

Chiba University

Graduate School of Medicine

Founded 1874



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Biochemistry and Genetics



◆ Overview

In our laboratory, we are investigating regulation of genes critical for daily behavioral, neuroplastic and metabolic rhythms, vascular diseases and angiogenesis, 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.

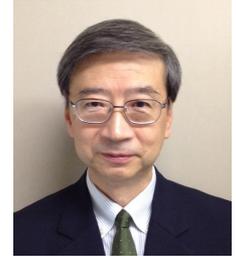
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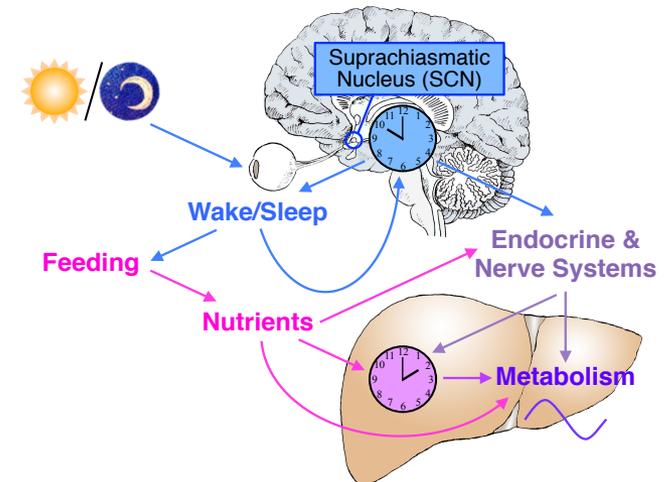
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◆ Research & Education

1. Regulation of genes critical for daily behavioral, neuroplastic and metabolic rhythms (Dr. Katsuro IWASE, Lecturer; Dr. Masaki TAKIGUCHI, Professor)
2. Search of antibody markers and functional analysis of cognate antigen proteins for disorders such as arteriosclerosis, cerebral infarction, cancer and autoimmune diseases. (Dr. Takaki HIWASA, Associate Professor)
3. Search and development of compounds controlling angiogenesis. (Dr. Hiromi ASHINO, Lecturer)



◆ Recent Publications

1. Miyauchi, O., Iwase, K., Itoh, K., Kato, M., Seki, N., Braissant, O., Bachmann, C., Shozu, M., Sekiya, S., Osada, H., and Takiguchi, M. (2013) Efficient subtractive cloning of genes activated by lipopolysaccharide and interferon γ in primary-cultured cortical cells of newborn mice. *PLoS ONE* **8**, e79236
2. Iwase, K., Ishihara, A., Yoshimura, S., Andoh, Y., Kato, M., Seki, N., Matsumoto, E., Hiwasa, T., Muller, D., Fukunaga, K., and Takiguchi, M. (2014) The secretogranin II gene is a signal integrator of glutamate and dopamine inputs. *J. Neurochem.* **128**, 233-245
3. Machida, T., Kubota, M., Kobayashi, E., Iwadate, Y., Saeki, N., Yamaura, A., Nomura, F., Takiguchi, M., and Hiwasa, T. (2015) Identification of stroke-associated-antigens via screening of recombinant proteins from the human expression cDNA library (SEREX). *J. Transl. Med.* **13**, 71

Cognitive Behavioral Physiology



◆ Overview

Mind and brain are the final frontiers for human beings. Information overload from the internet may cause stress which can affect our brain and mind. To develop more effective treatment and prevention for mental disorders, we conduct an extensive range of studies about mind and brain, based on the interaction among genes, environments and behaviors from basic molecular researches to clinical intervention trails, using various approaches including biological, medical, psychological and social scientific approaches.

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◆ Research & Education

Research of fear extinction using mouse models in learning and memory to understand anxiety and related disorders

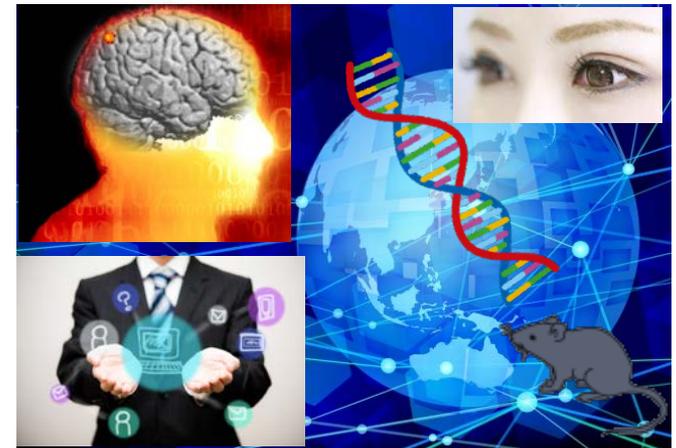
We are focusing on understanding molecular mechanisms of fear learning / extinction and development of new treatment approaches for anxiety disorders.

Analyses of human brain functions using functional brain imaging

Using magnetic resonance imaging (MRI), near-infrared spectroscopy (NIRS), transcranial direct current stimulation (tDCS) and so on, we study human brain functions including emotions, cognitions and behaviors.

Effectiveness of cognitive behavioral therapy (CBT) for mental disorders

We study clinical effectiveness of CBT for mental disorders including anxiety, depression, eating, developmental and somatic symptoms.



◆ Recent Publications

Yoshinaga N, et al. Cognitive Behavioral Therapy for Patients with Social Anxiety Disorder Who Remain Symptomatic following Antidepressant Treatment: A Randomized, Assessor-Blinded, Controlled Trial. *Psychother Psychosom* 2016;85:208-217

Sutoh C, et al. Transient contribution of left posterior parietal cortex to cognitive restructuring. *Sci Rep.* 2015;5:9199

Matsuda S, et al. Sex differences in fear extinction and involvements of extracellular signal-regulated kinase (ERK). *Neurobiology of learning and memory* 2015. 123. 117-124.

Shimizu E, et al. NMDA receptor-dependent synaptic reinforcement as a crucial process for memory consolidation. *Science.* 2000 Nov 10; 290: 1170-1174.

Functional Anatomy



◆ Overview

Our lab has two research groups. One group is working on the pathophysiology of neurodegenerative diseases and brain stroke. Another group theme is reproductive biology and medicine.

Regarding medical education, we are in charge of the lectures and practical training of histology and neuroanatomy for second- and third-year medical school students. Our lectures are mainly intended to bridge basic and clinical medicine.

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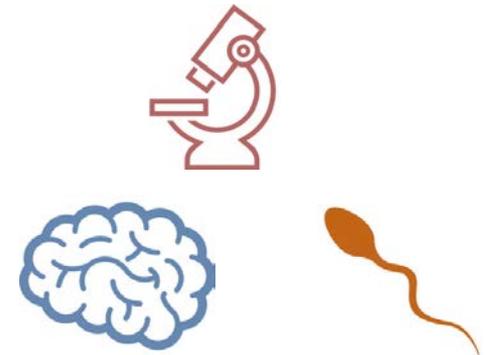
◆ Research & Education

Research

- 1, Pathophysiology of neurodegenerative diseases, including ALS and Parkinson's disease.
- 2, Molecular mechanism in which neurons respond to ischemic stress in brain stroke.
- 3, Reproductive biology and medicine.

Education

- 1, Neuroanatomy in 2nd academic year.
- 2, Histology in 3rd academic year.



◆ Recent Publications

- 1, Yamaguchi A, Kitajo K.(2012) The effect of PRMT1-mediated arginine methylation on the subcellular localization, stress granules, and detergent-insoluble aggregates of FUS/TLS. PLoS One. 7(11):e49267.
- 2, Yamaguchi A, Takanashi K.(2016) FUS interacts with nuclear matrix-associated protein SAFB1 as well as Matrin3 to regulate splicing and ligand-mediated transcription. Sci Rep. 2016 Oct 12;6:35195.
- 3, Sakamoto M, Miyazaki Y, Kitajo K, Yamaguchi A. (2015) VGF, Which Is Induced Transcriptionally in Stroke Brain, Enhances Neurite Extension and Confers Protection Against Ischemia In Vitro. Transl Stroke Res. 6(4):301-308.

Psychiatry



◆ 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

- Dopamine supersensitivity psychosis as a pivotal factor in treatment-resistant schizophrenia. Suzuki T, Kanahara N, Yamanaka H, et al. *Psychiatry Res.* 2015 Jun 30;227(2-3):278-82.
- A prospective comparative study of risperidone long-acting injectable for treatment-resistant schizophrenia with dopamine supersensitivity psychosis. Kimura H, Kanahara N, Komatsu N, et al. *Schizophr Res.* 2014 May;155(1-3):52-8.
- Optimal extent of dopamine D2 receptor occupancy by antipsychotics for treatment of dopamine supersensitivity psychosis and late-onset psychosis. Iyo M1, Tadokoro S, Kanahara N, et al. *J Clin Psychopharmacol.* 2013 Jun;33(3):398-404.

Ophthalmology and Visual Science

◆ Overview

Our department carries out applied and fundamental research projects and actively involved in the implementation of different innovations.

Investigating mechanisms involved in the pathogenesis of various retinal diseases (diabetic retinopathy, AMD, retinitis pigmentosa, etc), facilitating future drug development for vision loss prevention, implementing achievements of ophthalmology and scientific research into practical health care, are our main goals. The full range of operations performed in the department determine the direction of scientific and practical work.

Researchers from our department are highly qualified personnel in postgraduate and clinical studies, actively attend international conferences and symposia with presentations, publish results of studies in international peer-reviewed journals.



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◆ Research & Education

1. Surgical retina: retinal detachment, proliferative vitreoretinopathy, proliferative diabetic retinopathy, macular hole, epiretinal membrane
2. Medical retina: age-related macular degeneration, diabetic retinopathy, diabetic macular edema, retinal vein occlusion, retinitis pigmentosa
3. Glaucoma: medical and surgical treatments including trabeculectomy, trabeculoplasty, and tube implant
4. Uveitis: infliximab treatment for refractory Behcet's disease
5. Corneal diseases
6. Neuro ophthalmology
7. Orbital diseases: tumor and plastic surgery
8. Low vision care
9. Neuroprotection & regeneration

◆ Recent Publications

1. Akiba R, Yokouchi H, Mori M, Oshitari T, Baba T, Sawai S, Kuwabara S, Yamamoto S. Retinal morphology and sensitivity are primarily impaired in eyes with neuromyelitis optica spectrum disorder (NMOSD). *PLoS One*. 2016;11(12):e0167473.
2. Baba T, Tanaka S, Nizawa T, Oshitari T, Yamamoto S. Scleral imbrication combined with pars plana vitrectomy without internal limiting membrane peeling for myopic schisis. *Retina*. 2016;36(10):1927-34.
3. Bikbova G, Oshitari T, Baba T, Yamamoto S. Altered expression of NF- κ B and SP1 after exposure to advanced glycation end-products and effects of neurotrophic factors in AGEs exposed rat retinas. *J Diabetes Res*. 2015;2015:543818.

Neurology



◆ Overview

The 21st century is the “Century of Neuroscience”. Therefore we adopt a multidisciplinary approach using various methodologies such as molecular biology, physiology, neuroimaging, and proteomics for each neurological disorder to clarify the pathogenesis on a molecular level and to develop novel treatments. All staff members are striving towards medical treatment, research, education, and a social contribution in the field of neurological diseases by cultivating excellent neurologists.

