Kyono K, Suzuki-Toyota F, Toyama Y, Maekawa M, Noda T, Toshimori K. Oocyte activation ability correlates with head flatness and presence of perinuclear theca substance in human and mouse sperm. *Hum Reprod.* 24(10):2588-2595.2009.
- 3) Yamatoya K, Yoshida K, Ito C, Maekawa M, Yanagida M, Takamori K, Ogawa H, Araki Y, Miyado K, Toyama Y, Toshimori K. Equatorin: identification and characterization of the epitope of the MN9 antibody in the mouse. *Biol Reprod.* 81(5): 889-897. 2009.

Developmental Biology (G2)

◆ Overview

The nervous system is central to what makes human beings what they are. However, there are still many mysteries concerning its function. By studying developmental mechanisms of the nervous system, we are aiming to clarify the high-order function of the nervous system in view of its design, as well as to construct the basis for regenerative medicine making use of the developmental mechanisms. We are constantly working on new research projects using the latest techniques in molecular and developmental biology.



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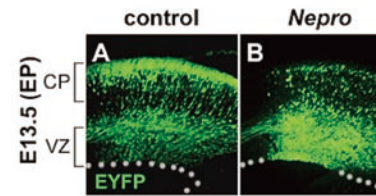
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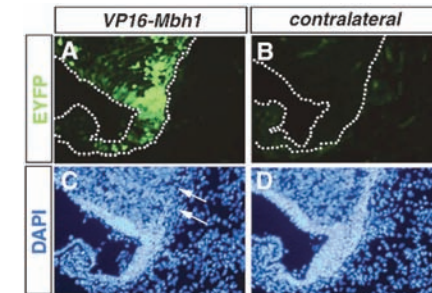


◆ Research & Education

1. Molecular mechanisms of neural development
2. Biology of neural stem cells
3. Determination of neuronal identity
4. Formation and function of neural networks



Nepro maintains early neural stem cells in the neocortex.



The *Mbh* genes are necessary for the differentiation and migration of cerebellar granule cells.

◆ Recent Publications

1. Muroyama Y, Saito T (2009) Identification of *Nepro*, a gene required for the maintenance of neocortex neural progenitor cells downstream of Notch. **Development** **136**, 3889-3893.
2. Kawauchi D, Saito T (2008) Transcriptional cascade from *Math1* to *Mbh1* and *Mbh2* is required for cerebellar granule cell differentiation. (2008) **Dev. Biol.** **322**, 345-354.
3. Saito T (2006) *In vivo* electroporation in the embryonic mouse central nervous system. **Nature Protocols** **1**, 1552-1558.

Comparative Pathology (G3)



◆Overview

We are in charge of research support activities involving animal experiments in different departments at Chiba University Inohana campus. We are also involved in management activities concerning animal experiments at Chiba university. We are aggressively incorporating information and communication technology (ICT) to streamline support activities.

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◆Research & Education

1. Management of Laboratory Animal Center, Chiba University

- Regulation of animal experiments in the center
- Control of infection of laboratory animals in the center
- Development and improvement of management system in the center

2. Application of Information and Communication Technology (ICT) for the management system in the center

3. Education of bases of ICT

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(Photo: Laboratory Animal Center, Graduate School of Medicine, Chiba University)



◆Recent Publications

Effects of adenoviral vector-mediated BDNF expression on the bullectomy-induced apoptosis of olfactory receptor neurons. *Molecular Brain Reserch.* 2004; 129: 88-95

Prevalence of *Toxoplasma Gondii* and other intestinal parasites in cats in Chiba prefecture, Japan. *Jpn J Trop Med Hyg.* 2000; 28: 365-368....



Reproductive Medicine (G4)

◆ Overview

Our research activity is multidisciplinary and innovative with aims of improving women's health. Current projects include: basic and clinical study on hormonal therapy of the endometrial cancer, surgical and medical management of advanced ovarian cancer, establishment of a novel animal model and the discovery of new therapeutic strategy for uterine leiomyoma, pathogenesis and clinical management of trophoblastic diseases, predictors of placenta accreta, molecular diagnosis of hereditary endocrine diseases.

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◆ Research & Education

1. Biomarkers for decision making of intermittent debulking surgery,
2. Detection of residual tumors on the second laparotomy after neoajuvant chemotherapy for advanced ovarian cancer
3. Establishment of a novel explant model of uterine leiomyoma and its application for discovery of new therapeutic agents
4. Metabolome analysis of uterine leiomyoma
5. Cytogenesis and molecular immunohistochemical diagnosis of hydatidiform mole
6. Epigenetic control of trophoblastic invasion to myometrium
7. Cohort study of trophoblastic disease in Chiba prefecture.
8. Cryopreservation of human ovarian tissues
9. Discovery of the serologic marker of the placenta accreta
10. Genetic diagnosis of endocrine diseases

◆ Recent Publications

- The risk of post-molar gestational trophoblastic neoplasia is higher in heterozygous than in homozygous complete hydatidiform moles. Baasanjav B, Usui H, Kihara M, Kaku H, Nakada E, Tate S, Mitsuhashi A, Matsui H, Shozu M. Hum Reprod. 2010
- High aromatase expression in uterine leiomyoma tissues of African-American women. Ishikawa H, Reierstad S, Demura M, Rademaker AW, Kasai T, Inoue M, Usui H, Shozu M, Bulun SE. J Clin Endocrinol Metab. 2009, 94:1752-6.
- Serum YKL-40 as a marker for cervical adenocarcinoma. Mitsuhashi A, Matsui H, Usui H, Nagai Y, Tate S, Unno Y, Hirashiki K, Seki K, Shozu M. Ann Oncol. 2009 20:71-7.

Molecular Genetics (H1)



◆ Overview

Pathological conditions of refractory autoimmune disease are being clarified on a molecular level due to the recent progress in molecular biology. However, many patients with allergies or autoimmune diseases are still forced to undergo treatment with steroids or immunosuppressants, which may be accompanied by significant adverse drug reactions.

We consider that medical research will go in the right direction if basic research and clinical medicine are both implemented, and bidirectional interactions from basic research to clinical medicine, and vice versa, are maintained. In our department, we intend to develop a new treatment method for refractory autoimmune disease and allergic disease by optimizing the network between basic research and clinical medicine.

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◆ Research & Education

1. Mechanism underlying allergic inflammation in asthma
 - a) Role of IL-23-Th17 cell axis in allergic inflammation
 - b) Role of dectin-1 signaling in allergic inflammation
 - c) Role of NF- κ B signaling in mast cells
2. Molecular mechanism of helper T cell differentiation
 - a) Role of BTLA in follicular helper T cell function
 - b) Role of cMaf in IL-21 production in T cells
 - c) Role of IL-22 production from LT α cells
3. Development of new drugs against immune diseases
 - a) Effect of co-signal modulators in autoimmune diseases
 - b) Role of geranylgeranylation in the development of autoimmune diseases
4. Mechanism underlying autoimmune diseases
 - a) Microarray analysis of PBMC in RA patients
 - b) Role of Th2 cells in IgG4-related diseases
 - c) Use of doppler ultrasonography of joints for the evaluation of RA therapy

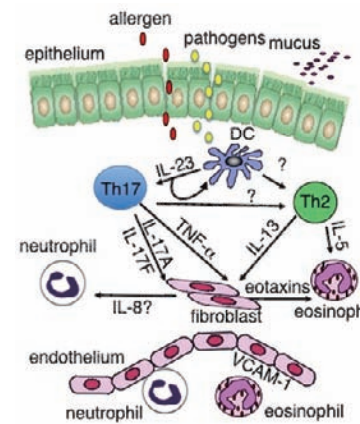


Fig. 1. Role of IL-23-Th17 cell axis in allergic inflammation

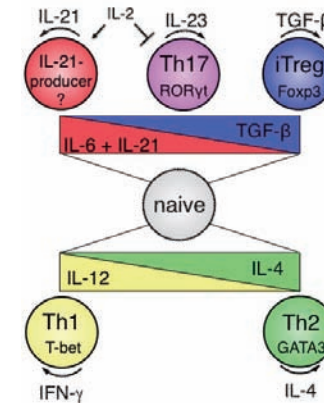


Fig. 2. Differentiation of IL-21-producing T cells

◆ Recent Publications

1. Tokumasa N, Suto A, Kagami S-i, Furuta S, Hirose K, Watanabe N, Saito Y, Shimoda K, Iwamoto I, Nakajima H. Expression of Tyk2 in dendritic cells is required for IL-12, IL-23, and IFN- γ production and the induction of Th1 cell differentiation. *Blood*. 110: 553-560, 2007.
2. Suto A, Kashiwakuma D, Kagami S-I, Hirose K, Watanabe N, Yokote K, Saito Y, Nakayama T, Grusby MJ, Iwamoto I, Nakajima H. Development and characterization of IL-21-producing CD4⁺ T cells. *J. Exp. Med.* 205:1369-1379, 2008.
3. Wakashin H, Hirose K, Maezawa Y, Kagami S-I, Suto A, Watanabe N, Saito Y, Hatano M, Tokuhisa T, Iwakura Y, Puccetti P, Iwamoto I, Nakajima H. IL-23 and Th17 cells enhance Th2 cell-mediated eosinophilic airway inflammation in mice. *Am. J. Respir. Crit. Care Med.* 178:1023-1032, 2008.

Developmental Genetics (H2)

◆ Overview

In the department of developmental genetics, we are conducting medical research by applying techniques of embryo engineering. Our research covers “the formation and maintenance of immunological memory,” “the in vivo mechanism of cell canceration,” and “the production of animal models of human diseases and their application to treatments,” to which techniques of embryo engineering are applied. Through these research processes, we hope that our students will not only study the merits and demerits of new biology-related technology, but also grow rich in humanity as future members of society. In the department of developmental genetics, the presentation of research papers and discussion are conducted in English so that students can learn the importance of preparing and presenting papers in English. We consider that English ability is essential for globally-competent researchers and full-fledged members of society. We also recommend that our graduate students study abroad after finishing their postgraduate studies.



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◆ Research & Education

1. Differentiation and maintenance of Immune memory cells

- High affinity memory B cells
- Germinal center formation (Bcl6, IL-21)
- Memory T cells (Th2, Th17, Tfh, CD8T cells)

2. Development of a new therapy for Allergic diseases

- Asthma models
- IgE production

3. In vivo Oncogenesis using Transgenic mouse technology

- Bcl6
- ADAR1

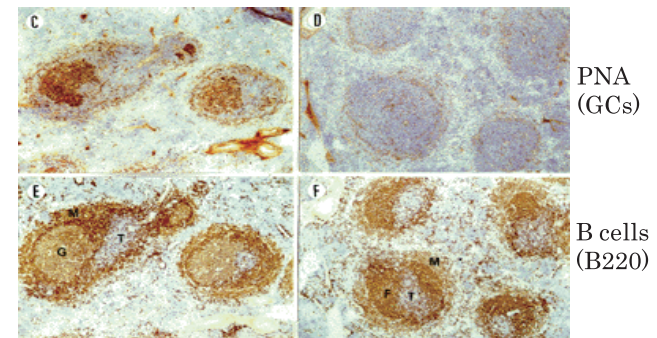
4. Animal models for human diseases using Knockout (gene targeting) mouse technology

- Immune deficiency

No Germinal Center in Bcl6-KO mice

Wild Type

Bcl6-KO



PNA
(GCs)

B cells
(B220)

◆ Recent Publications

1. Kitayama, D., Sakamoto, A., Arima, M., Hatano, M., Miyazaki, M., and Tokuhisa, T. A role for Bcl6 in sequential class switch recombination to IgE in B cells stimulated with IL-4 and IL-21. *Mol. Immunol.*, 45:1337-1345, 2008.
2. Ichii, H., Sakamoto, A., Arima, M., Hatano, H., Kuroda, Y., and Tokuhisa, T. Bcl6 is essential for the generation of long-term memory CD4+ T cells. *Int. Immunol.*, 19:427-433, 2007.
3. Yoshida, K., Sakamoto, A., Yamashita, K., Arguni, E., Horigome, S., Arima, M., Hatano, M., Seki, N., Ichikawa, T., and Tokuhisa, T. Bcl6 controls Granzyme B expression in effector CD8 T cells. *Eur. J. Immunol.*, 36:3146-3156, 2006.

Immunology (H3)

◆ Overview

The basic research focus in this department is Immunology, particularly the Immunological Memory. Translational research on allergic disorders and cancer has been promoted in collaboration with clinical doctors as well as researchers in RIKEN. The educational goal of the graduate school is to “cultivate professional researchers.” We hope to create an even more international global research environment over the next 5 years, and wish to discover the principles associated with the control of immunological memory as well as to present and verify treatment concepts in translational research, thus leading to significant developments in immunological research. Professor Nakayama, as a program leader of the Chiba University global center of excellence (G-COE) program entitled with “Global Center for education and research in Immune System Regulation and Treatment”, has been attempting to cultivate human resources aiming to stimulate and globalize graduate students since 2008.