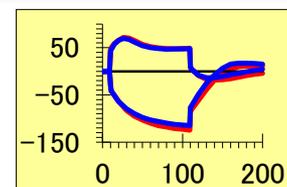
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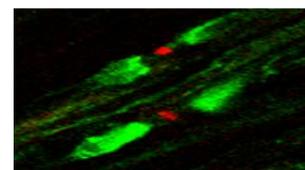
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◆ Research & Education

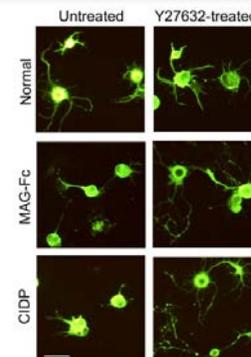
1. Pathogenesis of neuro-immunological diseases
2. Neuronal/axonal ion channel physiology
- 3 Brain functional-molecular imaging
4. Molecular biology of neurodegenerative disorders...
6. Development of new treatments for motor neuron diseases.
7. Pathogenesis and treatment of neuropathic pain syndrome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



Threshold electrotonus in ALS



ion channels



Axonal growth assay in rat DRG neurons

◆ Recent Publications

- 1) Misawa S, Sato Y, Katayama K, Nagashima K, Aoyagi R, Sekiguchi Y, Sobue G, Koike H, Yabe I, Sasaki H, Watanabe O, Takashima H, Nishizawa M, Kawachi I, Kusunoki S, Mitsui Y, Kikuchi S, Nakashima I, Ikeda S, Kohara N, Kanda T, Kira J, Hanaoka H, Kuwabara S; Japanese POEMS Syndrome for Thalidomide (J-POST) Trial Study Group.. Safety and efficacy of thalidomide in patients with POEMS syndrome: a multicentre, randomised, double-blind, placebo-controlled trial. **Lancet Neurology** 2016 Oct;15(11):1129-37.
- 2) Shibuya K, Sugiyama A, Ito S, Misawa S, Sekiguchi Y, Mitsuma S, Iwai Y, Watanabe K, Shimada H, Kawaguchi H, Suhara T, Yokota H, Matsumoto H, Kuwabara S. Reconstruction magnetic resonance neurography in chronic inflammatory demyelinating polyneuropathy. **Annals of Neurology** 2015 Feb;77(2):333-7
- 3) Kuwabara S, Yuki N. Axonal Guillain-Barré syndrome: concepts and controversies. **Lancet Neurology** 2013 Dec;12(12):1180-8.

Neurological Surgery



◆ Overview

Department of Neurological Surgery maintains an active clinical service, educations, and researches. We provide leading-edge technologies for complex conditions in the following areas: malignant brain tumors, sellar and parasellar lesions, skull base surgery, spinal disease, and neuronal surgery, spinal disease, and neuronal function disorders. Our patients can have access to less-invasive surgical procedures and the most novel therapies. We also offer excellent training program in neurosurgery for neurosurgical residents, in corporation with other related hospitals and medical centers in Chiba.

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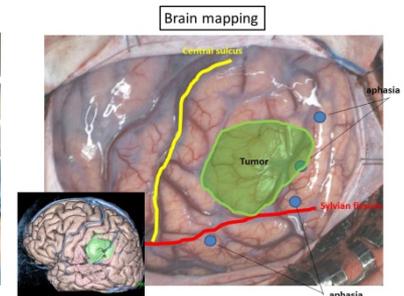


◆ Research & Education

We focus on the following research areas:

1. Diagnosis and treatment of malignant brain tumors
2. Immune-gene therapy for glioblastoma
3. Photodynamic therapy for gliomas
4. Diagnosis and treatment of sellar-parasellar lesions
5. Endoscopic surgery for various intracranial lesions
6. Carotid artery stenting
7. Endovascular treatment for cerebral aneurysms
8. Surgical treatment for movement disorders
9. Epilepsy surgery
10. Flow dynamics of cerebrospinal fluid
11. Treatment of spinal spondylosis and spinal cord tumors
12. Mechanisms of neurovascular compression syndromes

Awake surgery



We perform an awake surgery for a patient with gliomas collaborating with many experts in the other departments including Anesthesiology, Rehabilitation, and Clinical Laboratory and Testing.

◆ Recent Publications

- 1) Iwadate Y, Suganami A, Tamura Y, Matsutani T, Hirono S, Shinozaki N, Hiwasa T, Takiguchi M, Saeki N. The pluripotent stem-cell marker alkaline phosphatase is highly expressed in refractory glioblastoma with DNA hypomethylation. *Neurosurgery* 80: 248-256, 2017
- 2) Iwadate Y, Shinozaki N (Co-first), Matsutani T, Uchino Y, Saeki N. Molecular imaging of 1p/19q deletion in oligodendroglial tumor with ¹¹C-Methionine positron emission tomography. *J Neurosurg Psych* 87: 1016-1021, 2016.
- 3) Suganami A, Iwadate Y (Co-first), Shibata S (Co-first), Yamashita M, Tanaka T, Shinozaki N, Aoki I, Saeki N, Shirasawa H, Okamoto Y, Tamura Y. Liposomally formulated phospholipid-conjugated ondocyanine green for intra-operative brain tumor detection and resection. *Int J Pharmaceutics* 496: 401-406, 2015.

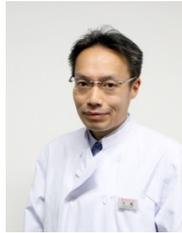
Orthopaedic Surgery



◆ 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 animal model.

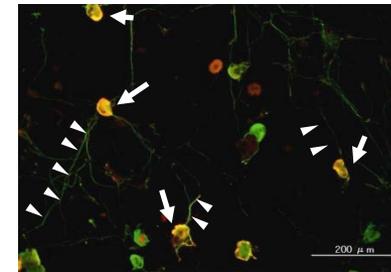
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◆ Research & Education

1. Pathomechanism of low back pain, osteoporosis, and sarcopenia
2. Regeneration therapy for spinal cord injury
3. Molecular mechanisms of shock wave therapy
4. Cartilage regeneration
5. Pathogenesis of ossification of posterior longitudinal ligament
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

1. Shiga Y, Orita S, Kubota G, et al. Freeze-Dried Platelet-Rich Plasma Accelerates Bone Union with Adequate Rigidity in Posterolateral Lumbar Fusion Surgery Model in Rats. *Sci Rep.* 6: 36715, 2016.
2. Ohtori S, Orita S, Yamauchi K, et al. Classification of Chronic Back Muscle Degeneration after Spinal Surgery and Its Relationship with Low Back Pain. *Asian Spine J.* 10: 516-21, 2016.
3. Abe K, Orita S, Mannoji C, et al. Perioperative Complications in 155 Patients Who Underwent Oblique Lateral Interbody Fusion Surgery: Perspectives and Indications From a Retrospective, Multicenter Survey. *Spine (Phila Pa 1976).* 42: 55-62, 2017.

Pharmacology



◆ Overview

Pharmacotherapy occupies an essential part of medicine, where transporters have been established as a key drug target molecule in various diseases, such as hypertension, hyperuricemia, diabetes, depression, and cancers. In order to seek a new opportunity toward innovative drug development, we are working on a variety of research aiming at clarification of physiological as well as pathophysiological roles of transporters expressed in various tissues. In addition, we also conduct a research to clarify the regulatory mechanisms of intercellular signaling through nitric oxide (NO) in relation to functional alternation in physiology and pathophysiology with use of biochemical and molecular biological techniques.

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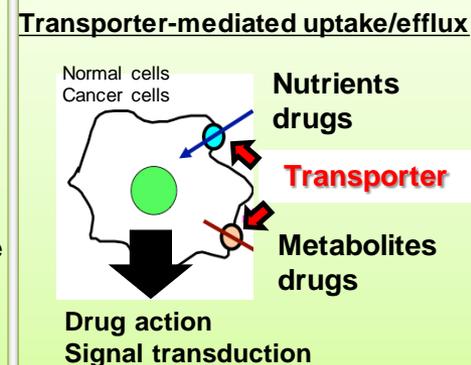
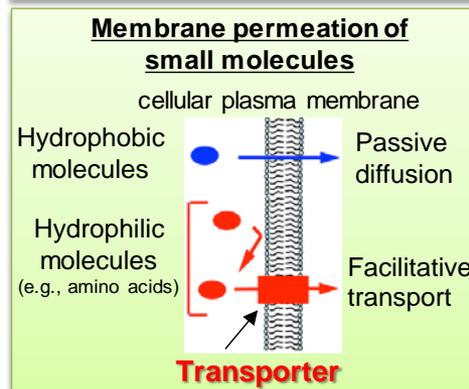
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◆ Research & Education

1. Characterization of clinico-pathological and pharmacological roles of transporters, including L-type amino acid transporters, in various tissues and cancers.
2. Development of new anti-cancer agents/strategy targeting to cancer-associated transporter gene products and their functions.
3. Development of new non-invasive diagnostic methods for determination of serum metabolites, which are substrates of transporters.
4. Regulatory roles of nitric oxide (NO) in cellular signaling through S-nitrosylation.
5. Mechanisms of inter-cellular signaling by NO.

Transporters play important roles in determination of pharmacological effects of various drugs



◆ Recent Publications

- Hayashi K, Jutabha P, Endou H, Sagara H, Anzai N. LAT1 is a critical transporter of essential amino acids for immune reactions in activated human T cells. *J Immunol.* 2013; 191: 4080-5.
- Anzai N, Endou H. Urate transporters: an evolving field. *Semin Nephrol.* 2011; 31(5): 400-9.

Diagnostic Pathology



◆ Overview

In our department, we aim to understand the pathology of various lesions in an integrated manner by grossly examining the affected organs, analyzing microscopic features and further clarifying genetic/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. We are advancing research and education mainly on pulmonary diseases and diagnostic surgical pathology/cytology in general as described below:

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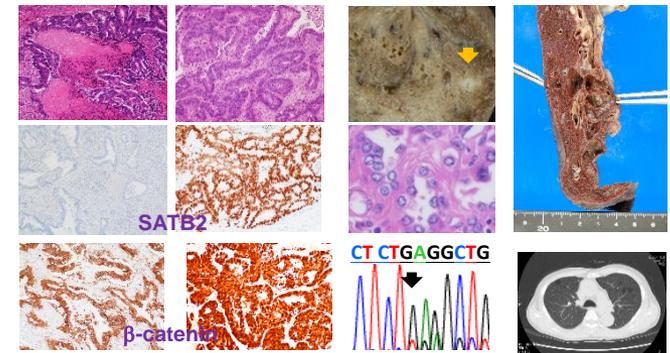
◆ Research & Education

1. Pathology of pulmonary diseases

- Birt-Hogg-Dube syndrome: analysis of histopathology, genetic abnormality and epidemiology
- Variants of pulmonary adenocarcinomas: clinicopathological, immunohistochemical and genetic analysis of fetal and enteric adenocarcinomas
- Sclerosing pneumocytoma: NGS analysis of genetic abnormality
- Adenoid cystic carcinoma: FISH analysis and its application for diagnosis
- Pleuroparenchymal fibroelastosis: morphometric analysis

2. Diagnostic surgical pathology

3. Diagnostic cytopathology



Enteric adenocarcinoma vs. metastatic colonic carcinoma (Matsushima J et al. Hum Pathol, in submission)

Pulmonary lesions in Birt-Hogg-Dube syndrome (Furuya M et al. PLoS One, 2016)

◆ Recent Publications

1. Furuya M, Tanaka R, Okudela K, Nakamura S, Yoshioka H, Tsuzuki T, Shibuya R, Yatera K, Shirasaki H, Sudo Y, Kimura N, Yamada K, Uematsu S, Kunimura T, Kato I, Nakatani Y. Pulmonary Neoplasms in Patients with Birt-Hogg-Dubé Syndrome: Histopathological Features and Genetic and Somatic Events. PLoS One. 2016;11(3):e0151476 2.
2. Suzuki M, Yazawa T, Ota S, Morimoto J, Yoshino I, Yamanaka S, Inayama Y, Kawabata Y, Shimizu Y, Komatsu M, Notohara K, Koda K, Nakatani Y. High-grade fetal adenocarcinoma of the lung is a tumour with a fetal phenotype that shows diverse differentiation, including high-grade neuroendocrine carcinoma: a clinicopathological, immunohistochemical and mutational study of 20 cases. Histopathology. 2015;67(6):806-16.

Respiratory Medicine

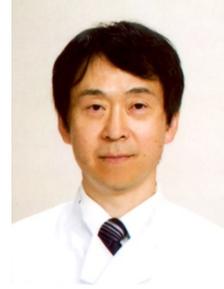


◆ Overview

In Respiratory Medicine, we have been and will be conducting medical services, medical research and educational activities, learning towards respiratory diseases, regarding respiratory structure and functions, pulmonary pathophysiology, pathobiology and molecular biology. Respiratory diseases include 1) pulmonary circulatory disorders such as pulmonary hypertension and pulmonary thromboembolism, 2) interstitial pneumonia such as pulmonary fibrosis, 3) chronic obstructive pulmonary disease, 4) sleep apnea syndrome, 5) pulmonary infectious diseases, 6) allergic diseases such as bronchial asthma, 7) lung malignancies, and so on.

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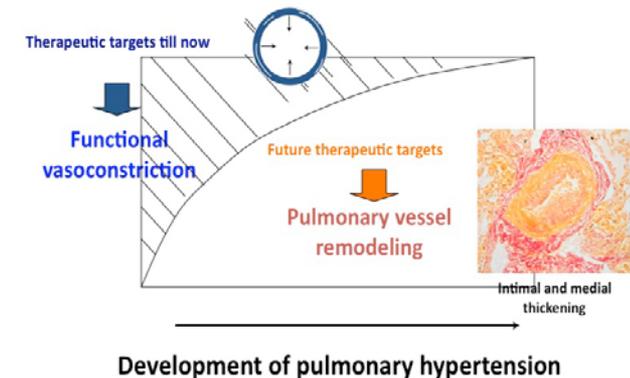


◆ Research & Education

The aims of research to be elucidated are as follows.

1. Remodeling of pulmonary artery in pulmonary arterial hypertension (PAH) and therapy for PAH.
2. Development and progression of chronic pulmonary thromboembolic hypertension (CTEPH) and therapy for CTEPH.
3. Cell death, remodeling and repair process in pulmonary diseases.
4. Adaptation to hypoxia.
5. Pathogenesis and therapy for interstitial lung diseases.
6. Integrated omics analysis in respiratory diseases to search for new biomarkers and therapeutic targets.
7. Pathogenesis and therapy for chronic obstructive pulmonary disease (COPD).
8. Pathophysiology and therapy for sleep apnea syndrome.
9. Pathophysiology and therapy for pulmonary infectious diseases.
10. Diagnosis and therapeutic strategies for pulmonary malignant diseases.

Pathogenesis of pulmonary hypertension



◆ Recent Publications

- Suzuki T, et al. Endothelial-to-mesenchymal transition in lipopolysaccharide-induced acute lung injury drives a progenitor cell-like phenotype. *Am J Physiol Lung Cell Mol Physiol*. 310; L1185-L1198, 2016
- Sakao S, et al. Increased right ventricular fatty acid accumulation in chronic thromboembolic pulmonary hypertension. *Ann Am Thorac Soc*.12:1465-1472, 2015.
- Kawasaki T, et al. Vascular repair by tissue-resident endothelial progenitor cells in endotoxin-induced lung injury. *Am J Respir Cell Mol Biol*. 53:500-512, 2015.

Cardiovascular Medicine



◆ 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 peripheral artery diseases of the lower limbs. We are doing a number of educational conferences as well.

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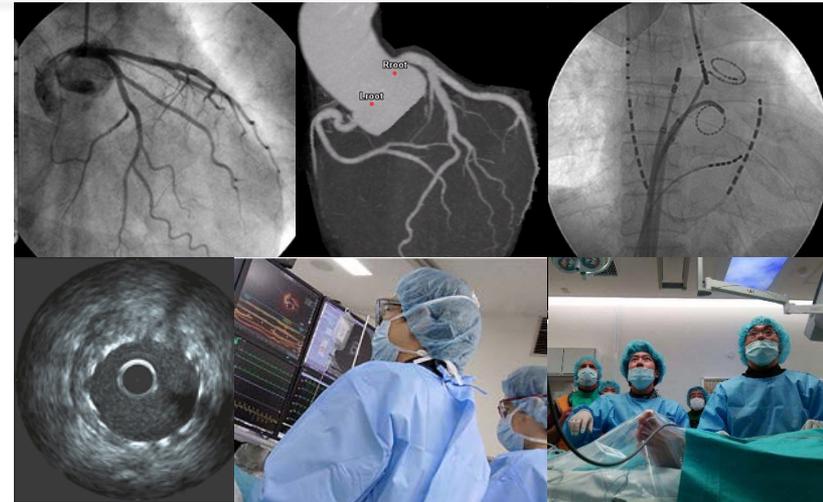
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◆ Research & Education

1. Imaging of cardiovascular disease
2. Analysis of molecular mechanisms of heart failure and treatment
3. Analysis of cardiovascular diseases using information of genomics and proteomics
4. Mechanical stress-induced cardiomyocyte responses
5. Angiogenesis and vascular senescence
6. Hypertension
7. Interventional treatment for coronary artery diseases, valvular diseases and arrhythmia



◆ Recent Publications

- Visualizing induced silent steam pop with intracardiac echocardiography. Kondo Y, Ueda M, Kobayashi Y. *Europace* 2017 Apr 18. doi: 10.1093/europace/eux085.
- Respiratory function in candidates for cardiac 320-slice CT: Relationship between coronary arterial findings, left ventricle size, and ventricular function, with emphysema, FEV1.0%, %VC, and prognosis. Takaoka H, Funabashi N, Uehara M, Ozawa K, Kobayashi Y. *Int J Cardiol* 2016;224(1):4-7.
- Kanda M, Nagai T, Takahashi T, Liu ML, Kondou N, Naito AT, Akazawa H, Sashida G, Iwama A, Komuro I, Kobayashi Y. Leukemia Inhibitory Factor enhances endogenous cardiomyocyte regeneration after myocardial infarction. *PLoS One*. 2016;11(5):e0156562.

General Thoracic Surgery



◆ Overview

Our department covers various thoracic diseases which require surgery or endoscopic intervention, such as thoracic malignancies, infections, pulmonary dysfunction. As to lung cancer, the main theme of us since 1962, molecular targets for multi-disciplinary strategy are investigated. Especially, idiopathic pulmonary fibrosis-concomitant lung cancer is a challenging issue. For the respiratory dysfunction, both lung transplantation and regenerative medicine are our objects. Murine orthotopic transplant model has been established in our laboratory, and prevention of the allogeneic rejection is studied. Compensatory lung growth after surgery is a key to lung regenerative research, and both radiologic approach for clinical cases and type-II alveolar cell transfer in mice are investigated.

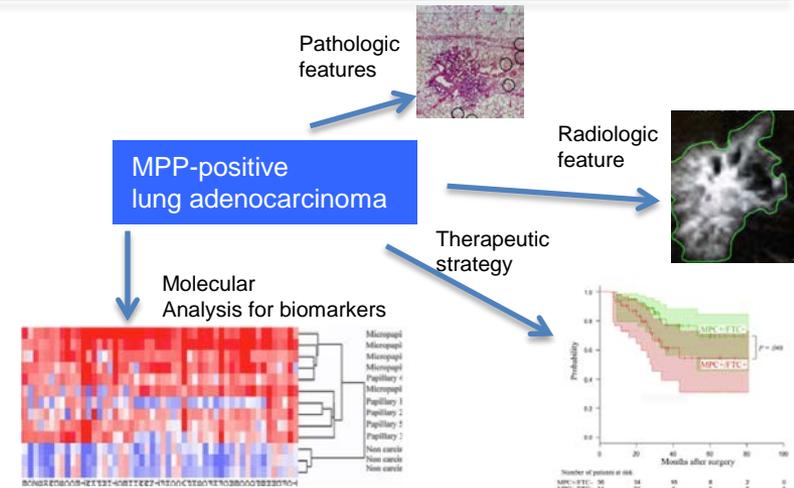
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◆ Research & Education

1. Diagnosis, surgery and multi-disciplinary treatments for thoracic malignancies such as lung cancer, mediastinal tumors, chest wall tumor, pleural tumors, etc.
2. Analysis of molecular mechanisms in lung carcinogenesis and progression of lung cancer, especially the case accompanied by micropapillary component(MPP) in the tumor tissues and interstitial lung diseases in the background (partly collaborated with Prof. Kaneda, Dept. of Molecular Oncology)
3. Basic and clinical investigation of immunotherapy by activation of NKT cells for non-small cell lung cancer (collaborated by Prof. Motohashi, Dept. of Medical Immunology)
4. Compensatory lung growth after surgery in clinical cases and murine model.
5. Development of bronchoscopic interventions and instruments
6. Elucidation of mechanism and development of prevention for allogeneic rejection of transplanted lung
7. Establishment of the evaluation for tracheobronchoplasty



◆ Recent Publications

- Iwata T, Yoshida S, Fujiwara T, Wada H, Nakajima T, Suzuki H, Yoshino I. Effect of perioperative pirfenidone in lung cancer with idiopathic pulmonary fibrosis. *Ann Thorac Surg* 2016;102:1905-1910.
- Morimoto J, Nakajima T, Suzuki H, Nagato K, Iwata T, Fukuyo M, Ota S, Nakatani Y, Yoshino I. Impact of free tumor clusters on prognosis after resection of pulmonary adenocarcinoma. *J Thorac Cardiovasc Surg* 2016;152:64-72.
- Nakajima T, Shingyouji M, Anayama T, Kimura H, Yasufuku K, Yoshino I. Spectrum analysis of endobronchial ultrasound radiofrequency of lymph nodes in patients with lung cancer. *Chest* 2016; 149:1393-1399.

Anesthesiology

◆ Overview

It is our mission to achieve safety and comfort of every single patient undergoing surgery, receiving palliative care or suffering chronic pain and dyspnea. In accord with our mission, we conduct both clinical and basic research testing novel approaches to solve the clinical problems and clinically-meaningful hypotheses based on our own clinical experiences. We specifically focus on managements of respiratory symptoms such as hypoxemia, upper airway obstruction, and unpleasant clinical symptoms such as pain and dyspnea.



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◆ Research & Education

1. Safe and comfortable perioperative management for patients

- Control of breathing during perioperative period
- Upper airway maintenance and reflexes
- Development of new respiratory monitoring systems
- Postoperative delirium

2. Palliative care medicine

- Managements of various unpleasant symptoms
- Mechanisms of chronic pain

3. Molecular biology

- Unfolded protein response (UPS) to various perioperative stresses
- UPR in various systemic diseases and pathogenesis

◆ Recent Publications

1. Sato S, et al. Mask ventilation during induction of general anesthesia: influences of obstructive sleep apnea. *Anesthesiology* 2017;126:28-38.
2. Jin H, et al. Sublethal endoplasmic reticulum stress caused by the mutation of immunoglobulin heavy chain-binding protein induces the synthesis of a mitochondrial protein, pyrroline-5-carboxylate reductase 1. *Cell Stress Chaperones* 2017;22:77-85.
3. Kato S, et al. Submental negative pressure application decreases collapsibility of the passive pharyngeal airway in nonobese women. *J Appl Physiol* 2015;118:912-20.

Molecular Pathology



◆ Overview

In Department of Molecular Pathology, we are studying pathogenesis and pathophysiology of the diseases, especially in digestive 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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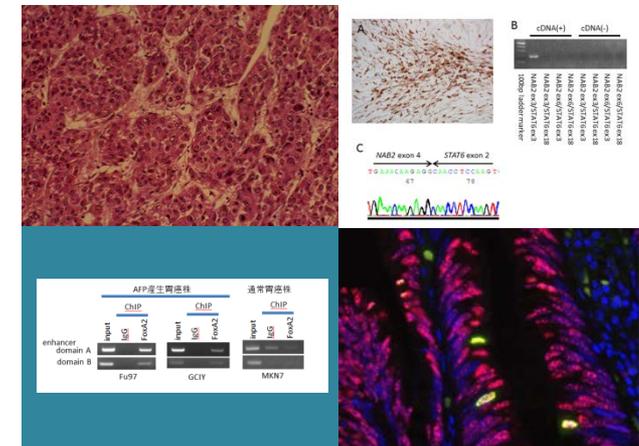
◆ Research & Education

1. Experimental pathology

- Molecular analysis of AFP-producing adenocarcinoma
- Tumor differentiation and transdifferentiation

2. Histopathological analysis

- Pancreatobiliary diseases
- AFP-producing tumors and hepatoid adenocarcinoma



◆ Recent Publications

1. Tanaka K, Kishimoto T, Ohtsuka M, Nakatani Y, Miyazaki M. Importance of NAB2-STAT6 Fusion in the Diagnosis of Pancreatic Solitary Fibrous Tumor with Hamartoma-Like Features: A Case Report and Review of the Literature. *Case Rep Pathol* 2015;2015:149606.
2. Kishimoto T, Fugo K, Kiyokawa T. Intracellular position of G2/M-phase nuclei in neoplastic and non-neoplastic pseudostratified glands suggests the occurrence of interkinetic nuclear migration. *Med Mol Morphol.* 2013;46:210-6
3. Yamamura N, Kishimoto T. Epigenetic regulation of GATA4 expression by histone modification in AFP-producing gastric adenocarcinoma. *Exp Mol Pathol.* 2012;93:35-39.