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◆ Research & Education

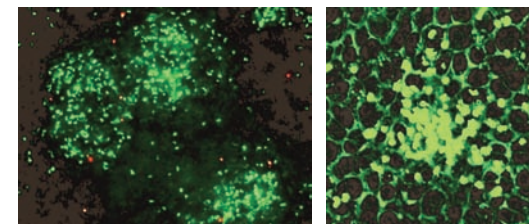
1. Generation and Maintenance of Immune system

- 1) Generation and maintenance of memory Th1/Th2 cells
- 2) Immune responses and inflammation regulated by CD69
- 3) GATA3, its regulation and effector function

2. Regulation of Allergic Airway Inflammation (Asthma)

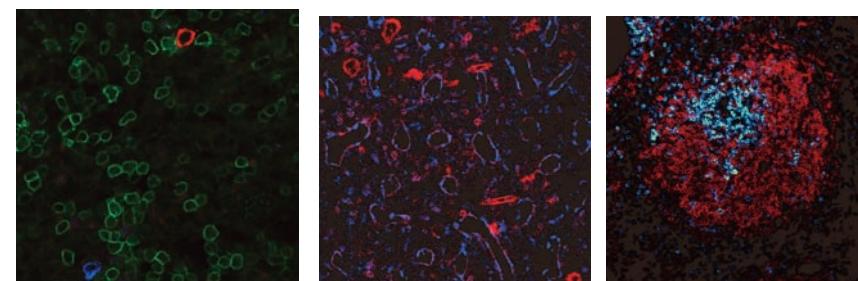
- 1) Regulation of Th2-driven airway inflammation: Molecular studies in mouse models
- 2) In vivo imaging of allergic asthma

Th2 Focus



Hasegawa et al. JACI. 2009

Localization of lymphocyte



Spleen Memory CD4 T cell Plasmablasts Bone Sinus Blood vessel Spleen CD4 T cell B cell follicle

◆ Recent Publications

- 1) Tokoyoda, K., Hauser A. E., Nakayama, T., and Radbruch, A.: Organization of immunological memory by bone marrow stroma. *Nat. Rev. Immunol.* 10:193-200 (2010).
- 2) Hasegawa, A., et al.: Color-coded real-time cellular imaging of T lymphocyte accumulation and focus formation in mouse asthma model. *J. Allergy Clin. Immunol.* 125(2):461-468.e6, 2010.
- 3) Hosokawa, M. T., et al.: CD69 controls the pathogenesis of allergic airway inflammation. *J. Immunol.* 183:8203-8215 (2009).
- 4) Tokoyoda, K., et al.: Professional memory CD4⁺ T lymphocytes preferentially reside and rest in the bonemarrow. *Immunity* 30:721-730 (2009).
- 5) Nakayama, T., and Yamashita, M.: Initiation and maintenance of Th2 cell identity. Truncated title: Regulation of Th2 responses. *Curr. Opin. Immunol.* 20:265-271 (2008).
- 6) Yamashita, M., et al.: Bmi1 regulates memory CD4 T cell survival via repression of the *Noxa* gene. *J. Exp. Med.* 205:1109-1120 (2008).

Pediatrics (H4)



◆ Overview

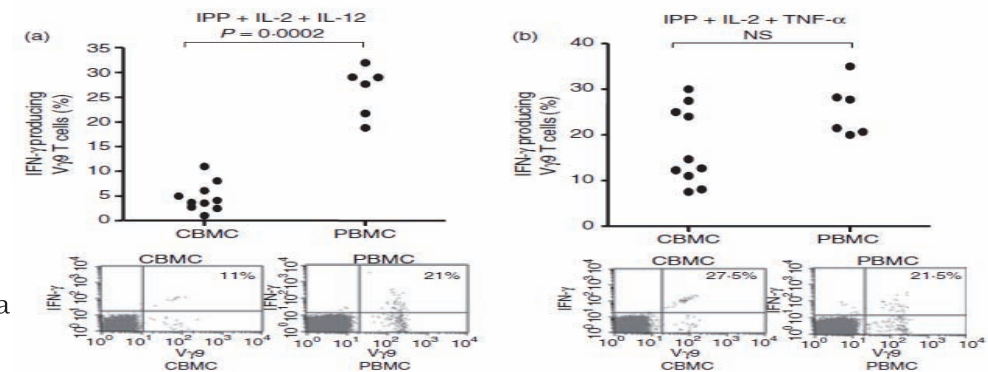
In the Department of Pediatrics, we are mainly conducting research into immunological/allergic diseases, with a central focus on clarifying the pathogenic mechanisms of allergy and therapeutic intervention in it. We are analysing genetic expression, cytokines, and proteomics. In recent years, we have been trying early interventional treatment of allergic diseases through cord blood analysis. Besides these immunological/allergic diseases, we are also conducting research activities under the themes of bacteriological examination and epidemiological investigation of Haemophilus influenzae and pneumococcal infection, hepatocyte transplantation for congenital hepatic diseases, molecular biological analysis of mitochondrial respiratory chain deficiency, and analysis of abnormal hedgehog signaling pathway.

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◆ Research & Education

- Mechanism and risk factors for development of allergy
 - cytokines (in blood, breast-milk, etc.), function of lymphocytes
 - signal transduction and regulation of gene expression.
 - birth cohort studies, viruses and environmental factors
- Prevention and early intervention for allergic diseases
pre, pro-biotics, clinical trials of drugs, immunotherapy
- Etiology and pathophysiology of autoimmune diseases
juvenile onset Sjögren's syndrome, Graves' disease (using novel mice model)
- Epidemiological study of pneumonia and meningitis in children.
- Bacteriological study of Haemophilus influenzae and Streptococcus pneumoniae
- Hepatocyte transplantation to the patients with metabolic liver disease
- Biological and molecular study of mitochondrial respiratory chain defect
- Hedgehog signaling and human disorders



◆ Recent Publications

- Campos E, et al. Differential effects of TNF-alpha and IL-12 on IPP-stimulated IFN-gamma production by cord blood Vgamma9 T cells. *Immunology* 127:171-177, 2009
- Fujii K, et al. Homozygous Female Becker muscular dystrophy. *Am J Med Genet* 149A:1052-1055; 2009
- Fukasawa C, et al. The effects of disodium cromoglycate on enhanced adherence of Haemophilus influenzae to A549 cells infected with respiratory syncytial virus. *Pediatric Research* 66: 168-173, 2009
- Suzuki Y, et al. CD14 and IL4R gene polymorphisms modify influence of day care attendance on total and specific serum IgE levels in school children. *J Allergy Clin Immunol* 123:1408-11, 2009

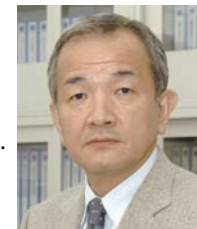
Orthopaedic Surgery (J1)



◆ Overview

We are conducting research into regenerative medicine concerning the articular cartilage and spinal cord using stem cells and cytokines, molecular biological research into the developmental mechanism of low back pain and its desensitization, and the development and research of knee joint prostheses with good durability. Both our basic and clinical research into enthesopathy using shock waves is globally accepted. We have started a voluntary clinical trial of the administration of granulocyte-colony stimulating factor (G-CSF) to spinal cord injury patients, based on the basic data indicating that G-CSF is effective for spinal cord injuries (in the rat).

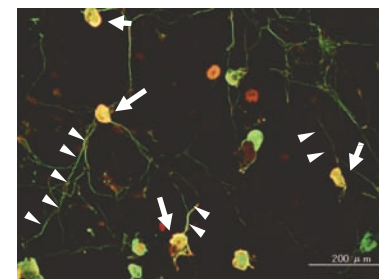
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◆ Research & Education

1. Pathomechanism of low back pain
2. Treatment of spinal cord injury
3. Molecular mechanisms of shock wave therapy
4. Cartilage regeneration
5. Pathogenesis of cervical spondylotic myelopathy
6. Pathogenesis of osteoarthritis of the knee joint
7. Pathogenesis of osteoarthritis of the hip joint
8. Sports medicine
9. MRI imaging of the bone and joint
10. Pathogenesis and treatment of trauma and injury of the bone and joint
11. Orthopedic biomechanics
12. Pathogenesis of disorders of the upper extremity and the hand



Nerve in-growth into degenerated lumbar vertebral disc is key mechanisms of discogenic low back pain.

Neural cells containing calcitonin-gene related peptide (yellow, indicated by arrows) extended neural filaments upon co-culture of lumbar vertebral disc from a chronic low back pain patient. Arrow heads indicate newly formed extended filaments.

◆ Recent Publications

Low affinity receptor (p75 neurotrophin receptor) inhibitory antibody reduces pain behavior and CGRP expression in DRG in the mouse sciatic nerve crush model. Fukui Y, Ohtori S, Yamashita M, Yamauchi K, Inoue G, Suzuki M, Orita S, Eguchi Y, Ochiai N, Kishida S, Takaso M, Wakai K, Hayashi Y, Aoki Y, Takahashi K. J Orthop Res. 2009

Deletion of macrophage migration inhibitory factor attenuates neuronal death and promotes functional recovery after compression-induced spinal cord injury in mice. Nishio Y, Koda M, Hashimoto M, Kamada T, Koshizuka S, Yoshinaga K, Onodera S, Nishihira J, Okawa A, Yamazaki M. Acta Neuropathol. 2009 Mar;117(3):321-8.

Detection of pain-related molecules in the subchondral bone of osteoarthritic knees. Ogino S, Sasho T, Nakagawa K, Suzuki M, Yamaguchi S, Higashi M, Takahashi K, Moriya H. Clin Rheumatol. 2009.

Oto-rhino-laryngology and Head & Neck Surgery (J2)



◆Overview

We are all working on head and neck oncology, which is one of the main research fields in our department. We are aggressively performing reconstructive surgery aiming to preserve and recover the morphology and function of the resected regions by covering the lost region, as well as simple tumor excision. At the same time, we are making new diagnoses and developing treatments aimed at improving the treatment outcomes and patients' quality of life (QOL), and are promoting clinical research into cellular immune treatment using the natural killer (NK) T-cell immune system. We are also devoting our efforts to allergy-associated research. We have made many achievements in basic and clinical research concerning the pathological condition of allergic rhinitis, and our department is central to research and treatment of allergic rhinitis in Japan.

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◆Research & Education

1. Study of pathology and treatment of allergic rhinitis.
2. Clinical and basic investigation of head and neck cancer.
3. Morphological and physiologic study of speech organ.
4. Genetic approach to the various diseases of Otorhinolaryngology.
5. Study of microcirculation in head and neck tissues.
6. Pathophysiological study of nasal mucosa.
7. Physiological study of olfaction and gestation.
8. Study of functional reconstruction of head and neck cancer.
9. Diagnosis and treatment of diseases of salivary glands.


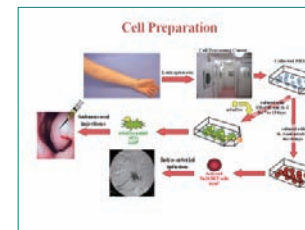
Advantages of SLIT against traditional SCIT

traditional SCIT (subcutaneous immunotherapy)	alternative SLIT (sublingual immunotherapy)
	
...severe adverse reaction (anaphylactic shock)	...mild adverse reaction, if occur (oral itching)
...with pain	...without pain
...need to attend a hospital	...no need to attend a hospital (self-administered at home)

SLIT is more safe and beneficial method for patients than SCIT!

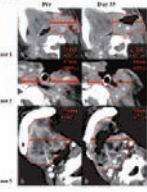
Pollen Exposure Unit at Chiba University (u-Chamber)

The largest capacity in Japan

Clinical Response

Class	Classical Control	Humanized Anti-CD3
Class 1	100%	100%
Class 2	100%	100%
Class 3	100%	100%
Class 4	100%	100%
Class 5	100%	100%
Class 6	100%	100%
Class 7	100%	100%
Class 8	100%	100%



◆Recent Publications

- Uchida T, Horiguchi S, Tanaka Y, Yamamoto H, Kunii N, Motohashi S, Taniguchi M, Nakayama T, Okamoto Y, Phase 1 study of α -galactosylceramide-pulsed antigen presenting cells administration to the nasal submucosa in unresectable or recurrent head and neck cancer. *Cancer Immunology and Immunotherapy* .2008;57:337-345.
- Horiguchi S, Okamoto Y, Yonekura S, Okawa T, Yamamoto H, Kunii N, Sakurai D, Fujimura T, Nakazawa K, Yasueda H. A randomized controlled trial of sublingual immunotherapy for Japanese cedar pollinosis. *International Archives of Allergy and Immunology*.2008;146:76-84.
- Shimizu S, Tsukada J, Sugimoto T, Kikkawa N, Sasaki K, Chazono H, Hanazawa T, Okamoto Y, Seki N. Identification of a novel therapeutic target for head and neck squamous cell carcinomas: A role for the neurotensin-neurotensin receptor 1 oncogenic signaling pathway. *International Journal of Cancer* .2008;123:1816-1823.

Emergency and Critical Care Medicine (J3)



◆ Overview

The research theme of our department is mainly the clarification of the pathophysiology of multiple organ failure and its treatment. Based on the idea that multiple organ failure is the summation of dysfunction of cells that comprise vital organs or systems, we want to take countermeasures against hypercytokinemia resulting from immuno-inflammatory response, which is the background condition to cellular dysfunction. In the clinical research field, we have made great achievements in acute blood purification, which is intended for cytokine modulation in critically ill patients, and have made a substantial global impact. Our analysis has revealed that the pathological condition of critically ill patients is associated with genetic factors, and we wish to achieve tailor-made therapy taking these factors into consideration. Meanwhile, in the basic research field, we are mainly working on the control of inflammatory response using mouse models of sepsis or cultured vascular endothelial cells. We are always striving to conduct research taking into consideration a bench-to-bedside clinical application such as the analysis of heart rate variability (HRV), which can monitor the collapse of *in vivo* homeostasis.