General Surgery



◆ Overview

Our laboratory is conducting research aiming at improving the performance of hepatobiliary, pancreas, breast mainly for surgical resection. Especially in the hepatobiliary pancreatic area, aggressive surgical resection of malignant tumor disease has been carried out, and the outcome of treatment has been improved. By clarifying the mechanism of postoperative complications, we have developed perioperative management including safer resection method and perioperative nutritional management. We have also reported improvement in treatment outcome by multidisciplinary treatment combined with other therapies such as chemotherapy. On the other hand, we are promoting transplantation therapy focusing on liver transplantation for liver diseases that can not be compensated. We also studied how to improve the patient's quality of life by carrying out breast-conserving surgery which reduces the range of resection without losing curability in the region of the breast. Through such research, we have reported a number of research results, based on the number of surgical operations in Japan, and contribute to improvement of the treatment outcome of diseases in this area.

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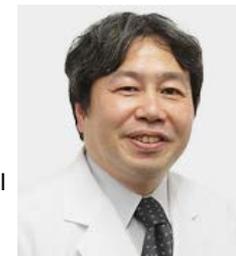
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◆ Research & Education

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

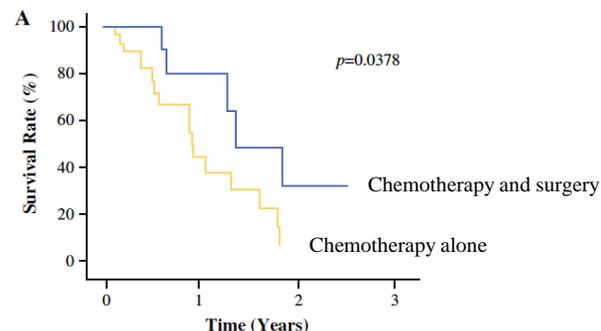
Cellular and organ regeneration after transplantation

3. Breast and thyroid surgery

Diagnostic strategy for breast and thyroid tumors

Surgical strategy for breast and thyroid tumors

Downsizing Chemotherapy for Initially Unresectable Locally Advanced Biliary Tract Cancer Patients Treated with Gemcitabine Plus Cisplatin Combination Therapy Followed by Radical Surgery.



◆ Recent Publications

- A New Proposal of Criteria For the Future Remnant Liver Volume in Older Patients Undergoing Major Hepatectomy For Biliary Tract Cancer. Watanabe Y, Kuboki S, Shimizu H, Ohtsuka M, Yoshitomi H, Furukawa K, Miyazaki M. Ann Surg 2016 (in press)
- Peripheral portal vein-oriented non-dilated bile duct puncture for percutaneous transhepatic biliary drainage. Shimizu H, Kato A, Takayashiki T, Kuboki S, Ohtsuka M, Yoshitomi H, Furukawa K, Miyazaki M. World J Gastroenterol. 2015; 21:12628-34.
- Incidence, risk factors, and management options for portal vein thrombosis after hepatectomy: a 14-year, single-center experience. Kuboki S, Shimizu H, Ohtsuka M, Kato A, Yoshitomi H, Furukawa K, Takayashiki T, Takano S, Okamura D, Suzuki D, Sakai N, Kagawa S, Miyazaki M. Am J Surg. 2015; 210:878-85.
- Expression of cell polarity protein scribble differently affects prognosis in primary tumor and lymph node metastasis of breast cancer patients. Sakakibara J, Sakakibara M, Shiina N, Fujimori T, Okubo Y, Fujisaki K, Nagashima T, Sangai T, Nakatani Y, Miyazaki M. Breast Cancer. 2016 (in press).

Molecular Infectiology



◆ 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 infectiology as well as the cultivation of excellent next-generation researchers, educators, and physicians as our important missions.

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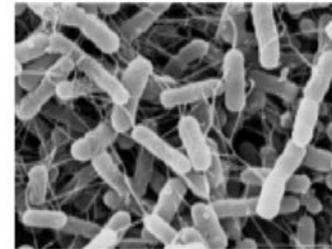


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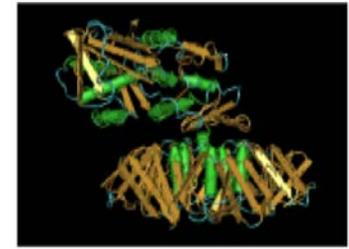


◆ Research & Education

1. The study on the mode of action of Shiga 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., K. Ichimura, M. Noda. 2016. The surface sensor NlpE of enterohemorrhagic *Escherichia coli* contributes to regulation of the type III secretion system and flagella by the Cpx response to adhesion. *Infect. Immun. Immun.*, 84, 537-549.
- Yahiro, K., T. Hirayama, J. Moss, M. Noda. 2016. New Insights into VacA intoxication mediated through its cell surface receptors. *Toxins* 8, 152.
- Shimizu, T., Hirai, S., Yokoyama, E., Ichimura, K., M. Noda. 2015. An evolutionary analysis of nitric oxide reductase gene *norV* in enterohemorrhagic *Escherichia coli* O157. *Infect. Genet. Evol.*, 33, 176-181.
- Yahiro, K., Y. Akazawa, M. Nakano, H. Suzuki, J. Hisatune, H. Isomoto, J. Sap, M. Noda, J. Moss, T. Hirayama. 2015. *Helicobacter pylori* VacA induces apoptosis by accumulation of connexin 43 in autophagic vesicles via a Rac1/ERK-dependent pathway. *Cell Death Discovery*. 1:15035.

Molecular Virology



◆ 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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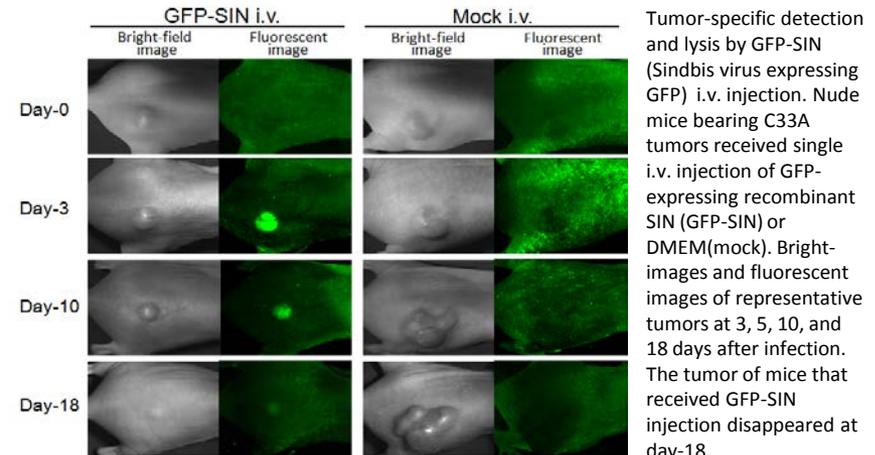
◆ Research & Education

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 protein
3. Hepatitis viruses

Education

1. Virology for medical students
2. Medical Science Research for medical students



◆ Recent Publications

- Free fatty acids or high-concentration glucose enhances hepatitis A virus replication in association with a reduction in glucose-regulated protein 78 expression. Nwe Win N, Kanda T, Nakamura M, Nakamoto S, Okamoto H, Yokosuka O, Shirasawa H. *Biochem Biophys Res Commun.* 2016; S0006-291X(16)32124-6.
- Effect of Hepatitis C Virus Genotype 1b Core and NS5A Mutations on Response to Peginterferon Plus Ribavirin Combination Therapy. Nakamoto S, Imazeki F, Arai M, Yasui S, Nakamura M, Haga Y, Sasaki R, Kanda T, Shirasawa H, Yokosuka O. *Int J Mol Sci.* 2015;16:21177-90.
- Alteration of cell cycle progression by Sindbis virus infection. Yi R, Saito K, Isegawa N, Shirasawa H. *Biochem Biophys Res Commun.* 2015;462:426-32.
- 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.

Infection and Host Defense



◆ Overview

We aim to eradicate infectious diseases caused by intracellular parasites, such as *Toxoplasma gondii* and *Plasmodium falciparum*, by understanding their pathogenesis and biology. *Toxoplasma* can infect to multiple organs and cause lesions on each region. In our laboratory, we analyze molecular and biological mechanisms of ocular lesion. In addition, we have received requests of PCR diagnosis of congenital and acquired toxoplasmosis from hospitals all over Japan. Using these specimens, we are uncovering molecular epidemiology of toxoplasmosis in Japan. In study of malaria parasites, we analyze parasite mitochondria and their genome in order to elucidate mechanisms of the emergence of antimalarial drug resistance.

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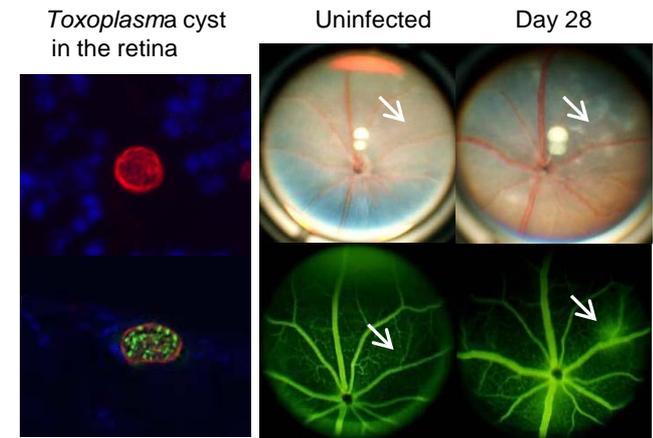
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◆ Research & Education

1. Analysis of pathogenesis of toxoplasmosis
 - Toxoplasmosis in the eyes (right figures) and the heart
 - Roles of adhesion molecules, cytokine and chemokine networks that regulate the protective and pathological immune responses after *T. gondii* infection.
 - Toxoplasmosis in the gut
 - Roles of Peyer's patches of the Invasion and stage conversion mechanisms
2. Analysis of mitochondrial function of protozoan parasites
 - Mechanisms of resistance for antimalarial drug targeting parasite mitochondria
 - Function of a monocarboxylic acid transporter of *Plasmodium*
 - A role of the TCA cycle of *Cryptosporidium*
3. Research for clinical parasitology
 - Development of a novel diagnosis method of toxoplasmosis
 - Investigation of congenital and acquired toxoplasmosis in Japan
 - Phylogenetic analysis of *Toxoplasma* isolated from human in Japan
4. Education about medical parasitology for medical students

Murine model of ocular toxoplasmosis



◆ Recent Publications

1. Belal US, Norose K, Mohamed RM, Sekine S, Nukaga T, Ito K, Abdellatif MZ, Abdelgelil NH, Yano A. Quantitative assessment of the effects of sulfamethoxazole on *Toxoplasma gondii* loads in susceptible WT C57BL/6 mice as an immunocompetent host model. *Parasitol Int* 65(1):1-4, 2016.
2. Hikosaka K, Hirai M, Komatsuya K, Ono Y, Kita K. Lactate retards the development of erythrocytic stages of the human malaria parasite *Plasmodium falciparum*. *Parasitol Int* 64(3):301-303, 2015
3. Kikumura A, Ishikawa T, Norose K. Kinetic analysis of cytokines, chemokines, chemokine receptors and adhesion molecules in murine ocular toxoplasmosis. *Br J Ophthalmol* 96:1259-1267, 2012.

Reproductive Medicine



◆ 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, development of preventive measure of endometrial cancer, molecular diagnosis of hereditary endocrine diseases.

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◆ Research & Education

1. Biomarkers for decision making of intermittent debulking surgery.
2. Molecular carcinogenesis of ovarian cancer and its therapeutic application.
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 diagnosis of hydatidiform mole.
6. Epigenetic control of trophoblastic invasion to myometrium.
7. Cohort study of trophoblastic disease at Chiba prefecture.
8. Genetic diagnosis of endocrine diseases.
9. Establishment of a fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer.
10. Prevention of neonatal brain damage.

◆ Recent Publications

- Phase II study of medroxyprogesterone acetate plus metformin as a fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer. Mitsuhashi A, Sato Y, Kiyokawa T, Koshizaka M, Hanaoka H, Shozu M. *Ann Oncol* 27:262-6, 2016
- Comparison Between Pathological Diagnosis and Cytogenetic Diagnosis by Short Tandem Repeat Polymorphism Analysis of Suspected Molar Pregnancies. Usui H, Kiyokawa T, Qu J, Nishikimi K, Tate S, Mitsuhashi A, Nakatani Y, and Shozu M. *J Reprod Med* 61: 219-223, 2016
- Elevated serum progesterone levels in postmenopausal women with mucinous ovarian tumors. Matsuoka A, Tate S, Nishikimi K, Ishikawa H, and Shozu M. *Menopause* 23: 544-549, 2016

Urology



◆ 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 and robotic surgeries.

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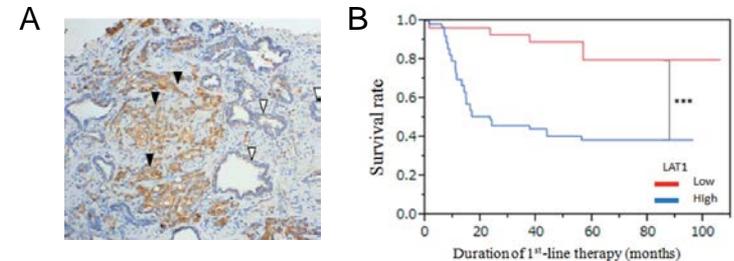
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◆ Research & Education

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



- A. A representative image shows LAT1 IHC expression in PC biopsy specimens. Black arrowheads indicate Gleason pattern 4. (Xu M. et al. J Urol 2016)
- B. Kaplan-Meier analysis of PSA recurrence-free survival by LAT1 and AR expression in LAT1 high and low. (Xu M. et al. J Urol 2016)

◆ Recent Publications

- “Regulation of E3 ubiquitin ligase-1 (WWP1) by microRNA-452 inhibits cancer cell migration and invasion in prostate cancer.” Goto Y, Kojima S, Kurozumi A, Kato M, Okato A, Matsushita R, Ichikawa T, Seki N. *Br J Cancer*. 2016 May 10;114(10):1135-44.
- “Up-Regulation of LAT1 during Antiandrogen Therapy Contributes to Progression in Prostate Cancer Cells.” Xu M, Sakamoto S, Matsushima J, Kimura T, Ueda T, Mizokami A, Kanai Y, Ichikawa T. *J Urol*. 2016 May;195(5):1588-97.
- “Nadir Testosterone after Long-Term Followup Predicts Prognosis in Patients with Prostate Cancer Treated with Combined Androgen Blockade.” Kamada S, Sakamoto S, Ando K, Muroi A, Fuse M, Kawamura K, Imamoto T, Suzuki H, Nagata M, Nihei N, Akakura K, Ichikawa T. *J Urol*. 2015 Nov;194(5):1264-70.

Molecular Diagnosis

◆ Overview

Upon technical innovations of big-data as well as omix analysis, the cutting-edge technologies such as single-cell sequencing and genome-editing system is emerging a big paradigm shift in the field of molecular biology and diagnosis. This is bonafide a kind of molecular biological movement of the Renaissance to answer the question of 120 years ago “D'où Venons Nous Que Sommes Nous Où Allons Nous”, a testament of Paul Gauguin. These technologies enable us, not only to dynamically, qualitatively, visually and systematically understand underlying mechanisms of single gene, single molecule, single cell and their complicated networks in vivo, also to pursue the mechanistic insight into “Life, Aging, Disease and Death”, and thereby control them. Our lab organizes research projects, focusing on tumor & stem cell biology, regenerative medicine, aging as well as disease pathophysiology with the theme in molecular biology and diagnosis of “Life-Aging-Disease-Death”, based on novel technologies & methodologies.



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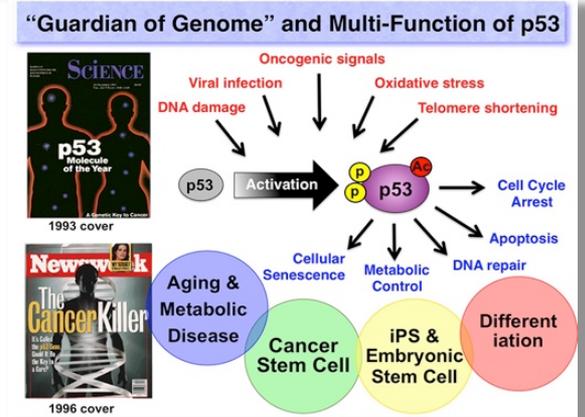
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◆ Research & Education

1. Application of omix analyses including genomics, proteomics, metabolomics and transcriptomics to elucidate the underlying mechanisms, particularly focusing on the regulatory system of transcriptional network and epigenetics for a variety of human disorders such as cancer, aging, immune disorders and life-style related disease.
2. Elucidation of role of tumor suppressor pathways and oncogenic signals as well as non-coding RNAs in the regulation of stem cell functions, nuclear reprogramming process as well as stem cell commitment & differentiation, especially for endocrine organs.
3. Application of genome-editing system using CRISPR/Cas9 in vitro & vivo, to reveal and understand the molecular pathogenesis of cancer, endocrine disorders, aging-associated & life-style-related disease including NASH (non-alcoholic steatohepatitis) and obesity.
4. Technical innovations of genetic testing & clinical sequencing as well as genetic counseling for next generation of personalized medicine.



◆ Recent Publications

1. Hashimoto N, Tanaka T. Role of miRNAs in the pathogenesis and susceptibility of diabetes mellitus. *J. Hum. Genet.* (2017) 62, 141-150.
2. Sakuma I, Higuchi S, Fujimoto M, Takiguchi T, Nakayama A, Tamura A, Kohno T, Komai E, Shiga A, Nagano H, Hashimoto N, Suzuki S, Mayama T, Koide H, Ono K, Sasano H, Tatsuno I, Yokote K, Tanaka T. Cushing syndrome due to ACTH-secreting pheochromocytoma aggravated by a glucocorticoid-driven positive-feedback loop. *J Clin Endocrinol Metab.* (2016) 101:841-846.
3. Hosokawa H, Tanaka T, Endo Y, Kato M, Shinoda K, Suzuki A, Motohashi S, Matsumoto M, Nakayama KI, Nakayama T. Akt1-mediated Gata3 phosphorylation controls the repression of IFN γ in memory-type Th2 cells. *Nat Commun.* (2016) 7: 11289.
4. Hosokawa, H, Tanaka, T, Suzuki, Y, Iwamura, C, Ohkubo, S, Endoh, K, Kato, M, Nakayama, T. Functionally distinct Gata3/Chd4 complexes coordinately establish T helper 2 (Th2) cell identity. *Proc Natl Acad Sci U S A.* (2013) 110 (12):4691-4696.

Emergency and Critical Care Medicine



◆ Overview

Our laboratory has long been interested in pathophysiology of multiple organ failure (MOF). We are particularly interested in hypercytokinemia as a mechanism underlying progression of the disease. We have established blood purification as a countermeasure against hypercytokinemia that allows us to regulate systemic inflammatory response. On the other hand, we have proposed the association of genetic polymorphisms with the clinical course of critical illnesses and necessity for precision medicine, and were also the first to identify the involvement of autophagy in sepsis. Our recent work has focused on pathophysiology of post-cardiac arrest syndrome, coagulopathy regulation, and so on. Our ultimate goal is to save the life of critically ill patient through our advanced research.

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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

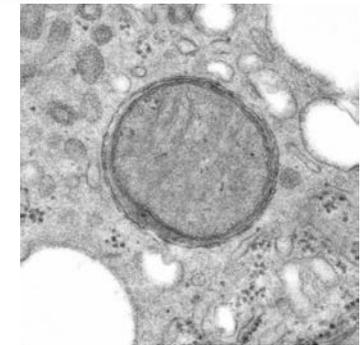
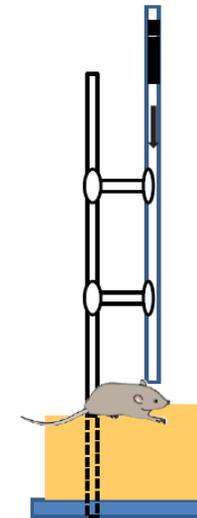
- Severity scores and evaluations for patients in intensive care units (ICUs)
- Routine serum cytokine measurements for monitoring of systemic inflammation of ICU patients
- Usefulness of acute blood purification as a countermeasure against hypercytokinemia
- Percutaneous cardiopulmonary support (PCPS) in the treatment of critically ill
- Therapeutic drug monitoring in ICU settings
- Coagulopathy in the pathophysiology of sepsis
- Mechanism of autophagy and immunoparalysis in sepsis
- Neutrophil elastase inhibitor and recombinant thrombomodulin against murine pneumonia

2. Genomics and proteomics in the critically ill to search novel biomarkers

- Heritable factors of the critically ill – Genetic variations in the critically ill patients
- mRNA expression monitoring in septic patients and post cardiac arrest syndrome (PCAS) patients
- Biomarkers of head injury (Diffuse axonal injury is induced in rats using Marmarou model; **see the right figure**→)

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

- Heart rate variability and serum biomarkers in PCAS patients



An electron microscopic view of an autophagosome in a renal tubular cell of a septic mouse (cecal ligation and punctures).

◆ Recent Publications

“Suppression of T cell autophagy results in decreased viability and function of T cells through accelerated apoptosis in a murine sepsis model.” Oami T, Watanabe E, Hatano M, Sunahara S, Fujimura L, Sakamoto A, Ito C, Toshimori K, Oda S. *Crit Care Med.* 2017; 45: e77-e85

“Pharmacokinetics of standard- and reduced-dose recombinant human soluble thrombomodulin in patients with septic disseminated intravascular coagulation during continuous hemodiafiltration.” Watanabe E, Yamazaki S, Setoguchi D, Sadahiro T, Tateishi Y, Suzuki T, Ishii I, Oda S. *Front Med.* 2017; 4: 15

“Interleukin-6 Levels Act as a Diagnostic Marker for Infection and a Prognostic Marker in Patients with Organ Dysfunction in Intensive Care Units.” Takahashi W, Nakada TA, Yazaki M, Oda S. *Shock.* 2016; 46: 254-60

Dermatology



◆ Overview

The mission of the department of dermatology in Chiba University is to provide a better environment and tools to achieve the following objectives and goals:

1. To provide the most appropriate medical treatment for patients who visit our department.
2. To help develop dermatologists with high ethical standards and responsibilities for patient care and always with skills to improve diagnostic and treatment techniques.
3. To better understand a wide range of abnormal skin conditions in addition to normal skin by cutting-edge science and ultimately to develop better treatments.

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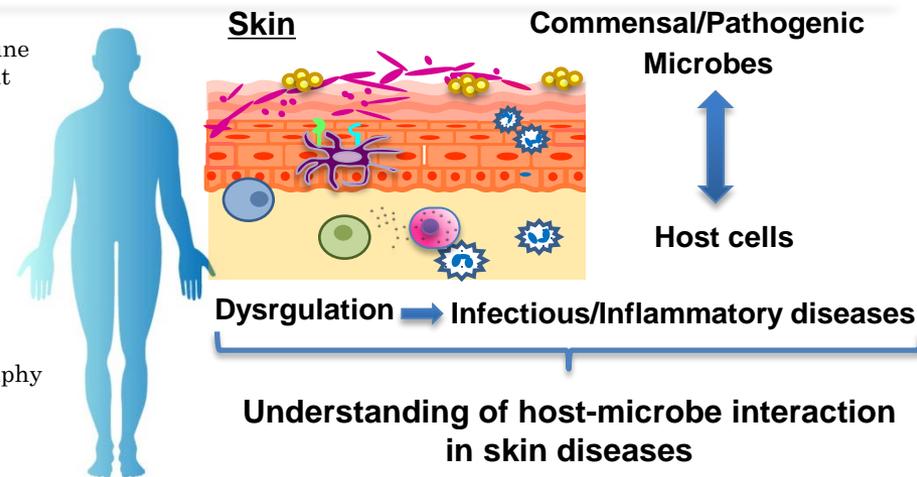


◆ Research & Education

Our research interests are to understand pathophysiological roles played by immune cells in the skin and more recently focus on roles of microbiome in the development of many skin diseases (See right figure) in addition to other interests.