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◆ Research & Education

Clinical and basic aspects on the pathophysiology of multiple organ dysfunction syndrome (MODS)

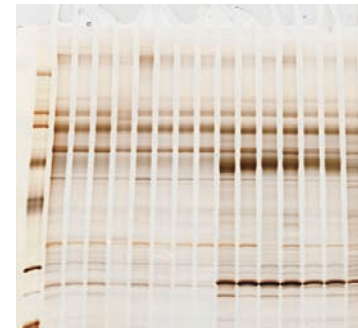
1. Regulation of systemic inflammation, i.e., SIRS, in the clinical and laboratory based studies

- Severity scores and evaluations for patients in intensive care units (ICUs)
- Routine serum cytokine measurements for monitoring of systemic inflammation of ICU patients
- Usefulness of acute blood purification as a countermeasure against hypercytokinemia
- The inflammatory reflex – A sepsis therapy via cholinergic antiinflammatory pathway
- Mechanism of homeostasis maintenance of autonomic nervous system with heart rate variability
- Mechanism of immunoparalysis in critically ill patients
- A basic study using a neutrophil elastase inhibitor against acute respiratory distress syndrome
- Percutaneous cardiopulmonary support (PCPS) in the treatment of critically ill
- Liver regeneration, regeneration of neurons after trauma

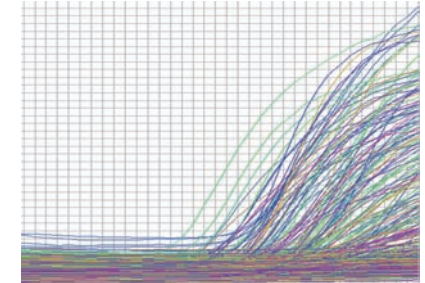
2. Genomics and proteomics in the critically ill

- Heritable factors of the critically ill – Genetic variations in the critically ill patients.
- mRNA expression monitoring in septic patients and microRNA analyses in septic animals
- Proteomics analyses in septic patients

3. Molecular biology and electro-physiologic approach to post-resuscitation brain injury



The SDS-PAGE image indicates protein bands in the sepsis (right) and the control (left) patient group.



Real-time PCR results on mRNA expressions in the mouse CLP model vs sham operation group using 384 sepsis-related gene probes.

◆ Recent Publications

“YKL-40 identified by proteomic analysis as a biomarker of sepsis.” Hattori N, Oda S, Sadahiro T, Nakamura M, Abe R, Shinozaki K, Nomura F, Tomonaga T, Matsushita K, Kodera Y, Sogawa K, Satoh M, Hirasawa H. *Shock*. 2009 Oct; 32(4): 393-400

“S-100B and neuron-specific enolase as predictors of neurological outcome in patients after cardiac arrest and return of spontaneous circulation: a systematic review.” Shinozaki K, Oda S, Sadahiro T, Nakamura M, Hirayama Y, Abe R, Tateishi Y, Hattori N, Shimada T, Hirasawa H. *Crit Care*. 2009; 13(4): R121

“Association between lymphotoxin-alpha (tumor necrosis factor-beta) intron polymorphism and predisposition to severe sepsis is modified by gender and age.” Watanabe E, Buchman TG, Hirasawa H, Zehnbauser BA. *Crit Care Med*. 2009 Sep 28. [Epub ahead of print]. (doi: 10.1097/CCM.0b013e3181bc805d.)

Plastic and Reconstructive Surgery (J4)



◆ Overview

We emphasize the evolutionary research into surgical treatment associated with the abnormal morphology of the craniomaxillo-facial bone, as well as embryological and genetic research and research on the growth of congenital abnormal craniofacial morphology. Research into skin flap hemodynamics based on analysis of the blood circulation to and the morphology of skin, subcutaneous tissue, fascia, muscles, and bone is also an important theme in reconstructive surgery. We also want to conduct stem cell implantation based on fat graft, and to conduct research into epidermis, dermis, and cartilage transplantation using tissue culture. We also conduct systematic research into hemangioma focusing on eyelid ptosis and vascular malformation.

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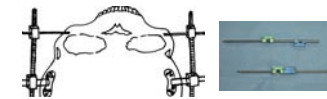


◆ Research & Education

1. Cranio-maxillofacial bone surgery
 - Reseach of distraction osteogenesis as a surgical technique and development of the optimal distraction devices
 - Embryological and genetic research of Craniofacial malformations and growth of craniofacial bone
 - Research concerning on the surgical treatment for Craniosynostosis
 - Anthropometric analysis of the human face of the Orientals
 - Morphological analysis of the nasal deformity in the cleft lip and palate
2. Microvascular circulation in the flap based on vasculature of skin to bone
 - Reonstruction of tissue defect using safe and stable modality with less morbidity
 - Functional reconstructive surgery after abrasion of the malignant tumors in various region
3. Reseach of stem cell graft and cuturesd cell graft
 - Would healing and research of the cultured epithelium.deimis, and cartilage
 - Fat graft based on multipotential fat-stem cell
4. Pathophysiology of the occurrence of hypertrophic scar and keloids after the surgical treatment
5. Pathophysiology of proptosis and its treatment strategy
6. Treatment protocol for Hemoangioma and vascular malformations by various laser irradiation



Newly fabricated internal distraction device for mandible and skull of small infants



Newly fabricated distraction device of transfacial pinning system for midface of small children

◆ Recent Publications

- Kaneshige Satoh, Takaharu Ohtsuka, Takumi Abe, Kazunori Yokota and Kenta Kunii. Haemangioma of the forehead: Radiographical diagnosis and definitive surgical treatment in a Japanese series. Scand J Plast Reconstr Surg and Hand Surg. 43: 75-81, 2009
- Satoh K, Mitsukawa N, Kadomatsu K. Marionette traction for Le Fort I maxillary Halo distraction in cleft patients. J. Plast. Reconstr. Aesth. Surg. 2008 Aug;61(8):984-6.
- Mitsukawa N, Satoh K, Hayashi T, Morishita T. Atypical Apert syndrome: sequential and segmental distraction osteogenesis of the skull, midface, and mandible. Scand J Plast Hand Surg. 43: 109-112, 2009

Medicine and Clinical Oncology (K1)



◆ Overview

Our department mainly deals with hepato-biliary-pancreatic and gastrointestinal diseases. Therapies for various diseases such as viral hepatitis, cirrhosis, hepatocellular carcinoma, esophageal varices, biliary cancers and stones, and pancreatitis and pancreatic cancers are explored and practiced based on their patho-physiology. Our group also studies on the renal diseases.

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◆ Research & Education

1. Molecular biology of hepatitis viruses and treatment of chronic hepatitis
2. Treatment of fulminant hepatitis
3. Autoimmune diseases in gastroenterology
4. Molecular biology of gastrointestinal cancers
5. Early diagnosis of hepatocellular carcinoma and their therapies
6. Chemotherapy of advanced gastroenterological cancers
7. Abdominal imaging diagnosis
8. Therapy of portal hypertension
9. Clinical researches on pancreatitis, pancreatic stones and bile duct stones
10. Pathology and therapy of renal diseases



◆ Recent Publications

- 1) Enhanced self-renewal capability in hepatic stem/progenitor cells drives cancer initiation. Chiba T, et al. *Gastroenterology*. 2007;133:937-50
- 2) Quantitative analysis of vascular endothelial growth factor in liver metastases from pancreatic carcinoma as a predictor of chemotherapeutic effect and prognosis. Tawada K, et al. *Clin Cancer Res*. 2008;14:7438-43.
- 3) Effect of signal intensity from the accumulated microbubbles in the liver for differentiation of idiopathic portal hypertension from liver cirrhosis. Maruyama H, et al. *Radiology*. 2009;252:587-94.



Psychiatry (K2)

◆ Overview

Under our philosophy “to make efforts to provide best practices to present patients now and to provide much better practice in future”, we have dedicated ourselves to clinical practices and researches for mental disorders, and provide education and training to medical students and young psychiatrists. Our features in practices are provision of world standardized practices by references of reported diagnostic and treatment guidelines and our original evidence based guidelines to outpatients and inpatients with mental disorders.

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◆ Research & Education

- We consider that researches for future are highly necessary for the purpose of providing the present forefront practices, since these researches enable us to observe the present practices in the viewpoint of the future and find their effectiveness and limitation.
- We have dedicated ourselves to mutual translational researches between basic sciences and clinical practices, especially to develop biomarkers, neuroimaging methods and novel medicines and to elucidate pathophysiology of mental disorders, in collaboration with the Centre for Forensic Mental Health and the Department of Cognitive Behavioral Physiology.
- We have also actively performed clinical trials of newly developed medicines and been developing new treatment methods by using trans-cranial magnetic stimulation. Furthermore, we have performed visiting nurses to patient homes to seek a new style of practice, i.e., a direct connection between the forefront and the community psychiatry and developed a relapse prevention programs for schizophrenia using information technology. In these circumstances, our department can provide the forefront medicine to patients with mental disorders and clinical trainings to young psychiatrists.
- We educate medical students and postgraduate students on psychiatry and provide trainings for young psychiatrists in the same levels as the world's top class countries at Chiba University Hospitals and associated hospitals.

◆ Recent Publications

- High occupancy of sigma1 receptors in the human brain after single oral administration of donepezil: a positron emission tomography study using [11C]SA4503. Ishikawa M, Sakata M, Ishii K, Kimura Y, Oda K, Toyohara J, Wu J, Ishiwata K, Iyo M, Hashimoto K. Int J Neuropsychopharmacol. 2009 Sep;12(8):1127-31.
- Does hypofrontality expand to global brain area in progression of schizophrenia?: a cross-sectional study between first-episode and chronic schizophrenia. Kanahara N, Shimizu E, Sekine Y, Uchida Y, Shibuya T, Yamanaka H, Hashimoto T, Asaka T, Sasaki T, Miyatake R, Ohkami T, Fukami G, Fujisaki M, Watanabe H, Shirayama Y, Hayashi H, Hashimoto K, Asano M, Iyo M. Prog Neuropsychopharmacol Biol Psychiatry. 2009 Apr 30;33(3):410-5.

Radiology (L1)



◆ Overview

Radiology consists of three sections, diagnostic imaging/interventional radiology, radiation oncology, and nuclear medicine imaging, which includes positron emission tomography (PET). In this field, there are steady advances in the instruments available for diagnosis and treatment due to the recent remarkable progress in computers and imaging analysis as well as technical inventions in science and engineering. This has resulted in a huge contribution to the progress of clinical medicine, and is constantly increasing in importance. To achieve more progress and advancement in this field, it is necessary to introduce new concepts that can exceed preexisting notions. Therefore we wish to harness the power of young students who are not caught up in the past. In other words, this is a field that is very open to the power and innovation of young students, allowing them to fully show their abilities.

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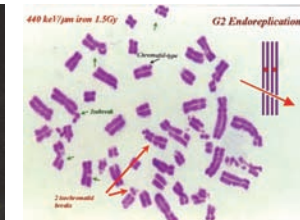
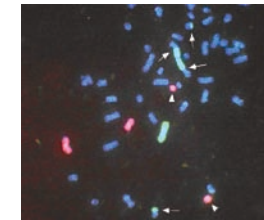
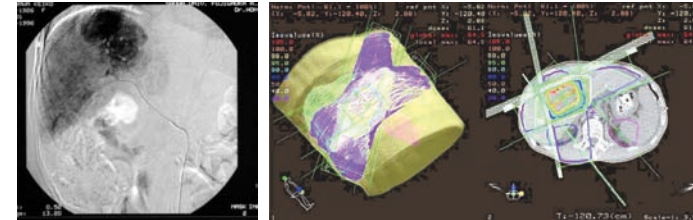
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◆ Research & Education

1. Diagnostic imaging
Clinical CT & MRI diagnosis
Angiography
2. Interventional radiology
3. Radiation oncology
Clinical radiotherapy (including brachytherapy)
Radiation biology
4. Nuclear Medicine (including PET)...



◆ Recent Publications

- Watanabe M, Isobe K, Ito H, et al. Intrafractional gastric motion and interfractional stomach deformity during radiotherapy. *Radiother Oncol* 2008, 87:425-431.
- Teshima T, Numasaki H, Ito H, et al. Japanese structure survey of radiation oncology in 2005 based on institutional stratification of patients of care study. *Int J Radiat Oncol Biol Phys* 2008, 72(1): 144-152.
- Ogawa K, Yoshii Y, Ito H, et al. Spinal recurrence from intracranial germinoma : Risk factors and treatment outcome for spinal recurrence. *Int J Radiat Oncol Biol Phys* 2009, 72(3): 1347-1354.
- Shimofusa K, Ueda T, Ito H, et al. Magnetic resonance imaging of hepatocellular carcinoma: a pictorial review of novel insights into patho- physiological features revealed by magnetic resonance imaging. *J Hepatobiliary Pancreat Surg* (online 07 Oct) 2009.

Hepatogastroenterologic Oncotherapy (L2)



◆ Overview

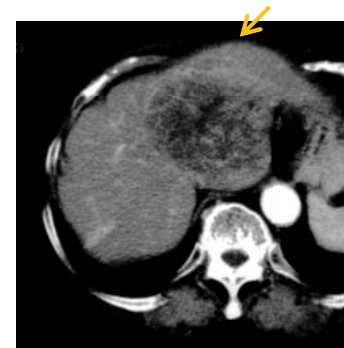
In June 1994, heavy particle radiotherapy for cancer using carbon ion beams was introduced at the National Institute of Radiological Sciences in Chiba prefecture, ahead of the rest of the world. Carbon ion beams are excellent, not only due to their physically-concentrated doses at the Bragg peak, but also due to their high relative biological effectiveness (RBE), compared with high-energy X-rays and proton beams, and an excellent curative effect can be expected. To date, clinical studies of carbon ion beams for malignant tumors of the head and neck, lung, liver, pancreas, gastrointestinal tract, prostate, gynecological organs, and ophthalmological organs have been conducted. This treatment was then approved as a highly advanced medical technology in November 2003. At our department, we are conducting clinical and basic research into multimodality cancer treatment with heavy particle radiotherapy and interventional radiology (IVR) for malignant tumors in the digestive region, especially cancers in the region of the liver, biliary tract and pancreas.