Our current specific aims are:

1. Roles of microbiome in the development of atopic dermatitis
2. Analyses of molecular signals in the skin inflammation evoked by bacteria infection
3. Roles of immune cells in superficial fungal infection
4. Analyses of evolution of skin-resident bacteria that triggers skin diseases
5. Roles of macrophage and mast cells in normal and disease skin
6. Development of methods for diagnostic skills by dermoscopy and ultrasonography
7. Utilities of 3D epidermis for personalized medicine
8. Mechanisms for skin vasculitis



◆ Recent Publications

1. "Establishment of a new three-dimensional human epidermal model reconstructed from plucked hair follicle-derived keratinocytes." Nakano M, Kamada N, Suehiro K, Oikawa A, Shibata C, Nakamura Y, Matsue H. (corresponding author) et al. *Exp. Dermatol.* 2016; 25:903-909.
2. "Proliferating trichilemmal tumour: a comparison of dermoscopic, ultrasonographic and histopathological features." Miyachi H, Togawa Y, Yamamoto Y, Oguma R, Suehiro K, Matsue H. 2016; *Eur. J. Dermatol.* 26:400-402.
3. "A case of leukocytoclastic vasculitis as IgG4-related skin disease." Nakagawa S, Nakamura Y, Yasui S, Yokosuka O, Matsue H. *Clin. Exp. Derm.* 2017;42:235-236.

Pediatric Surgery



◆ Overview

Department of Pediatric Surgery challenges to clarify the clinical and basic issues in neonatology, gastroenterology, hepatology, oncology, urology, thoracic surgery, and endoscopic surgery. Our team focuses on the prompt and accurate diagnosis, and the appropriate and less-invasive treatments of the underlying disease of each child, along with the comprehensive support for their family. Our goal includes developing pediatric surgeons with appropriate techniques and proper decision-making, and who keep the underlying research in mind. We also aim to offer educational training opportunities to medical students.

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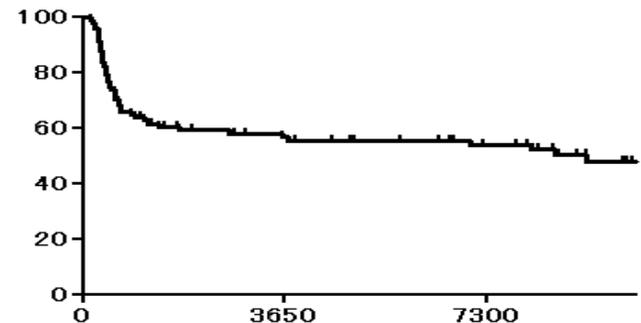
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◆ Research & Education

1. Molecular mechanism in development of pediatric malignant solid tumors
2. Immune/gene therapy for advanced neuroblastoma
3. Embryology of congenital digestive tract anomalies
4. Strategy based on prenatal assessment of the neonatal surgical diseases
5. Pathophysiology of pediatric hepatobiliary diseases
6. Management of short bowel syndrome
7. Pathogenesis and treatments of pediatric inflammatory bowel diseases
8. Abdominal imaging
9. Management of home parental nutrition
10. Applications of less-invasive endoscopic surgery
11. Development of novel surgical procedures and instruments
12. Provide academic programs to medical students and residents

Kaplan-Meier Curve for Native Liver Survival Rate (NLSR) among Biliary Atresia (BA) Patients at our Department.



Overall 10/20-year NLSRs at our institution were 57%/54%, compared to 53%/48% in Japanese BA Registry, respectively.

◆ Recent Publications

1. Saito T, Terui K, Mitsunaga T, Nakata M, Yoshida H. Significance of imaging modalities for preoperative evaluation of the pancreaticobiliary system in surgery for pediatric choledochal cyst. *J Hepatobiliary Pancreat Sci.* 2016;23:347-352.
2. Mise N, Takami M, Suzuki A, Kamata T, Harada K, Hishiki T, Saito T, Terui K, Mitsunaga T, Nakata M, Ikeuchi T, Nakayama T, Yoshida H, Motohashi S. Antibody-dependent cellular cytotoxicity toward neuroblastoma enhanced by activated invariant natural killer T cells. *Cancer Sci.* 2016;107:233-241.
3. Hishiki T, Saito T, Terui K, Mitsunaga T, Nakata M, Hayashi H, Yoshida H. Radioguided localization of neuroblastomas in laparoscopic surgery using (123)I- radiolabeled metaiodobenzylguanidine. *Pediatr Blood Cancer.* 2015;62:1297-1299.

Plastic and Reconstructive Surgery



◆ 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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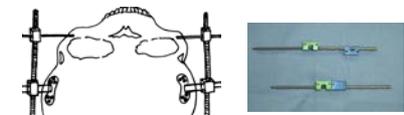


◆ Research & Education

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
 - Reconstruction 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

- Mitsukawa N, et al. Early midfacial distraction for syndromic craniosynostotic patients with obstructive sleep apnoea. J Plast Reconstr Aesthet Surg, 2013; 66:1206-1211.
- Mitsukawa N, et al. Midfacial distraction using a transfacial pinning technique for Syndromic craniosynostosis with obstructive respiratory disorders. J Plast Reconstr Aesth Surg, 2010; 63:1990-1994.
- Mitsukawa N, et al. Special distraction osteogenesis before bone grafting for alveolar cleft defects to correct maxillary deformities in patients with bilateral cleft lips and palates: distraction osteogenesis performed separately for each bone segment. J Cranio-Maxillofac Surg, 2014; 42: 623-628.
- Mitsukawa N, et al. Changing the Facial Features of Patients with Treacher Collins Syndrome: Protocol for Three-Stage Treatment for Hard- and Soft-Tissue Hypoplasia in the Upper Half of the Face. Ann Plast Surg, 2014; 73:39-42.

Bioenvironmental Medicine



◆ Overview

One of our aims is to establish the 21st century's new preventive medicine, focusing on the health of next generation. Birth cohort study will lead us to the core of the issue about possible adverse effects of environmental factors.

The another aims of this module are to provide students with the knowledge and ability to explore and gain knowledge of anatomy and biomechanics. Students will learn to describe the structure and function of the major bones, joints, muscles and soft tissue structures of the lower limb, upper limb and trunk.

◆ Research & Education

1. Birth cohort study: The Japan Environment and Children's Study (JECS), Chiba Study of Mother and Child Health (C-MACH)
2. Detection of biomarkers for chemical exposure
3. Study on the effects of environmental factors (environmental chemicals, nutrition, living environment etc.) on fetal health with omics analysis
4. Study on the preventive medicine based on the improvement of living environment
5. Risk assessment and risk management
6. Environmental education
7. Administration of Clinical Anatomy Lab (CAL)
8. Research of elbow, wrist and finger biomechanics
9. Improving surgical reconstruction techniques to enhance tendon and ligament reconstruction and nerve regeneration
10. Education of anatomy for medical students, co-medical staff and surgeons

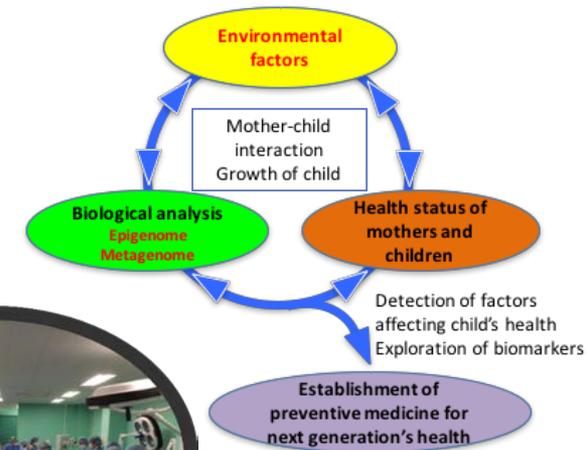
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◆ Recent Publications

- Cohort profile: Chiba study of Mother and Children's Health (C-MACH): cohort study with omics analyses. Sakurai K, Miyaso H, Eguchi A, Matsuno Y, Yamamoto M, Todaka E, Fukuoka H, Hata A, Mori C. *BMJ Open*. 2016; 6: e010531
- Associations between changes in the maternal gut microbiome and differentially methylated regions of diabetes-associated genes in fetuses: A pilot study from a birth cohort study. Tachibana K, Sakurai K, Watanabe M, Miyaso H, Mori C. *J Diabetes Investig*. 2016; doi: 10.1111/jdi.12598
- Anatomic cadaveric study of the extensile extensor digitorum communis splitting approach for exposing the ulnar coronoid process. Sukegawa K, Suzuki T, Ogawa Y, Ueno K, Kiuchi H, Knazuka A, Matsuura, Kuniyoshi K. *J Shoulder Elbow Surg*. 2016 Aug;25(8):1268-73.

Public Health



◆ Overview

We aim to identify factors for various disease development in order to find measures for prevention and treatment. In the genome-wide research of Kawasaki disease(KD), we have confirmed a total of six susceptibility genetic loci. The finding that two of them are likely involve in the Ca^{2+} /NFAT pathway prompted us to investigate possible application of Cyclosporin A in the treatment of KD. Nation-wide physician-led clinical trial is now on-going. Other projects with local government owned big data of individual health insurance claim, tax declaration, address and others have demonstrated several social determinants of health.

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◆ Research & Education

- Identification of genes relevant to Kawasaki disease (susceptibility, coronary artery complication)
- Sequence analysis of B cell receptor repertoire in Kawasaki disease patients
- Development of personalized medicine for Kawasaki disease
- Efficacy investigation of Cyclosporin A in the treatment of Kawasaki disease
- Hepatitis B virus reactivation after immunosuppressive therapy for rheumatoid arthritis
- Association between socio-economic status and access to medical care
- Spatial accessibility and utilization of health care services
- Income inequality as health determinant
- Genetic counseling
- Clinical genetics

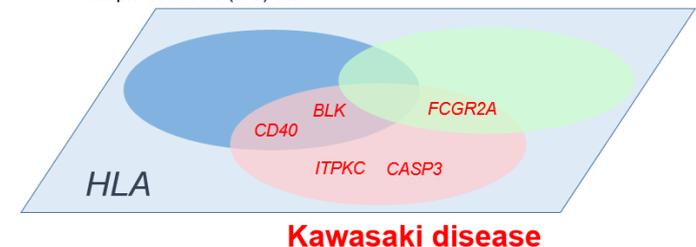
Insight into overlapping of genetic factors between KD and other immune / inflammatory diseases

Autoimmune diseases

- Rheumatoid arthritis (RA)
- Systemic lupus erythematosus (SLE)
- Multiple sclerosis (MS) etc.

Inflammatory bowel diseases

- Crohn's disease (CD)
- Ulcerative colitis (UC)



◆ Recent Publications

- Onouchi Y, Hata A et al. Variations in ORAI1 gene associated with Kawasaki disease. PLoS One. 11, e0145486, 2016.
- Fujita M, Hata A et al. Income related inequality of health care access in Japan: a retrospective cohort study. PLoS One. 15, e0151690, 2016.
- Fujita M, Hata A et al. Validity assessment of self-reported medication use by comparing to pharmacy insurance claims. BMJ Open. 9, e009490, 2015.
- Fujita M, Hata A et al. Predictive power of a body shape index for development of diabetes, hypertension, and dyslipidemia in Japanese adults: a retrospective cohort study. PLoS One. 10, e0128972, 2015.
- Onouchi Y, Hata A et al. A genome-wide association study identifies three new risk loci for Kawasaki disease. Nat Genet. 44, 517-521, 2012.
- Onouchi Y, Hata A et al. ITPKC and CASP3 polymorphisms and risks for IVIG unresponsiveness and coronary artery lesion formation in Kawasaki disease. Pharmacogenomics J. 13, 52-59, 2013..

Occupational and Environmental Medicine



◆ 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 investigations of 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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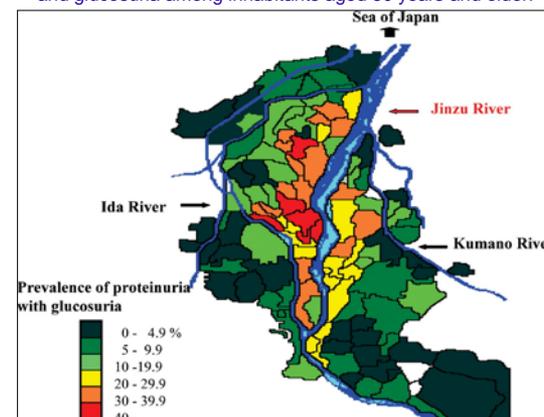
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◆ Research & Education

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.