Professor

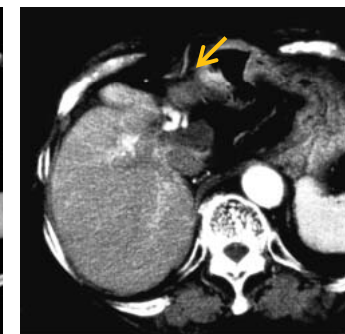
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◆ Research & Education

1. Clinical radiotherapy using carbon ion beam for hepatogastroenterologic cancer.
2. Chemotherapy and interventional radiology for Hepato-Biliary-Pancreatic cancer.
3. Multidisciplinary treatment for hepatogastroenterologic cancer.
4. Evaluation of treatment results after carbon ion radiotherapy, IVR and chemotherapy using diagnostic imaging.
5. Molecular biology of onco-related genes and mechanism of carcinogenesis in Hepato-Biliary-Pancreatic cancer.



Hepatocellular carcinoma



One year after carbon ion
beam radiotherapy

◆ Recent Publications

1. Kato H, Tsujii H, Miyamoto T, et al., Liver Cancer Working Group. Results of the first prospective study of carbon ion radiotherapy for hepatocellular carcinoma with liver cirrhosis. *Int J Radiat Oncol Biol Phys.* 59(5):1468-76., 2004
2. Yoshikawa M, Ono N, Yodono H, et al. Phase II study of hepatic arterial infusion of a fine-powder formulation of cisplatin for advanced hepatocellular carcinoma. *Hepatol Res* 38(5):474-483, 2008
3. Tawada K, Ishihara T, Kobayashi A, et al. Quantitative analysis of vascular endothelial growth factor in liver metastases from pancreatic carcinoma as a predictor of chemotherapeutic effect and prognosis. *Clin Cancer Res* 14(22):7438-7443, 2008

General Thoracic Surgery (M1)



◆ Overview

Our department covers various thoracic diseases which requires surgery or endoscopic intervention, such as malignancy, infection, pulmonary dysfunction. As to lung cancer, one of the main theme since 1962, molecular targets for multi-disciplinary strategy are investigated. Recently, preoperative ultrasound-guided needle aspiration under bronchofiber scopy has been established as a tissue sampling modality. For the respiratory dysfunction, both lung transplantation and regeneration are important issues. Now we focus type-II pneumocytes as a candidate of pulmonary stem cells (see figure), which may contribute to lung regeneration and originate lung carcinogenesis. Another novel theme is introduction of medical engineering to thoracic surgery. 4-D MRI is now under investigation as a tool for evaluation of pulmonary function around lung surgery.

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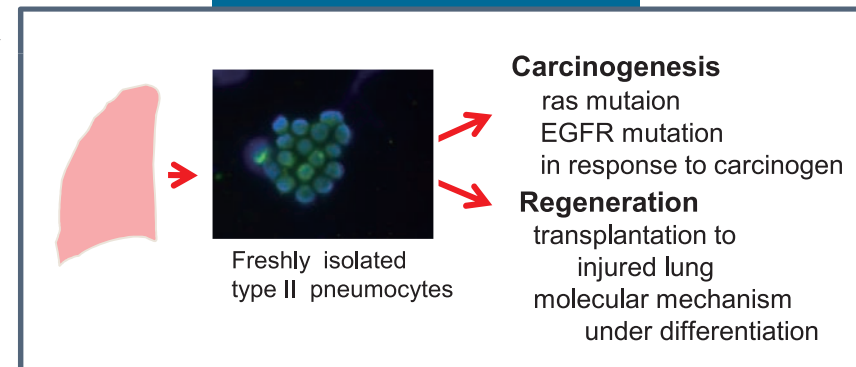


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◆ Research & Education

1. Diagnosis, surgery and multi-modal treatment for thoracic malignancies (lung cancers, tracheal tumors, chest wall tumors, mediastinal tumors and pleural tumors)
2. Analysis of molecular mechanisms in lung carcinogenesis and progression of lung cancer
3. Basic and clinical investigation of immunotherapy by activation of NKT cells for non-small cell lung cancer
4. Investigation of regenerative treatments for post-pulmonary resection state by bronchiolo-alveolar stem cells
5. Development of novel thoracoscopic surgery (VATS) using robotic arms
6. Development of novel bronchoscopic instruments
7. Four-dimensional MRI for novel evaluation tool of pulmonary function.

Research strategy



◆ Recent Publications

- Tian L, Suzuki M, Nakajima T, Kubo R, Sekine Y, Shibuya K, Hiroshima K, Nakatani Y, Fujisawa T, Yoshino I; and the Thoracic Surgery Group. Clinical significance of aberrant methylation of prostaglandin E receptor 2 (PTGER2) in non-smallCell lung cancer: association with prognosis,PTGER2 expression,and epidermal growth factor receptor mutation. *Cancer*.2008;113(6):1396-403.
- Yamada Y, Sekine Y, Yoshida S, Yasufuku K, Petrache I, Benson HL, Brand DD, Yoshino I, Wilkes DS. Type V collagen-induced oral tolerance plus low-dose cyclosporine prevents rejection of MHC class I and II incompatible lung allografts.. *J Immunol*. 2009 Jul 1;183(1):237-45.
- Mohamed S, Yasufuku K, Nakajima T, Hiroshima K, Kubo R, Iyoda A, Yoshida S, Suzuki M, Sekine Y, Shibuya K, Farouk A, Fujisawa T. Analysis of cell cycle-related proteins in mediastinal lymph nodes of patients with N2-NSCLC obtained by EBUS-TBNA: relevance to chemotherapy response. *Thorax*.2008;63(7):642-7.

Medical Immunology (M2)

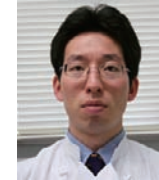
◆ Overview

Invariant Natural killer T (iNKT) cells show potent anti-tumor activity after activation with a specific ligand, α -galactosylceramide (α GalCer). In addition to direct cytotoxic effects, iNKT cells play a critical role in bridging both innate and acquired immunity. Therefore, the activation of iNKT cells in the tumor-bearing host inhibits tumor growth and rejects the tumor. The aim of our study is to develop an immunotherapy targeting the iNKT cell immune system for various malignant tumors. At present, we conduct several translational researches of iNKT cell-based immunotherapy in patients with lung cancer. Establishment of this new immunotherapy with minimal-invasiveness and few adverse events may improve the therapeutic outcome of lung cancer and then contribute to the health and social welfare.

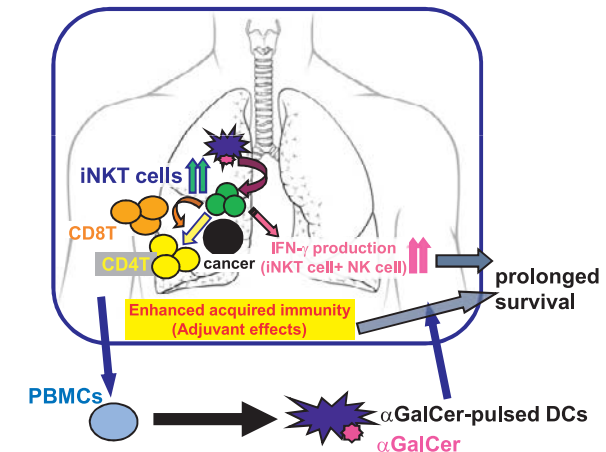
◆ Research & Education

1. Tumor immunotherapy aimed at invariant NKT cell activation
 - Molecular mechanisms of anti-tumor effects of iNKT cells
 - Induction of effective antigen presenting cells via CD1d/glycolipid
 - Detection of biomarkers for iNKT cell immunotherapy
2. Translational research of malignant diseases
 - Lung cancer
 - Head and neck cancer
 - other malignant neoplasm
 - Validation of cell processing procedure

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◆ Recent Publications

- A phase I-II study of α -Galactosylceramide-pulsed IL-2/GM-CSF-cultured peripheral blood mononuclear cells in patients with advanced and recurrent non-small cell lung cancer. Motohashi S, Nagato K, Kunii N, Yamamoto H, Yamasaki K, Okita K, Hanaoka H, Shimizu N, Suzuki M, Yoshino I, Taniguchi M, Fujisawa T, Nakayama T. *J. Immunol.* 182:2492-2501 (2009).
- Combination therapy of in vitro-expanded natural killer T cells and α -galactosylceramide-pulsed antigen-presenting cells in patients with recurrent head and neck carcinoma. Kunii N, Horiguchi S, Motohashi S, Yamamoto H, Ueno N, Yamamoto S, Sakurai D, Taniguchi M, Nakayama T, Okamoto Y. *Cancer Sci.* 100:1092-1098 (2009).
- Bmi1 regulates memory CD4 T cell survival via repression of the Noxa gene. Yamashita M, Kuwahara M, Suzuki A, Hirahara K, Shinnakasu R, Hosokawa H, Hasegawa A, Motohashi S, Iwama A, Nakayama T. *J. Exp. Med.* 205:1109-1120 (2008).

Cellular and Molecular Medicine (M3)



◆ Overview

Somatic stem cells are defined as primitive cells that are capable of both self-renewal and differentiation into any of the cell lineages of a given organ. Somatic stem cells undergo cell fate decisions, including self-renewal vs. differentiation. Our main interests are the molecular mechanisms that control fate decisions of somatic stem cells and manipulation of somatic stem cells for regenerative medicine. We are also interested in cancer stem cells that are closely related to somatic stem cells. We are mainly working on hematopoietic stem cells (HSCs) from the viewpoint of epigenetics, particularly histone modifications by the polycomb complexes. Translational research is also an important field. Ongoing projects are generation of self-renewing human HSCs from ES/iPS cells and expansion of cord blood HSCs *ex vivo*.

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◆ Research & Education

1. Molecular mechanisms that control normal and cancer stem cell system

Somatic stem cells (Hematopoietic stem cells...)

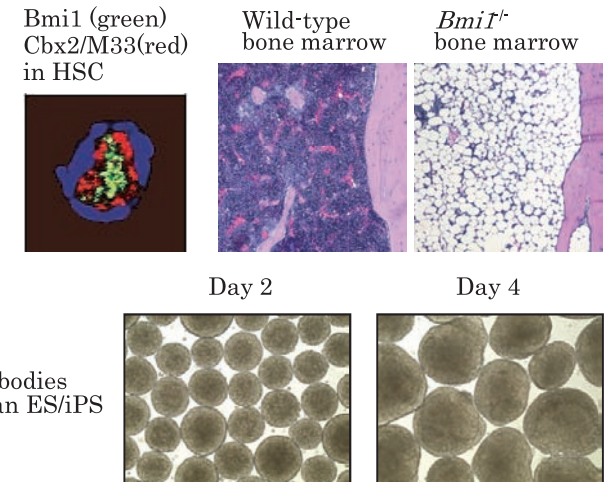
Cancer stem cells (Leukemic stem cells...)

Epigenetics, histone modification by the polycomb complexes

2. Stem cell-based translational research in regenerative medicine and cancer

Induction of hematopoietic stem cells from ES/iPS cells

Expansion of cord blood HSCs *ex vivo*



◆ Recent Publications

- Oguro H, et al. Poised lineage specification in multipotent hematopoietic stem and progenitor cells by the polycomb protein Bmi1. *Cell Stem Cell* 6, 279-286 (2010)
- Aoki R, et al. The polycomb-group gene product Ezh2 regulates proliferation and differentiation of murine hepatic stem/progenitor cells. *J Hepatology* in press.
- Nishino T, et al. Ex vivo expansion of human hematopoietic stem cells by a small-molecule agonist of c-MPL. *Exp Hematol* 37, 1364-1377 (2009)
- Chiba T, et al. Cancer stem cells in hepatocellular carcinoma: recent progress and perspective.(Review) *Cancer letters* 286, 145-153 (2009)
- Chiba T, et al. The polycomb gene product BMI1 contributes to the maintenance of tumor-initiating side population cells in hepatocellular carcinoma. *Cancer Res* 68, 7742-7749 (2008)

Cardiovascular Science and Medicine (M4)

◆ Overview

In our department, we are conducting researches on various kinds of cardiovascular diseases such as heart failure, coronary artery disease and arrhythmia from the multiple aspects (as below), and we have been trying to establish novel methods to treat such diseases including the cardiac regenerative therapy and the angiogenic therapy. In addition, we have been performing eminent cardiac catheter and arrhythmia treatments. We are one of the leading institutions among all university hospitals in Japan. We provide highly-advanced medical care, such as the revascularization therapy using the self peripheral blood mononuclear cells transplantation for cardiac dysfunction with severe coronary heart diseases as well as for peripheral artery diseases of the lower limbs. We are doing a number of educational conferences as well.



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◆ Research & Education

1. Regeneration and gene therapy for cardiovascular diseases
2. Analysis of molecular mechanisms of heart failure
3. Analysis of cardiovascular diseases using information of genomics and proteomics
4. Mechanical stress-induced cardiomyocyte responses
5. Cardiac development and differentiation
6. Angiogenesis and vascular senescence
7. Imaging of cardiovascular diseases
8. Interventional treatment for coronary artery diseases and arrhythmia

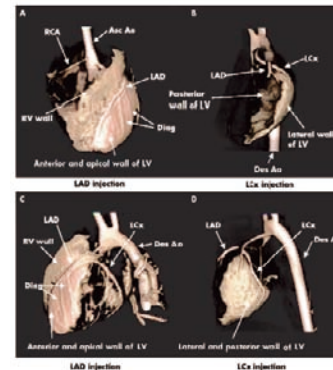


Figure 1. Vitale medical microtomography images of apical hearts using enhanced CT. Also high speed serial image contrast angiography (CT) captured 5 seconds after injection of contrast medium from the anterior aorta (A, B) and the left anterior aorta (C, D) revealed only the anterior, the apical intraventricular septum (MS) portion of the left ventricular (LV) myocardium, and the anterior wall of right ventricle (RV) myocardium supplied exclusively by the left anterior descending coronary artery (LAD) in pig 1 with LAD occlusion (A, C) and the lateral and posterior portion of LV myocardium by the left circumflex coronary artery (LCA) in pig 2 with LCA occlusion (B, D). The right coronary artery was visualized from the backflow from the catheter located in the LAD in pig 1(A) as well as the aorta, Asc. Aa., ascending aorta, Desc. Aa., descending aorta, Diap., diagonal branch.

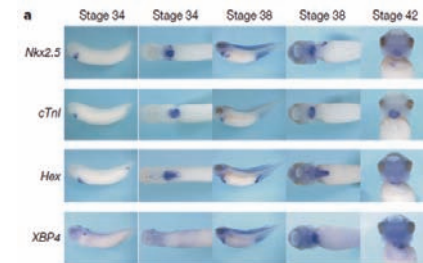


Figure 4 | IGFBP-4 is required for the maturation of the heart in *Xenopus* embryos. a, *In situ* hybridization analysis of *Nkx2.5* (an early cardiac marker), *cTnI* (a mature cardiac marker), *Hex* (a liver marker), and *IGFBP-4* (*XBP4*) mRNA expression at stages 34, 38 and 42. b, Knockdown of

◆ Recent Publications

- p53-induced inhibition of Hif-1 causes cardiac dysfunction during pressure overload. Sano M, Minamino T, Toko H, Miyauchi H, Orimo M, Qin Y, Akazawa H, Tateno K, Kayama Y, Harada M, Shimizu I, Asahara T, Hamada H, Tomita S, Molkentin JD, Zou Y, Komuro I. *Nature*. 2007 Mar 22;446(7134):444-8. 11.
- IGFBP-4 is an inhibitor of canonical Wnt signalling required for cardiogenesis. Zhu W, Shiojima I, Ito Y, Li Z, Ikeda H, Yoshida M, Naito AT, Nishi J, Ueno H, Umezawa A, Minamino T, Nagai T, Kikuchi A, Asashima M, Komuro I. *Nature*. 2008 Jul 17;454(7202):345-9.
- A crucial role for adipose tissue p53 in the regulation of insulin resistance. Minamino T, Orimo M, Shimizu I, Kunieda T, Yokoyama M, Ito T, Nojima A, Nabetani A, Oike Y, Matsubara H, Ishikawa F, Komuro I. *Nat Med*. 2009 Sep;15(9):1082-7.

Genome Research and Clinical Application (M6)



◆Overview

Functional alteration of cells is involved in the mechanisms of various diseases. When the physiological function of mature and differentiated cells is impaired, and not adequately controlled in *in vivo* tissues (pathological character), various pathological conditions are formed. Such cellular transformation is observed in vascular smooth muscle cells and fat cells in association with arteriosclerosis and diabetes mellitus. Clarification of pathological alteration of these cells on a genetic level as well as inhibition and repair of such alterations of character will lead to the development of new diagnoses and treatment methods. From such a viewpoint, we are promoting the development of novel sensitive biomarkers and specific treatments from the viewpoint of the pathological cells in various diseases.

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◆Research & Education

1. Development of cell-based pathological analyses and therapeutic systems for vascular and metabolic diseases.
2. Molecular mechanisms of pathological function expressions in vascular smooth muscle cells and adipocytes
3. Regulatory system of key molecule expressions in atherosclerosis and diabetes.
4. Interactive cascade of genetic and modifying factors in metabolic diseases
5. Mechanism of accumulative abnormalities in the regulatory systems for metabolic homeostasis
6. Development and analysis of animal models for metabolic disorders
7. Development and assessment of novel therapy for metabolic diseases

Fig. 1 Development of the vascular smooth muscle cells-specific bio-marker and treatment for atherosclerosis.

Intimal thickening after vascular injury is drastically reduced in LR11-deficient mice.

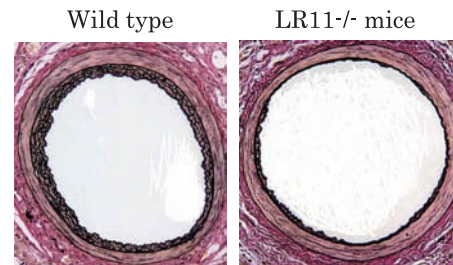
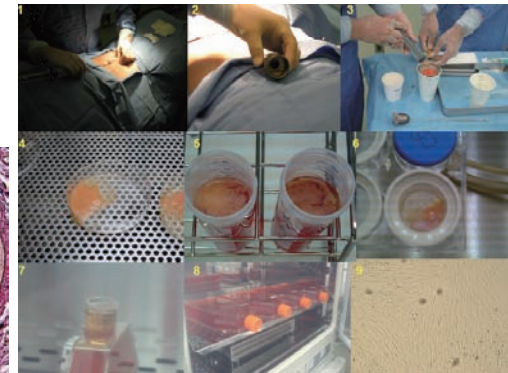


Fig. 2 Novel supplementation therapy using an autologous transplantation of the deficient gene-transfected adipocytes



◆Recent Publications

1. Jiang, M., Bujo, H., Ohwaki, K., Unoki, H., Yamazaki, H., Kanaki, T., Shibasaki, M., Azuma, K., Harigaya, K., Schnerider, W.J. and Saito, Y. (2008) AngII-stimulated migration of vascular SMC is dependent on LR11. *J. Clin. Invest.* 118, 2733-2746.
2. Rogaeva, E., Bujo, H., et al. (2007) The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. *Nat. Genet.* 39, 168-177.
3. Bujo, H. and Saito, Y. (2006) Modulation of smooth muscle cell migration by members of the low-density lipoprotein receptor family. *Arterioscler. Thromb. Vasc. Biol.* 26, 1246-1252. review



◆ Overview

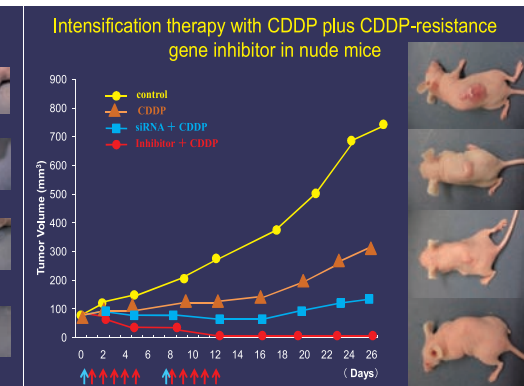
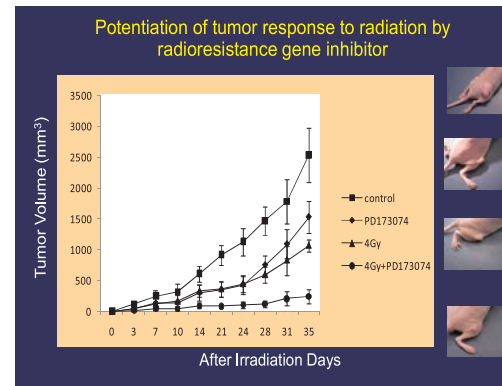
Our department, which was established in 1918, is a leading oral surgery department in Japan. Dr. Kenji Nittono, who is regarded as the founder of oral surgery in Japan, Dr. Heizo Nakamura, Dr. Torakichi Kanamori, Prof. Ikichi Sato and other pioneers of the early stages of oral surgery in Japan, have acted as leaders in this field. As a result, departments of oral surgery were established at Nihon University, Tokyo Medical and Dental University, and the Health Sciences University of Hokkaido. In 1962, it was established as a course and Dr. Ikichi Sato became the first professor Chiba University under the new system. Prof. Taturou Horikoshi, Prof. Ken-ichi Sato, and Prof. Hideki Tanzawa became chief professor in 1966, 1979, and 1997, respectively. We generally handle oral diseases both in clinical and research settings, but we have been studying oral cancer intensely from before, and our department has been continuing development involving many big-budget projects, like the center of excellence (COE) of research, education, and treatment of the 21st Century COE Program (2003-2008), the leaders' class of the *Educational Program for the Specialist of Cancer Treatment* (2007-2012), and as a representative researcher of Japan Science and Technology (JST) seeds contracted development work.

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◆ Research & Education

- Our main research interests in oral cancer have been in oral squamous cell carcinoma. We showed the possible associations with human papillomaviruses in Japan. Other studies have shown oncogenes and tumour suppressor alterations in oral squamous cell carcinoma.
- Out of number of candidates, Professor Hideki Tanzawa was selected as a Leader of big national projects, the 21st Century COE Program, which was a research and educational program concerning advanced gene therapy and heavy-ion radiotherapy for squamous cell carcinoma of the digestive organ (2003-2008), and the Educational Program for the Specialist of Cancer Treatment (2007-2012). He was also selected Chief Researcher of a big project funded by Japan Science and Technology Agency, creating a new technology of the chemotherapy (2007-2011).
- Our research team is now developing new methods and medicines for the effective radiotherapy, chemotherapy, inhibition of metastasis, and drug delivery system.



◆ Recent Publications

- Yamano Y, Uzawa K, Saito K, Nakashima D, Kasamatsu A, Koike H, Kouzu Y, Shinozuka K, Nakatani K, Negoro K, Fujita S, Tanzawa H. Identification of cisplatin-resistance related genes in head and neck squamous cell carcinoma. *Int J Cancer*. 2009 Jun 30.
- Onda T, Uzawa K, Nakashima D, Saito K, Iwadate Y, Seki N, Shibahara T, Tanzawa H. Lin-7C/VELI3/MALS-3: an essential component in metastasis of human squamous cell carcinoma. *Cancer Res*. 2007 Oct 15;67(20):9643-8.
- Higo M, Uzawa K, Kawata T, Kato Y, Kouzu Y, Yamamoto N, Shibahara T, Mizoe JE, Ito H, Tsujii H, Tanzawa H. Enhancement of SPHK1 in vitro by carbon ion irradiation in oral squamous cell carcinoma. *Int J Radiat Oncol Biol Phys*. 2006 Jul 1;65(3):867-75.

Frontier Surgery (M9)

◆ Overview

In our department, we are promoting research mainly in digestive surgery, focused on the digestive tract, as well as mammary gland/thyroid surgery, and transplantation surgery. We are developing surgical procedures for standard surgery, extended surgery, and salvage surgery, surgery involving the introduction and promotion of endoscopic surgery, and adjuvant therapies, mainly radiation and chemotherapy. The promotion of clinical research is an important research theme. We are also actively developing new treatment methods, and have been implementing genetic treatment using the p53 cancer suppressor gene for advanced esophageal cancer since 2000. We are also actively developing basic molecular treatment, and promoting research into histone deacetylase (HDAC) inhibitors and micro ribonucleic acid (RNA) as molecular treatment using epigenetics, mainly for esophageal cancer. We are also promoting research into immune treatment with dendritic cells using heat shock protein in the treatment of cancer by controlling intracellular molecular transfer, and aggressively promoting treatment with peptide vaccine in cooperation with Prof. Yusuke Nakamura at the Institute of Medical Science, the University of Tokyo.



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◆ Research & Education

A. Gastrointestinal Surgery

1. Surgical oncology and therapeutics of gastrointestinal cancer;

Imaging diagnosis, Imaging of intracellular molecule, Endoscopic diagnosis, Minimally invasive therapy, Surgical technique, Endoscopic resection, Laparoscopic surgery, Chemotherapy, Radiotherapy, Carbon ion radiotherapy, Immunotherapy, Gene therapy, Molecular therapy, Epigenetics and regulation of cell apoptosis, Regulation of intracellular molecular transfer, Individualized therapy, Regulation of surgical invasion, Nutrition, Regeneration of internal organs.

2. Functional physiology of gastrointestinal tract; Achalasia, Reflux esophagitis, Gastric emptying function, Intestinal mucosa, Defecatory function

B. Breast and Thyroid Surgery

1. Surgical oncology and therapeutics of breast cancer

2. Surgical oncology and therapeutics of thyroid cancer

C. Organ Transplantation

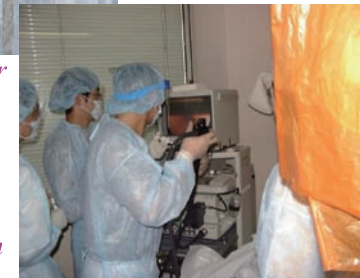
1. Organ preservation

2. Immune tolerance, Regulation of graft rejection



Administration of vector

*P53 gene therapy
for
esophageal cancer*



Taking biopsy specimen

◆ Recent Publications

- 1: Hayano K, Shuto K, Koda K, Yanagawa N, Okazumi S, Matsubara H. Quantitative measurement of blood flow using perfusion CT for assessing clinicopathologic features and prognosis in patients with rectal cancer. *Dis Colon Rectum*. 2009 Sep;52(9):1624-9.
- 2: Akutsu Y, Matsubara H, Shuto K, Uesato M, Mori M, Hoshino I, Shiratori T, Miyazawa Y, Ito H, Uno T. Clinical and pathologic evaluation of the effectiveness of neoadjuvant chemoradiation therapy in advanced esophageal cancer patients. *World J Surg*. 2009 May;33(5):1002-9.
- 3: Hoshino I, Matsubara H, Komatsu A, Akutsu Y, Nishimori T, Yoneyama Y, Murakami K, Sakata H, Matsushita K, Miyazawa Y, Brooks R, Yoshida M, Ochiai T. Combined effects of p53 gene therapy and leptomycin B in human esophageal squamous cell carcinoma. *Oncology*. 2008;75(1-2):113-9.

Functional Genomics (M11)

◆ Overview

The success of the Human Genome Project made a great impact on general life science research and produced a new academic field, genomics. By adapting the analysis methods of genomics to cancer research, many genetic abnormalities associated with cancer have been clarified, and it has become possible to clinically apply a diagnosis of the degree of malignancy and the susceptibility to cancer treatment. We are continuing to try and clarify the genetic control network of cancer based on a great deal of intrinsic life science information in the genome focusing on analysis of functional ribonucleic acid (RNA). By applying information gained in the above-mentioned way to cancer treatment, we are conducting research aimed at the realization of tailor-made medicines for patients.