◆ Recent Publications

Nogawa K, Suwazono Y, Ishizaki N, Aoshima K, Okamoto R, Nishijo M, Nakagawa H, Kido T. Attenuation of urinary cadmium in inhabitants of the environmentally exposed Jinzu River basin determined by applying a mixed linear model. *Bull Environ Contam Toxicol.* 2016 May;96(5):699-703.

Suwazono Y, Nogawa K, Morikawa Y, Nishijo M, Kobayashi E, Kido T, Nakagawa H, Nogawa K. All-cause mortality increased by environmental cadmium exposure in the Japanese general population in cadmium non-polluted areas. *J Appl Toxicol.* 2015 Jul;35(7):817-23.

Nogawa K, Kido T, Nishijo M, Nakagawa H, Suwazono Y. Benchmark dose of cadmium concentration in rice for renal effects in a cadmium polluted area in Japan. *J Appl Toxicol.* 2015 Jan;35(1):24-8.

Legal Medicine



◆ Overview

Legal medicine is an academic discipline in which researchers establish the causes of injury or death to utilize this knowledge for the sake of living people, with the objective of contributing to the protection of people's rights, the safety of society, and the improvement of social welfare.

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◆ Research & Education

Doctors, dentists, pharmacists, clinical laboratory technicians, and other graduate students have gained practical experience in their field while engaged in research. We are now actively recruiting as many students as possible for next year who are interested in legal medicine, while also offering seminars that build on the results of our practical work to train graduate students and other specialists from other nearby universities in addition to Chiba University. The following are some of the research topics currently under investigation by faculty and graduate students.

- Comparison of post-mortem CT and autopsy findings
- Estimation of age at death by using multidetector computed tomography images
- Age determination and DNA analysis from single tooth
- Research on illegal drugs



◆ Recent Publications

1. Torimitsu S, Makino Y, Saitoh H, Sakuma A, Ishii N, Yajima D, Inokuchi G, Motomura A, Chiba F, Yamaguchi R, Hashimoto M, Hoshioka Y, Iwase H. Sexual determination based on multidetector computed tomographic measurements of the second cervical vertebra in a contemporary Japanese population. *Forensic Sci Int.* 266, 588.e1-6, 2016.
2. Nagasawa S, Katagiri N, Nara A, Chiba F, Kubo Y, Torimitsu S, Yajima D, Akutsu M, Iwase H. Postmortem redistribution mechanism of donepezil in the rat. *Forensic Sci Int.* 266, 1-7, 2016.
3. Yamaguchi R, Makino Y, Chiba F, Torimitsu S, Yajima D, Shinozaki T, Iwase H. Fluid-Fluid Level and Pericardial Hyperdense Ring Appearance Findings on Unenhanced Postmortem CT Can Differentiate Between Postmortem and Antemortem Pericardial Hemorrhage. *AJR Am J Roentgenol.* 205(6), W568-77, 2015.

Molecular and Tumor Pathology



◆ Overview

In order to develop rational treatments and the diagnostic methods, we are going to understand pathology of disease using approaches on Molecular and Tumor biology, show principles in medicine, and be leaders to integrate heterogeneous technologies for medical innovation. Consequently, our activities are expanded to not only in oncology in life science, but also developing technologies to produce low-temperature plasma at normal atmospheric pressure, and to visualize pathophysiology in 1000-1800nm near infrared wave length, which are feasible to use for medicine in future. In such setting, we, in this department, train students in medical school and graduate school to be medical doctors and scientists in next generation.



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◆ Research

Pathology & Oncology

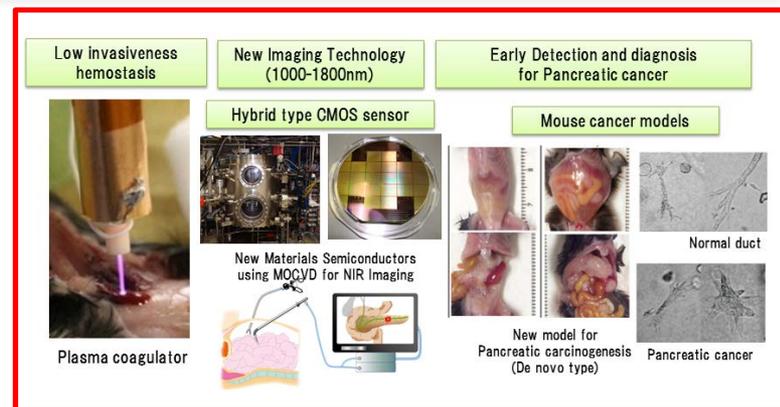
We analyze pathology to understand mechanisms of etiology and progression of disease (especially cancer) in humans. Generation of genetically-engineered mouse models that recapitulate human cancers, and immortalized cell culture from specific cells culture are basic approaches to study.

Glycobiology

We have developed new biomarkers evaluating disease progression such as liver fibrosis using glycol-proteomic approaches.

Near-Infrared Light Imaging

Based on our success to create a camera visualizing pathophysiology detected in 1000-1800nm near infrared wave length, we try to establish new diagnostic concepts using the imaging technology



◆ Recent Publications

Miyamoto K, Ikehara S, Takei H, Akimoto Y, Sakakida H, Ishikawa K, Ueda M, Ikeda J, Yamagishi M, Kim J, Yamaguchi T, Nakanishi H, Shimizu N, Hori M, Ikehara Y. Red Blood Cell Coagulation Induced by Low-temperature Plasma Treatment. *Archives of Biochemistry and Biophysics*. 2016.

Ikehara S, Sakakita H, Ishikawa K, Yamaguchi T, Kim J, Ueda M, Ikeda J, Nakanishi H, Shimizu N, Hori M, Ikehara Y, Plasma blood coagulation without involving the activation of platelets and coagulation factors. *Plasma Processes and Polymers*. 2015; 12 (12) : 1348–1353. doi: 10.1002/ppap.201500132

Yamaguchi T, Ikehara S, Nakanishi H, Ikehara Y, A genetically engineered mouse model developing rapid progressive pancreatic ductal adenocarcinoma. *The Journal of Pathology*. 2014; 234(2): 228–238

Kuno A^s, Ikehara Y^s, Tanaka Y, Ito K, Matsuda A, Sekiya S, Hige S, Sakamoto M, Kage M, Mizokami M, Narimatsu H*. A serum "sweet-doughnut" protein facilitates fibrosis evaluation and therapy assessment in patients with viral hepatitis. *Sci Rep*. 2013; 3:1065. doi: 10.1038/srep01065.

Narimatsu H*, Sawaki H, Kuno A, Kaji H, Ito H, Ikehara Y, A strategy for discovery of cancer glyco-biomarkers in serum using newly developed technologies for glycoproteomics. *FEBS Journal*. 2010; 277(1) : 95-105.

Medical Immunology



◆ 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.

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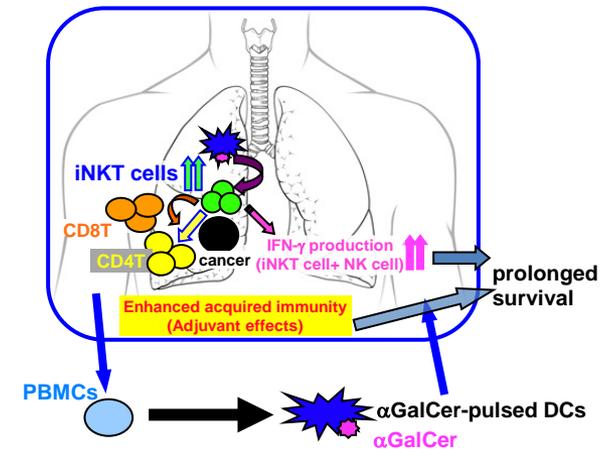
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◆ Research & Education

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 for malignant diseases
 - Lung cancer
 - Head and neck cancer
 - Other malignant neoplasm
 - Validation of cell processing procedure



◆ Recent Publications

- Kamata, T., Suzuki, A., Mise, N., Ihara, F., Takami, T., Makita, Y., Horinaka, A., Harada, K., Kunii, K., Yoshida S., Yoshino, I., Nakayama, T., Motohashi, S. Blockade of Programmed Death-1/Programmed Death Ligand pathway enhances the antitumor immunity of human invariant Natural Killer T cells. *Cancer Immunol Immunother.* 65:1477-1489 (2016)
- Mise, N., Takami, M., Suzuki, A., Kamata, T., Harada, K., Hishiki, T., Saito, T., Terui, K., Mitsunaga, T., Nakata, M., Ikeuchi, T., Nakayama, T., Yoshida, H., Motohashi, S. Antibody-dependent cellular cytotoxicity toward neuroblastoma enhanced by activated invariant NKT cells. *Cancer Sci.* 107:233-241 (2016)
- Aoki, T., Hino, M., Koh, K., Kyushiki, M., Kishimoto, H., Arakawa, Y., Hanada, R., Kawashima, H., Kurihara, J., Shimojo, N., Motohashi, S. Low Frequency of Programmed Death Ligand 1 Expression in Pediatric Cancers. *Pediatr. Blood Cancer* 63:1461-4 (2016)

Oral Science

◆ 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.

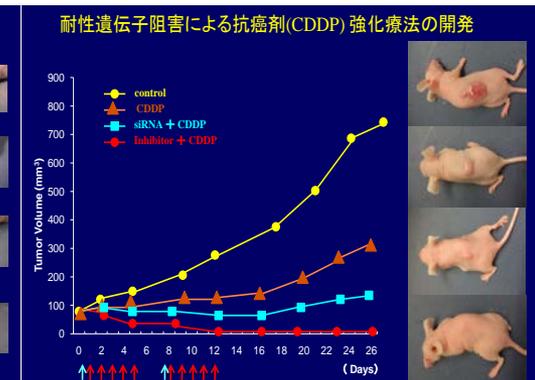
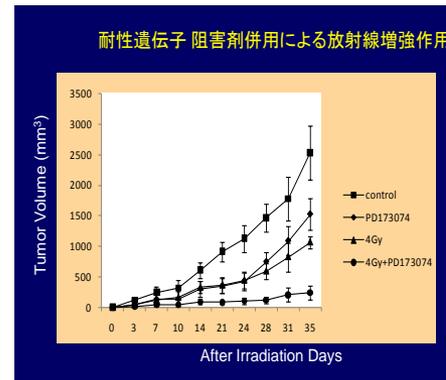


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◆ Research & Education

- 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

- Ishida S, Kasamatsu A, Endo-Sakamoto Y, Nakashima D, Koide N, Takahara T, Shimizu T, Iyoda M, Shiiba M, Tanzawa H, Uzawa K. Novel mechanism of aberrant ZIP4 expression with zinc supplementation in oral tumorigenesis. *Biochem Biophys Res Commun*. 2017 Jan 29;483(1):339-345.
- Koide N, Kasamatsu A, Endo-Sakamoto Y, Ishida S, Shimizu T, Kimura Y, Miyamoto I, Yoshimura S, Shiiba M, Tanzawa H, Uzawa K. Evidence for Critical Role of Lymphocyte Cytosolic Protein 1 in Oral Cancer. *Sci Rep*. 2017 Feb 23;7:43379.
- Yoshimura S, Kasamatsu A, Nakashima D, Iyoda M, Kasama H, Saito T, Takahara T, Endo-Sakamoto Y, Shiiba M, Tanzawa H, Uzawa K. UBE2S associated with OSCC proliferation by promotion of P21 degradation via the ubiquitin-proteasome system. *Biochem Biophys Res Commun*. 2017 Apr 15;485(4):820-825.

Oto-rhino-laryngology and Head & Neck Surgery



◆ Overview

Head and neck oncology is one of the main research fields in our department. We are aggressively performing tumor excision, as well as reconstructive surgery aiming to preserve and recover the morphology and function of the resected regions by covering the removed tissue. At the same time, we are developing treatments aimed at improving the outcomes and patients' quality of life, and are promoting clinical research into cellular immune treatment using the natural killer T-cell immune system. Basic oncology research, such as micro RNA analysis is extensively performed. 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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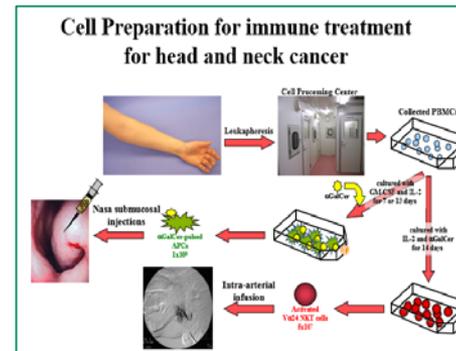
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◆ Research & Education

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. Pathophysiological study of nasal mucosa.
6. Study of functional reconstruction of head and neck cancer.
7. Diagnosis and treatment of diseases of salivary glands



Environmental challenge chamber in Chiba University



The pollen challenge test chamber to accelerate the development a new effective treatment modality.