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◆ Research & Education

Cancer Genome Analysis

1. Identification of molecular targets for cancer diagnosis

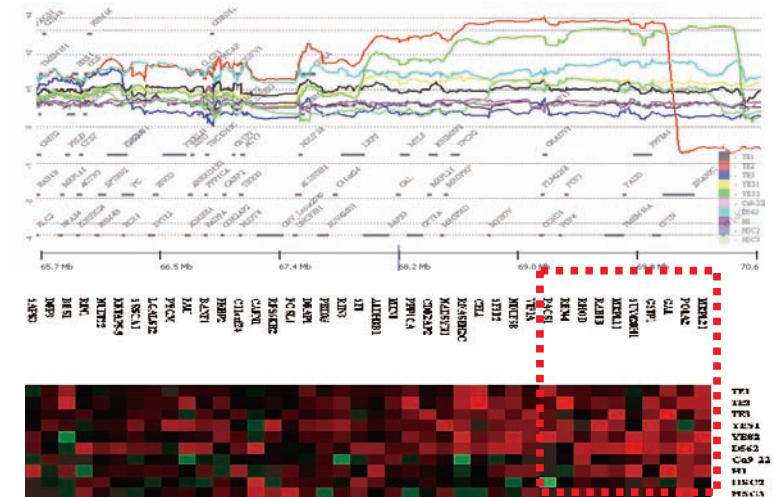
Array-based gene expression and chromosomal alterations approaches have been used to document solid tumor features. Genome-wide gene expression analyses have revealed novel candidate genes for cancer initiation and progression in esophageal cancer, head and neck squamous cell carcinoma, and bladder cancer.

2. Molecular classification of cancer cells based on gene expression profiling

While lymph node metastasis is a major factor associated with poor prognosis in cancer, little is known of its molecular mechanisms. The aim of this study was to identify genes differentially expressed between non-cancerous and cancerous lung tissues, and to investigate the gene expression profiles of 41 primary lung adenocarcinomas to select sets of gene predictors for lymph node metastasis of lung cancer. Gene expression profiles were obtained using oligonucleotide microarrays, and predictor sets constructed by evaluating the statistical significance of expression levels of selected genes. Gene analysis revealed 15 predictor genes for lymph node metastasis of lung adenocarcinoma.

3. Identification of tumor suppressive microRNAs based on microRNA expression profiling

miRNAs are small noncoding RNA gene products about 22-nucleotide (nt) long, which are cleaved from 70- to 100-nt hairpin-shaped precursors (pre-miRNA). Although their precise biology is not fully understood, miRNAs are found in diverse organisms and epigenetically function as negative regulators of gene expression through posttranslational mRNA degradation. A more recent link between miRNA function and cancer pathogenesis is supported by studies examining the signatures of miRNA in clinical samples. miRNAs are aberrantly expressed in human cancer, indicating that they may have a novel oncogenic or tumor suppressive function.



◆ Recent Publications

Ichimi T, Enokida H, Chiyomayu T, Kawakami K, Nakagawa M, [Seki N](#) (2009)

Identification of novel microRNA targets based on microRNA signatures in bladder cancer.

Int J Cancer 125:345-352.

Sugimoto T, [Seki N](#), Shimizu S, Kikkawa N, Tsukada J, Shimada H, Sasaki K, Hanazawa T, Okamoto Y (2009)

The galanin signaling cascade is a candidate pathway regulating oncogenesis in human squamous cell carcinoma. Gene Chromosome Cancer 48,132-142

Simizu S, Tsukada J, Sugimoto T, Kikkawa N, Sasaki K, Chazono H, Hanazawa T, Okamoto Y, [Seki N](#) (2008)

Identification of a novel therapeutic target for head and neck squamous cell carcinomas: A role for the neurotensin-neurotensin receptor 1 oncogenic signaling pathway.

Int J Cancer 123, 1816-1823

Bioinformatics (M12)



◆ Overview

With the basic principle, “For smiles of patients and their families,” we are working on research with the objective of contributing to the “Development and enhancement of medical treatment” by the “Discovery of useful drugs to treat refractory or rare diseases.” We have established a “Logical Drug Discovery System” using computers. Based on this technology, we have constructing immunoadhesins, combining the extracellular domain of human interleukin 10 receptor 1 (IL-10R1) with the Fc regions of human IgG1 heavy chain and investigated their capability of blocking the biological activities of human IL-10. Furthermore, we have developing “peptide drugs,” which can control the function of epidermal growth factor receptor (EGFR: a membrane protein associated with the functional recovery in patients with diseases like lung cancer or spinal cord injury).

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◆ Research & Education

1. Computer Simulation

in silico molecular evolution and screening system

Help Fight Childhood Cancer

---(http://www.worldcommunitygrid.org/research/hfcc/overview.do?language=en_US)

2. Cancer Immunology

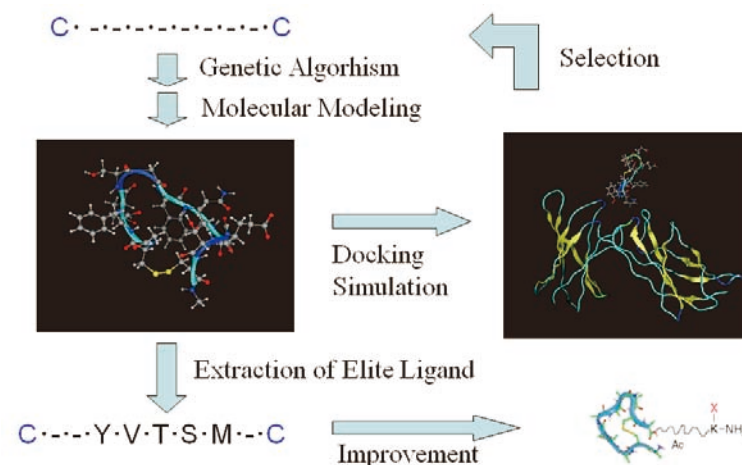
Immunoadhesins for IL-10

NKG2D, MICA, MICB, ULBP

3. Gene Regulation

Peptide Drugs for Ligands and Receptors

Peptide Mimetics for Transcription Factors



◆ Recent Publications

- “Human interleukin 10 receptor 1/IgG1-Fc fusion proteins: immunoadhesins for human IL-10 with therapeutic potential.” Terai M, Tamura Y, Alexeev V, Ohtsuka E, Berd D, Mastrangelo MJ, Sato T. *Cancer Immunol Immunother*. 2009 Aug;58(8):1307-17.
- “Wild-type AIRE cooperates with p63 in HLA class II expression of medullary thymic stromal cells.” Tonooka A, Kubo T, Ichimiya S, Tamura Y, Ilmarinen T, Ulmanen I, Kimura S, Yokoyama S, Takano Y, Kikuchi T, Sato N. *Biochem Biophys Res Commun*. 2009 Feb 13;379(3):765-70.
- “Insight into estrogenicity of phytoestrogens using in silico simulation.” Sugiyama H, Kumamoto T, Suganami A, Nakanishi W, Sowa Y, Takiguchi M, Ishikawa T, Tamura Y. *Biochem Biophys Res Commun*. 2009 Jan 30;379(1):139-44.

Biomedical Science (M14)



◆ Overview

In the department of biomedical science, we are conducting analysis of the pathological condition of human diseases using genetically-engineered mice and also perform research on the development of treatment methods. Among these, we are particularly focusing on diseases caused by an abnormality of neural crest cells, cancer, and immunoallergic diseases. We are also conducting basic research into the molecular control mechanism of cellular proliferation, differentiation, and cellular death, using these mice.

Besides the above-mentioned research, we are providing research technology support, involving the production of transgenic mice or knock-out mice, freeze preservation of fertile eggs, and melting and implantation of the eggs.

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◆ Research & Education

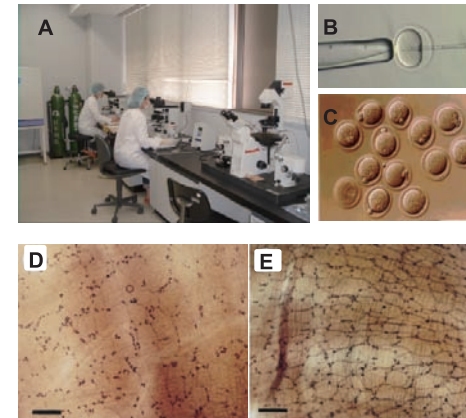
1. Generation and analysis of mouse model of human disease
2. Molecular genetics of neurocristopathy
3. Cancer research using genetically modified mice
4. Research on mechanism and treatment of Immune and allergic diseases using genetically modified mice

Photos

A. Microinjection laboratory

B and C. DNA microinjection into fertilized eggs

D and E. Visualization of enteric neurons by NADPH-diaphorase histochemistry. Number of enteric neuron is increased in Ncx deficient (E) mouse compared to that of wild type(D) mouse. Ncx deficient mouse is considered to be an animal model of human intestinal neuronal dysplasia (IND).



◆ Recent Publications

- "A kelch family protein Nd1-L functions as a metastasis suppressor in cancer cells via Rho family proteins mediated mechanism. Ohta Y, Fujimura L, Nishio S, Arima M, Sakamoto A, Shimada H, Ochiai T, Tokuhisa T, Hatano M. *Int J Oncol*. 2009 in press.
- "Prickle promotes neurite outgrowth via the Dishevelled dependent pathway in C1300 cells" Fujimura L, Watanabe-Takano H, Sato Y, Tokuhisa T, Hatano M. *Neurosci Lett*. 2009; 467: 6-10.
- "A lysosomal protein negatively regulates surface T cell antigen receptor expression by promoting CD3z degradation" Ouchida R, Yamasaki S, Hikida M, Masuda K, Kawamura K, Wada A, Mochizuki S, Tagawa M, Sakamoto A, Hatano M, Tokuhisa T, Koseki H, Saito T, Kurosaki T, Wang J-Y. *Immunity* 2008; 29:33-43.

Cardiovascular Surgery (M15)

◆Overview

Surgical therapy plays a major role in management of cardiovascular disease. We focus on heart failure, which is a rapidly growing epidemic problem. Multidisciplinary approach including surgical operation, artificial organ and regenerative medicine is mandatory for better patient management. We conduct both clinical and basic research on these aspects and expand our laboratory works into clinical practice as a translational research.

Decreasing surgical invasiveness is another key for obtaining better surgical outcomes. We employ minimally invasive treatment modalities including robotic surgery, percutaneous vascular or valve treatment and propose new application of these options.

Our training program accept 3 year course on all aspect of cardiovascular surgery, including congenital, coronary, valvular, vascular, and heart failure operations in collaboration with affiliated hospitals.



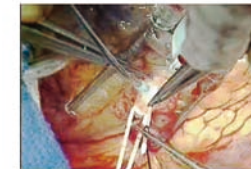
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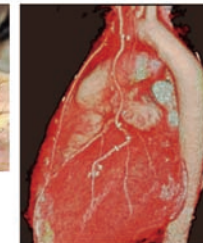


◆Research & Education

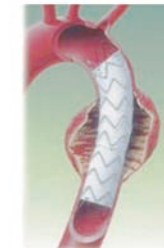
1. Heart failure surgery ; mitral valve repair, left ventricular restoration, LVAS bridge to recovery.
2. Less invasive cardiovascular surgery ; small incision valve and coronary surgery, stent grafting for aortic aneurysm, percutaneous valve replacement, robotic surgery
3. Regeneration therapy for heart failure
4. Heart transplantation ; rejection mechanism, xenotransplantation
5. Ischemia-reperfusion injury
6. Surgical therapy for pulmonary thromboembolism



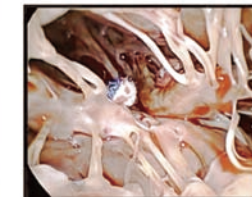
Off pump CABG



Robotic surgery



Aortic stenting



Heart failure surgery



◆Recent Publications

- Takeda K, Matsumiya G, Matsue H, Hamada S, Sakaki M, Sakaguchi T, Fujita T, Sawa Y. Use of quantitative analysis of remote myocardial fibrosis with delayed-enhancement magnetic resonance imaging to predict outcomes after surgical ventricular restoration for ischemic cardiomyopathy. J Thorac Cardiovasc Surg 2008;136:1514-21
- Ishida K, Masuda M. Thromboendarterectomy for severe chronic thromboembolic pulmonary hypertension. Asian Cardiovasc Thorac Ann. 2007;15;229-33.
- Matsumiya G, Saitoh S, Sakata Y, Sawa Y. Myocardial recovery by mechanical unloading with left ventricular assist system. Circ J 2009;73:1386-92

The Office of Medical Education

◆Overview

To cultivate efficient medical profession and researchers who will be responsible for the next generation, we have introduced advanced medical education, such as outcome-based education, and promoted substantiation of medical education.

To improve our education, we are conducting class evaluation of each course, faculty development, and are improving the credibility and validity of tests.

We are supporting international exchange of students, and since 2007 have been engaging in a foreign exchange program with the University of Illinois at Chicago, based on an interdepartmental student exchange agreement.



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◆Research & Education

1. Curriculum planning and practice for undergraduate health professional education
2. Curriculum planning and practice for graduate health professional education
3. Curriculum planning and practice for continuing health professional education
4. Curriculum planning and practice of continuing education for citizen
5. Research for teaching and evaluation relevant to social needs
6. Faculty development and practice for health profession

Faculty development



◆Recent Publications

1)Tanabe M,Tagawa M, Sadahiro T, Oda S:Effectiveness of a training program using a mannequin-based simulator for central venous catheterization. Medical Education(Japan), 40(5),327,2009

2)Miyazaki M, Sakai I, Ide N, Iida R, Tanabe M, Ishii I, Tagawa M, Yamamoto T, Asahina M, Nakamura T, Iida K:

The Development of learning outcome evaluation items for interprofessional education in Japan, AMEE Conference, Prague Czech, 2008

Department Medical Informatics and Management



◆ Overview

Our aim is to create hospital information system, to integrate them, and to utilize them for hospital management. Our division was established as the first one in national universities in Japan and we have been serving long patient records for thirty years which is one of the longest in the world for international data mining trial as well as in clinical use.

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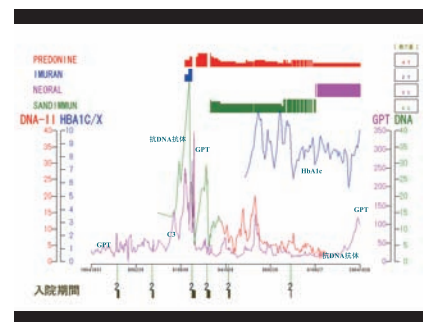
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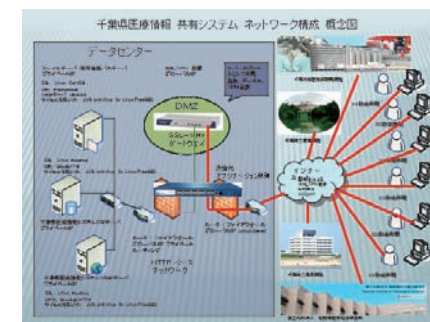
URL : <http://133.82.146.2/medinf/medinf.html>

◆ Research & Education

- 1 EMR As the first division of medical informatics in Japanese national universities, we have been developing hospital information systems, electronic medical record (EMR) systems as a frontrunner and now electronic health record (EHR).
- 2 EHR We have just started to construct the medical network of Chiba prefecture to connect more than 4,000 medical facilities with our common regional clinical paths.
- 3 Data mining With our huge database, we have been providing datasets for data mining study in medicine for international meeting as well as national projects. We are now deeply interested in the usage of discharge summaries for assessment of the diagnoses and retrieval of similar cases and collaboration with several hospitals in order to create a huge database of the case summaries. We are also aiming at discovery of side effects of multi-drug interaction.



Laboratory data for 30 years at a glance



Medical Regional Network in Chiba Prefecture

◆ Recent Publications

Takahiro Suzuki, Hideto Yokoi, Shinsuke Fujita, Katsuhiko Takabayashi. Automatic DPC Code Selection from Electronic Medical Records : Text Mining Trial of Discharge Summary. *Methods Inf Med* 2008 47:541-548.

Takabayashi K, Wiederhold G et al. Commentaries on "Informatics and medicine: from molecules topopulations" *Methods Inf Med*. 2008 47: 296-317.

Department of Diagnostic Medicine



◆ Overview

We specialize in clinical problem solving and ambulatory medicine. We solve a patient's undiagnosed symptom or health problem by comprehensively approaching all biopsychosocial problems without being restricted to an organ system or disease.

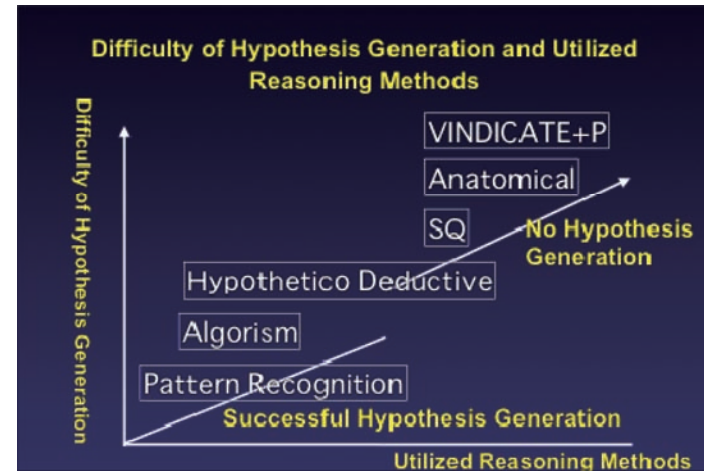
We also emphasize the importance of the medical interview from the standpoint of being able to diagnose a majority of disease or illness from the interview alone.

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◆ Research & Education

1. Research on diagnostic reasoning and its effective teaching methods
2. Research on validity and reliability of medical history and physical examination
3. Research on clinical problem solving –how to generate hypotheses
4. Research on patients' threshold to see a physician
5. Research on sustainable community medicine



◆ Recent Publications

Kim S, Ikusaka M, Mikasa G, et al. Clinical Study of 7 Cases of Familial Mediterranean Fever with MEFV Gene Mutation. Internal Medicine. 46: 221 – 225, 2007

Basugi A, Ikusaka M, Mikasa G, et al. Usefulness of Three Simple Questions to Detect Red Flag Headaches in Outpatient Settings Japanese Journal of Headache 33: 30-33, 2006

Ohira Y, Basugi A, Kim S, Mikasa G, Nishizawa S and Ikusaka M, Diagnosing Infected Urachal Cysts in the outpatient setting: a review of 5 cases Primary Care Japan 5: 40-45, 2007

Division of Pharmacy



◆ Overview

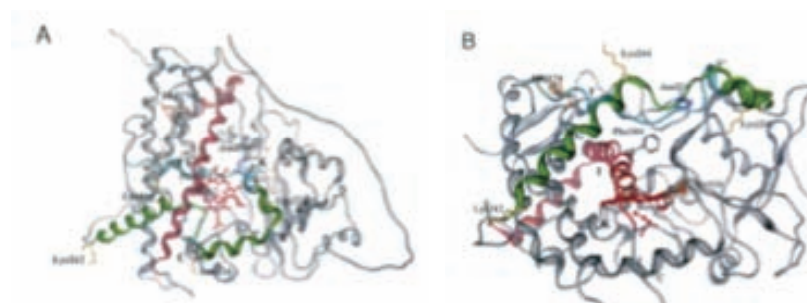
To use drugs adequately, it is important to clarify their pharmacokinetics as well as factors of individual difference in the effect and onset of adverse drug reactions. Therefore, we have been investigating the clinical application of genetic polymorphism associated with the expression of functional proteins that are important regulatory factors for pharmacokinetics of drugs. We have also been investigating the purpose of clarifying the characteristics of drug-metabolizing enzymes in the fetal period and pharmacokinetics in the neonatal period, since there are still many unknown points regarding drug-metabolizing enzymes and pharmacokinetics in these periods. Furthermore, there are foam cells that contain a lot of cholesterol ester in arteriosclerotic lesions. Therefore, we are conducting research to clarify the mechanism of foaming of macrophages and the transformation of vascular smooth muscle cells in arteriosclerosis.

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:

◆ Research & Education

1. Appropriate clinical use of drugs
 - Characterization of drug metabolism in fetus and neonates
 - Prediction of drug interactions
 - Pharmacotherapy based on polymorphism of drug metabolizing enzymes
2. Development of medical treatment for disease
 - Mechanism (s) of arteriosclerosis and development of treatment



Three-dimensional structure of CYP3A7 determined by Computer modeling. A, whole three-dimensional structure of CYP3A7. B, active site structure of CYP3A7

◆ Recent Publications

- “Growth inhibition and differentiation of cultured smooth muscle cells depend on cellular crossbridges across the tubular lumen of type I collagen matrix haneycombs.” Suzuki T, Ishii I, Kotani A, Masuda M, Hirata K, Ueda M, Ogata T, Sakai T, Ariyoshi N, Kitada M. *Microvasc. Res.* 2009;77:143-149
- “Population pharmacokinetics of oral busulfan in young Japanese children before hematopoietic stem cell transplantation.” Nakamura H, Sato T, Okada K, Miura G, Ariyoshi N, Nakazawa, K and Kitada, M. *Ther. Drug Monit.* 2008;30 (1):75-83
- “Helices F-G are important for the substrate specificities of CYP 3A7.” Torimoto N, Ishii I, Toyama K, Hata M, Tanaka K, Shimomura H, Nakamura H, Ariyoshi N, Ohmori S, Kitada M. *Drug Metab. Dispos.* 2007;35: 484-492

Division of Clinical Neuroscience



◆ Overview

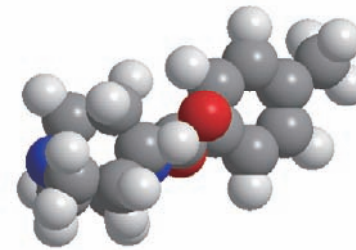
The research of Division of Clinical Neuroscience is directed towards understanding the pathophysiology of neuropsychiatric diseases such as schizophrenia, mood disorders, anxiety disorders, and substance use disorders. Using the brain imaging techniques (positron emission tomography (PET), etc.), molecular biological techniques and psychopharmacological techniques (e.g., pre-clinical and clinical studies), we have been studying to develop the new diagnostic and therapeutic methods for clarifying the pathophysiology of neuropsychiatric diseases. In addition, we have been collaborating with other research groups in the worlds (China, USA, Sweden, Israel, Denmark etc).

Professor :
KENJI HASHIMOTO, Ph.D.

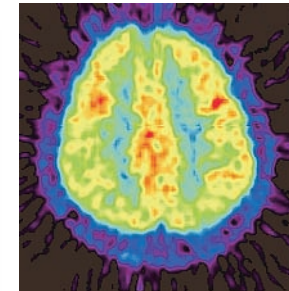
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◆ Research & Education

1. Biological markers of neuropsychiatric diseases
2. Pathophysiology of neuropsychiatric diseases
3. Animal models of neuropsychiatric diseases
4. Neuropsychopharmacology
5. Molecular neurobiology and therapeutic drugs for methamphetamine (or MDMA) abuse/dependence
6. Role of D-amino acids in the brain function
7. Development and application of novel PET ligands for brain function
8. Brain imaging studies of neuropsychiatric diseases (e.g., schizophrenia and Alzheimer's disease) using PET



[¹¹C]CHIBA-1001: A novel PET ligand for $\alpha 7$ nAChRs



A PET image of [¹¹C]CHIBA-1001 in the human brain

◆ Recent Publications

1. Hashimoto K. Emerging role of glutamate in the pathophysiology of major depressive disorder. **Brain Res. Rev.** 2009; 61 (2): 105-123.
2. Hashimoto K, et al. Co-administration of D-amino acid oxidase inhibitor potentiates the efficacy of D-serine on prepulse inhibition deficits after administration of dizocilpine. **Biol. Psychiatry** 2009; 65 (12): 1103-1106.
3. Hashimoto K, et al. [¹¹C]CHIBA-1001 as a novel PET ligand for $\alpha 7$ nicotinic receptors in the brain: A PET study in conscious monkeys. **PLoS ONE** 2008; 3 (9): e3231.
4. Hashimoto K, et al. Phencyclidine-induced cognitive deficits in mice are improved by subsequent subchronic administration of the novel selective $\alpha 7$ nicotinic receptor agonist SSR180711. **Biol. Psychiatry** 2008; 63(1): 92-97.

Forensic Mental Health



◆Overview

Forensic mental health is a field of applied psychiatry that deals with legal problems associated with mental disorders, targeting the interdisciplinary area between psychiatry and the law. Recently, the legal system in Japan concerning mental disorders has greatly changed, including a revision of the adult guardianship system and the enforcement of the “Act on Medical Care and Treatment for Persons Who Have Caused Serious Cases Under the Condition of Insanity” and the “Act on Criminal Trials Examined under Lay Judge System.” In our department, we conduct joint research with legal scholars and professionals on the expectations of forensic mental health in such a new situation. To promote such research, we welcome young people to join our department.

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◆Research & Education

1. Administration of the “Act on Medical Care and Treatment for Person Who Have Caused Serious Cases Under the Condition of Insanity”
2. International comparison of treatment systems for the mentally disordered offenders
3. Human rights protection for the mentally disordered
4. Psychiatric examinations for criminal courts
5. Mental capacity assessment in Adult Guardianship.



◆Recent Publications

1. Yoshito Igarashi(2009) Current Situations and Issues of the Act on Medical Care and Treatment for Persons Who Have Caused Serious Cases Under the Condition of Insanity. Japanese Journal of Forensic Mental Health 4(1)40-50.(in Japanese)
2. Yoshito Igarashi (2009) The citizen judge system and psychiatric expert examination. Japanese Journal of Psychiatric Treatment 24(6) 747-751.(in Japanese)
3. Yoshito Igarashi(2007) An outline of the Medical Treatment and Supervision Act. Psychiatry 10(3) 185-192. (in Japanese)

Applied Psychiatry



◆ Overview

In the department of medical treatment and rehabilitation support, we conduct surveys of the actual status of treatment and support of the rehabilitation in society of mentally handicapped people who have acted in significantly criminal ways when in a state of insanity, and developmental research into new treatments and support for rehabilitation into society, as well as education concerning these. To promote research and education, we use neuroimaging technology such as positron emission tomography, single photon emission computed tomography, and magnetic resonance spectroscopy. We also cultivate researchers in these academic fields.

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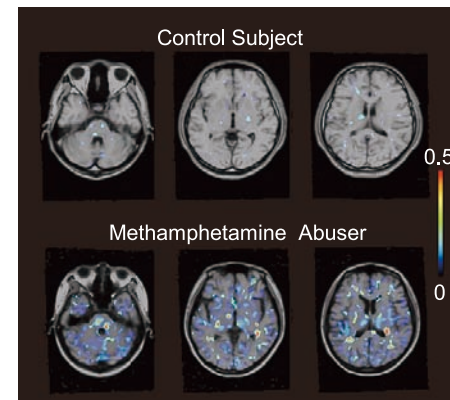
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◆ Research & Education

1. Research on the new medical treatment and rehabilitation program for mental disorders
2. Research on the new diagnostic methods for mental disorders by means of neuroimaging technique for example, positron emission tomography and single photon emission computerized tomography
3. Research on the pharmacokinetics of drugs for central nervous system by using positron emission tomography
4. Research on the pathogenesis of methamphetamine-related psychiatric disorder by means of neuroimaging technique



Magnetic resonance imaging-positron emission tomography fusion images of [¹¹C](R)-PK11195 binding potential in a control subject and a methamphetamine abuser. A marked increase in [¹¹C](R)-PK11195 binding was observed in widespread areas of the brain of the methamphetamine abuser. The color bar indicates a level of binding potential.

◆ Recent Publications

- Nakamura K., Sekine Y., Ouchi Y., *et al.* (in press) Brain serotonin and dopamine transporter bindings in adults with high-functioning autism. *Arch. Gen. Psychiatry*.
- Kanahara N., Shimizu E., Sekine Y., *et al.* Does hypofrontality expand to global brain area in progression of schizophrenia? : A cross-sectional study between first-episode and chronic schizophrenia. (2009) *Prog. Neuropsychopharmacol. Biol. Psychiatry*. 33, 410-415.
- Sekine Y., Ouchi Y., Sugihara G., *et al.* (2008) Methamphetamine causes microglial activation in the brains of human abusers. *J. Neurosci*. 28, 5756-5761.

Molecular Biology



◆ Overview

Our group is involved in research on molecular and cellular medical mycology with the goal of deciphering the molecular functions involved in pathogenicity and drug resistance by elucidation of the cell structure and cell physiological functions at the molecular level, through analysis of genes and proteins, and at the organelle and cellular level. We are conducting basic research on the molecular and cellular biology of pathogenic yeasts including *Cryptococcus neoformans* using both biochemistry and molecular biology methods based on gene and protein science and genome information as well as ultrastructural morphology and cell biology methods such as electron microscopy.

Professor :
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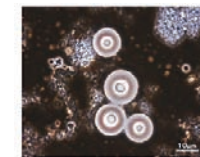


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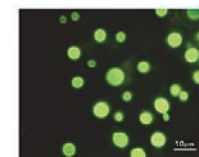
◆ Research & Education

1. Genomics and proteomics of pathogenic yeast
2. Molecular and cellular analysis of yeast pathogenicity, drug resistance, and cell cycle regulation
3. Molecular and cellular medical mycology
4. Biochemistry and molecular biology of signal transduction in pathogenic yeast *Cryptococcus neoformans*

Microscopy of *Cryptococcus neoformans*

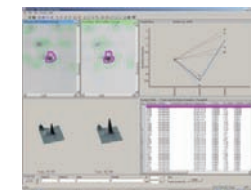


(Mouse brain: India ink staining)



(Rat lung: Fungiflora Y staining)

Proteome analysis of *Cryptococcus neoformans*



◆ Recent Publications

1. "Growth strategy of the pathogenic yeast *Cryptococcus neoformans* submerged culture under different cultivation formats." Raclavsky V, Husickova V, Moranova Z, Ohkusu M, Fischer O, Precek J, Trtkova J, Takeo K, Kawamoto S. *Folia Microbiol.* 2009; 53(4): 349-352.
2. "Peculiar clusters of daughter cells observed in *Cryptococcus neoformans* grown in sealed microtiter plates." Raclavsky V, Pavlicek J, Novotny R, Moranova Z, Ohkusu M, Trtkova J, Takeo K, Kawamoto S. *Folia Microbiol.* 2009; 53(4): 369-371.
3. "Contribution of the mannan backbone of cryptococcal glucuronoxylomannan and a glycolytic enzyme of *Staphylococcus aureus* to contact-mediated killing of *Cryptococcus neoformans*." Ikeda R, Saito F, Matsuo M, Kurokawa K, Sekimizu K, Yamaguchi M, Kawamoto S. *Journal of Bacteriology* 2007; 189(13): 4815-4826.

Division of BioResources



◆ Overview

Microbes like fungi and actinomycetes are huge and important resources for medical and biological sciences, environmental science, industrial technologies, and even in space technologies in the 21st century. Microbes are diverse in species and genes. Studying these resources is of significant importance in understanding “what is life”, to enrich our daily life, as well as to overcome infectious diseases.

Aims of our research group are collecting, sorting and storing pathogenic fungi and actinomycetes. We are also interested in basic studies of these microorganisms for the purpose of overcoming infectious diseases and utilize microbes for welfare of humans. The projects are partly supported by the National BioResource Projects.

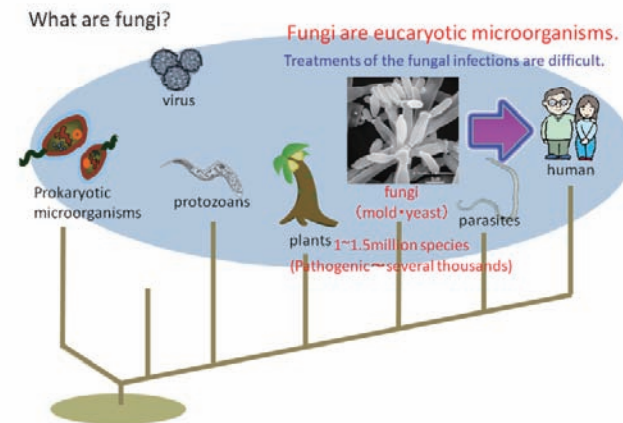
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◆ Research & Education

1. Studies of phylogenetic relationships of fungi and actinomycetes based on molecular, chemical, physiological and morphological analyses.
2. Molecular- and cell-biological studies of fungi and actinomycetes, e.g. functional proteins, 2nd metabolites, genes for producing 2nd metabolites, pathogenesis factors, genes contributing pathogenicity, cell wall carbohydrates and genes for their metabolisms.
3. Development of new techniques to identify fungi and actinomycetes for clinical purposes and epidemiological studies.
4. Collect fungi and actinomycetes from all over the world.
5. Identify fungi and actinomycetes of clinical origins (as service and welfare to our society).
6. Others.



◆ Recent Publications

1. Kogure, T., Shimada, R., Ishikawa, J., Yazawa, K., Brown, J. M., Mikami, Y. & Gonoï, T. (2010) *Antimicrob Agents Chemother*. In press.
2. Takeda, K., Kang, Y., Yazawa, K., Gonoï, T. & Mikami, Y. (2010) *J Med Microbiol* **59**, 165-71.
3. Oarada, M., Igarashi, M., Tsuzuki, T., Kamei, K., Hirasaka, K., Nikawa, T., Miyazawa, T., Nakagawa, K. & Gonoï, T. (2010) *Biosci Biotechnol Biochem* **74**, 620-6.
4. Aoyama, K., Kang, Y., Yazawa, K., Gonoï, T., Kamei, K. & Mikami, Y. (2009) *Mycopathologia* **168**, 175-83.
5. Hanafy, A., Kaocharoen, S., Jover-Botella, A., Katsu, M., Iida, S., Kogure, T., Gonoï, T., Mikami, Y. & Meyer, W. (2008) *Med Mycol* **46**, 685-96.

Division of Clinical Research



◆ Overview

Our department has constructed a close network with nationwide medical organizations and research institutes as a core of clinical research centers of excellence for mycoses across the country, and is promoting research into the mechanism of infection and pathophysiology of human mycoses including the diagnosis and treatment, epidemiology, and virulence factors of fungi. We are also conducting research on the relationships between environmental fungi and various diseases including disorders of pulmonary circulation and interstitial pneumonia, based on the hypothesis that chronic inhalation of airborne fungi in the environment, which has recently been attracting attention, is a cause of these diseases. At the same time we are also in charge of clinical practice and consultations concerning mycoses in collaboration with Chiba University Hospital.

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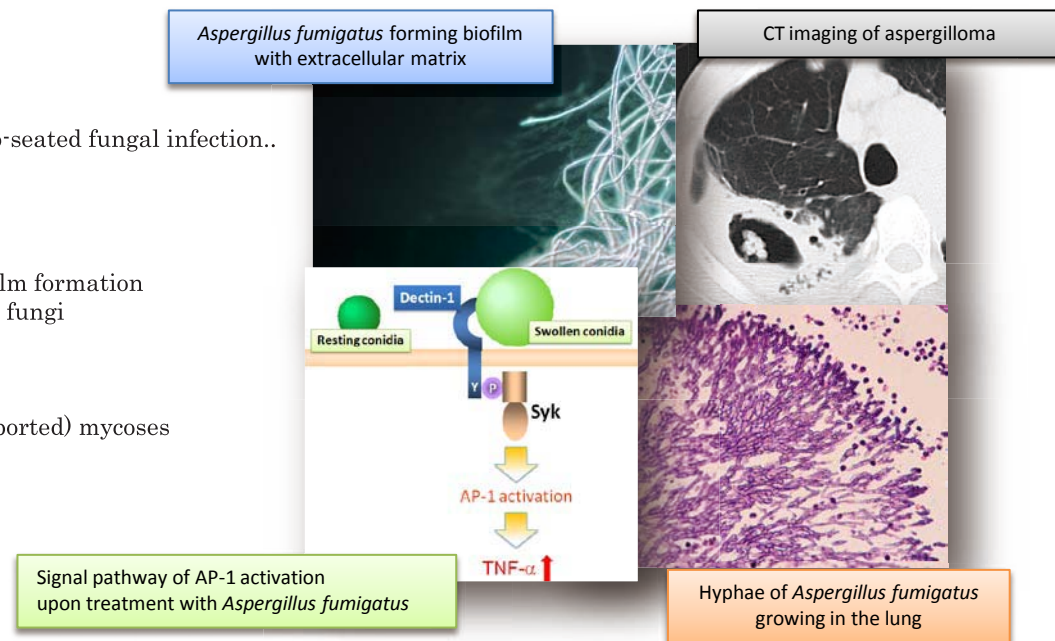
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◆ Research & Education

1. Development of diagnostic and therapeutic measures in deep-seated fungal infection..
 - Serodiagnosis & Genetic diagnosis / identification
 - Antifungal agents
2. Interaction between host and fungi
 - Innate immunity to fungal infection
 - Mechanism of infection including virulence factors and biofilm formation
3. Diseases caused by the inhalation of environmental airborne fungi
 - Pulmonary hypertension/pulmonary arterial remodeling
 - Hypersensitivity pneumonitis
 - Sick Building Syndrome
4. Epidemiology of deep-seated mycoses including endemic (imported) mycoses



◆ Recent Publications

1. Ochiai E, Kamei K, Watanabe A, Nagayoshi M, Tada Y, Nagaoka T, Sato K, Sato A, Shibuya K: Inhalation of *Stachybotrys chartarum* causes pulmonary arterial hypertension in mice. Int J Exp Pathol 89(3):201-8, 2008.
2. Toyotome T, Adachi Y, Watanabe A, Ochiai E, Ohno N, Kamei K: Activator protein 1 is triggered by *Aspergillus fumigatus* beta-glucans surface-exposed during specific growth stages. Microb Pathog. 44(2):141-50, 2008.
3. Kamei K, Watanabe A: *Aspergillus* mycotoxins and their effect on the host. Med Mycol 43 Suppl 1:S95-9, 2005

Laboratory of Infection and Immunity



◆ Overview

To protect our health against threat of various pathogen infections, it is essential to understand our immune system. We focus on viral and fungal infection, and analyze how our cells detect these pathogens and initiate immune responses to eradicate them.

In the case of viral infection, recent advance of the research revealed that viral sensor molecules, including RIG-I-like receptors (RLRs), specifically detect viral non-self nucleic acids and activate antiviral responses. We are trying to clarify the molecular machinery of this signaling cascade and its physiological significance.

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◆ Research & Education

Research Interests

1. Functional analysis of cytoplasmic sensor molecules for viral infection.

- RNA Recognition mechanism by RLRs.
- Discrimination between self and non-self RNA by RLRs.

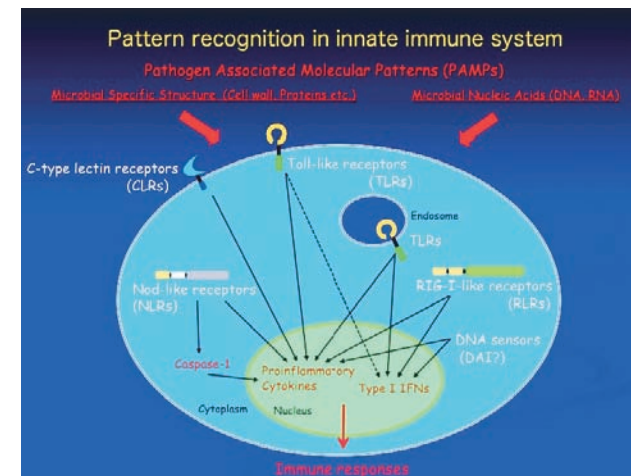
2. Signal transduction via RLRs and its physiological function.

- Activation machinery of RLR-mediated signaling
- Interaction between RLRs and signaling molecules

3. Functional analysis of sensor molecules for fungal infection.

- Analysis of gene knockout mice of the sensors
- Signal transduction via fungal sensor molecules

4. Identification of novel sensor molecule(s) for fungal infection.



◆ Recent Publications

- 1) Yoneyama M, Fujita T: Recognition of viral nucleic acids in innate immunity. *Rev. Med. Virol.*, 20, 4-22, 2010 (review)
- 2) Takahashi K, Yoneyama M (equal contribution), Nishihori T, Hirai R, Kumeta H, Narita R, Gale M Jr, Inagaki F, Fujita T: Non-self RNA-Sensing Mechanism of RIG-I Helicase and Activation of Antiviral Immune Responses. *Mol. Cell*, 29, 428-440, 2008
- 3) Yoneyama M, Kikuchi M, Natsukawa T, Shinobu N, Imaizumi T, Miyagishi M, Taira K, Akira S, Fujita T: The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. *Nat. Immunol.*, 5, 730-737, 2004



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2010. 4