◆ Recent Publications

1. Sakurai D, Yonekura S, Iinuma T, Sakurai T, Morimoto Y, Mita Y, Arai T, Suzuki S, Okuma Y, Kaneko S, Okamoto Y. Rhinology. 2016; 54: 221-230. Sublingual immunotherapy for allergic rhinitis: subjective versus objective tools to evaluate its success. Rhinology. 54: 221-230.
2. Horinaka A, Sakurai D, Ihara F, Makita Y, Kunii N, Motohashi S, Nakayama T, Okamoto Y. Invariant NKT cells are resistant to circulating CD15+ myeloid-derived suppressor cells in patients with head and neck cancer. Cancer Sci. 2016; 107: 207-16.
3. Endo Y, Hirahara K, Iinuma T, Shinoda K, Tumes DJ, Yamamoto H, Okamoto Y, Nakayama T. The IL-33/ST2-p38 axis confers memory Th2 cell pathogenicity in the airway. Immunity. 2015; 42: 294-308

Diagnostic Radiology & Radiation Oncology



◆ Overview

Diagnostic Radiology & Radiation Oncology consists of three sections, diagnostic imaging/interventional radiology (IVR), radiation oncology, and nuclear medicine, which includes functional imaging such as positron emission tomography (PET). In this field, there are marked advances in instruments for diagnosis and high-precision radiotherapy due to the recent remarkable progress in computer technologies as well as information and communication technology (ICT). This has resulted in a huge contribution to the progress of clinical medicine, and now the role of radiology is evolving. To achieve more advancement in radiology, it is important to introduce new generation people in this field. We welcome variety of young students interested in creating something new. This field is very open to the power and innovation of young students, allowing them to fully bloom their abilities.

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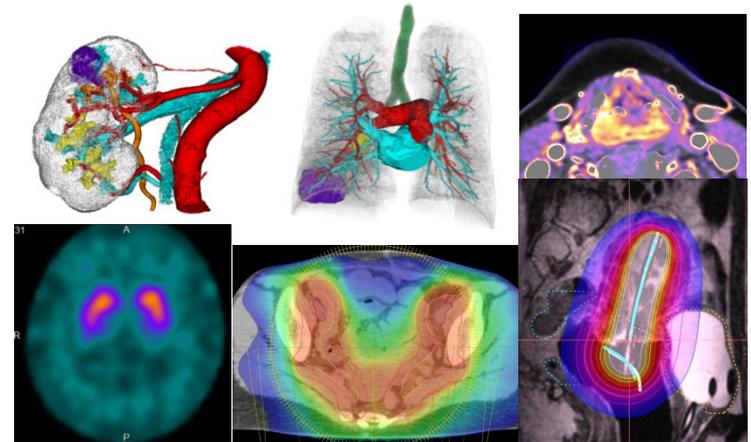
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◆ Research & Education

1. Diagnostic imaging
CT & MRI diagnosis
Angiography
2. Interventional radiology (IVR)
3. Radiation oncology
High-precision external beam radiation therapy
Image-based brachytherapy
Radiation biology
Radiation physics and dosimetry
4. Nuclear Medicine (including PET)
Functional imaging
Radionuclide targeted therapy



◆ Recent Publications

- Kurokawa M, Watanabe Nemoto M, et al. Initial experience of radiotherapy plus cetuximab for Japanese head and neck cancer patients. *J Radiat Res.* 2015;56:849-855.
- Watanabe Nemoto M, Nozaki-Taguchi N, Togasaki G, et al. New approach to relieving pain and distress during high-dose-rate intracavitary irradiation for cervical cancer. *Brachytherapy.* 2015;14:642-647.
- Mukai H, Motoori K, Horikoshi T, et al. Basal cell adenoma of the parotid gland; MR features and differentiation from pleomorphic adenoma. *Dentomaxillofac Radiol* 2016;45(4).

Medical Oncology



◆ Overview

Our activity includes 1) treatment of patients with various cancers who require chemotherapy, molecular targeted therapy and immune-checkpoint therapy, 2) clinical and translational researches of oncology, and 3) education/training of medical oncology for undergraduate and graduated students. The department provides Ph. D. course of medical oncology.

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◆ Research & Education

Research topics

- Clinical trials relating drug therapy for lung cancer.
- Clinical trials relating drug therapy for malignant mesothelioma.
- Clinical researches on rare cancers.
- Translational/clinical trials for cancer of unknown primary site.
- Basic researches relating chemo- and/or radio-resistance.
- Basic researches on epithelial-mesenchymal transition.

Education

- Undergraduate education for medical oncology and palliative care.
- Medical oncology training for graduated students and post-graduated trainees.
- Training multi-disciplinary oncology teams.

Our collaborating clinical research groups

North East Japan Study Group (NEJSG)

Thoracic Oncology Research Group (TORG)

The Tokyo Cooperative Oncology Group (TCOG)

◆ Recent Publications

1. Hida T, Nokihara H, Kondo M, Hak Kim Y, Azuma Y, Seto T, Takiguchi Y, et al. Randomised phase 3 trial of alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer. *Lancet*. 2017;(in press).
2. Sakaida E, Iwasawa S, Kurimoto R, Ebata T, Imai C, Oku T, Sekine I, Tada Y, Tatsumi K, Takiguchi Y. Safety of a short hydration method for cisplatin administration in comparison with a conventional method-a retrospective study. *Jpn J Clin Oncol*. 2016;46(4):370-377.
3. Kurimoto R, Iwasawa S, Ebata T, Ishiwata T, Sekine I, Tada Y, Tatsumi K, Koide S, Iwama A, Takiguchi Y. Drug resistance originating from a TGF-beta/FGF-2-driven epithelial-to-mesenchymal transition and its reversion in human lung adenocarcinoma cell lines harboring an EGFR mutation. *Int J Oncol*. 2016;48:1825-1836.

Medical Physiology



◆ 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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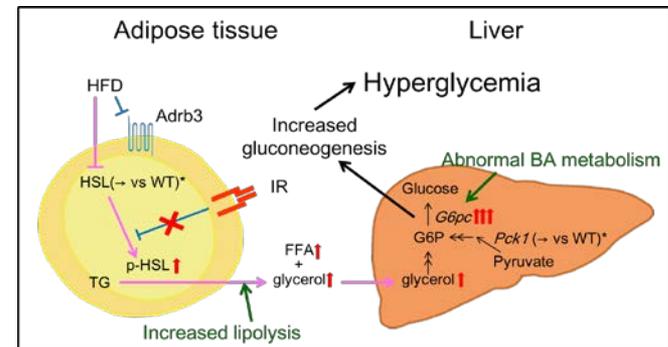
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◆ Research & Education

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

Mechanism of High Fat Diet-induced Diabetes Mellitus



Lee *et al.* Scientific Reports 5:17565, 2015

◆ Recent Publications

- “Distinct action of the α -glucosidase inhibitor miglitol on SGLT3, enteroendocrine cells, and GLP1 secretion.” Lee EY, Kaneko S, Jutabha P, Zhang X, Seino S, Jomori T, Anzai N, Miki T. (2015) *J Endocrinol* 224(3):205-14.
- “Unsuppressed lipolysis in adipocytes is linked with enhanced gluconeogenesis and altered bile acid physiology in *Insr^{P1195L/+}* mice fed high-fat-diet.” Lee EY, Sakurai K, Zhang X, Toda C, Tanaka T, Jiang M, Shirasawa T, Tachibana K, Yokote K, Vidal-Puig A, Minokoshi Y, Miki T. (2015) *Scientific Reports* 5:17565.
- “Importance of adult *Dmbx1* in long-lasting orexigenic effect of agouti-related peptide.” Hirono S, Lee EY, Kuribayashi S, Fukuda T, Saeki N, Minokoshi Y, Iwanaga T, Miki T. (2016) *Endocrinology* 157(1):245-57.

Biomedical Science



◆ 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

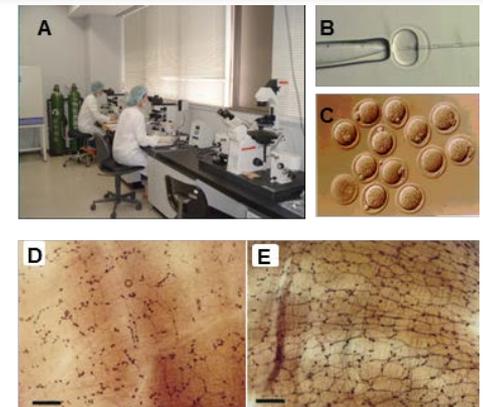
1. Generation and analysis of mouse model of human disease
2. Molecular genetics of neurocristopathy
3. Role of p38 in inflammation
4. Research on mechanism and treatment of Immune and allergic diseases using genetically modified mice

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

1. Watanabe-Takano H, Takano K, Sakamoto A, Matsumoto K, Tokuhisa T, Endo T, Hatano M. DA-Raf-dependent inhibition of the Ras-ERK signaling pathway in type 2 alveolar epithelial cells controls alveolar formation. *Proc Natl Acad Sci USA*. 2014;E2219-2300.
2. Teratake Y, Kuga C, Hasegawa Y, Sato Y, Kitahashi M, Fujimura L, Watanabe-Takano H, Sakamoto A, Arima M, Tokuhisa T, Hatano M. Transcriptional repression of p27 is essential for murine embryonic development. *Sci Rep*. 2016; 6: 26244.
3. Ogasawara T, Hatano M, Satake H, Ikari J, Taniguchi T, Tsuruoka N, Watanabe-Takano H, Fujimura L, Sakamoto A, Hirata H, Sugiyama K, Fukushima Y, Nakae S, Matsumoto K, Saito H, Fukuda T, Kurasawa K, Tatsumi K, Tokuhisa T, Arima M. Development of chronic allergic responses by dampening Bcl6-mediated suppressor activity in memory T helper 2 cells. *Proc Natl Acad Sci USA*. 2017; 114:E741-E750.
4. Umezawa H, Naito Y, Tanaka K, Yoshioka K, Suzuki K, Sudo T, Hagihara M, Hatano M, Tatsumi K, Kasuya Y. Genetic and Pharmacological Inhibition of p38 α Improves Locomotor Recovery after Spinal Cord Injury. *Front Pharmacol*. 2017; 8:72.

Developmental Biology



◆ Overview

The nervous system is essential to make human beings what they are. There are, however, still many mysteries concerning how it is built. We are focused on developmental mechanisms of the nervous system, which will provide insights into regenerative medicine to rebuild it after its damage. We are constantly working on new research projects using the latest techniques in molecular and developmental biology. We have developed the *in vivo* electroporation method in mouse embryos and identified a unique gene, *Nepro*, which is necessary for the maintenance of early neural stem cells. We have recently found a novel mechanism for controlling dendrites of neurons.



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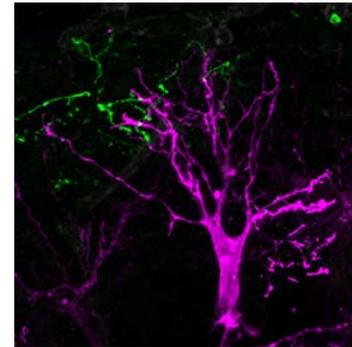
◆ Research & Education

1. Molecular mechanisms for the maintenance of early neural stem cells in the neocortex

Mammalian early neural stem cells have the potential to give rise to many types of neurons and glia. We have been studying the molecular mechanisms, which are key to utilizing multipotent neural stem cells for application, by characterizing functions of early neural stem cell-specific genes that we have found.

2. Formation and function of neural circuits

We are also interested in how neuronal subtype-specific features are determined, how neural circuits are formed and how the circuits work *in vivo* at molecular and cellular levels. We have been addressing them, using conditional gain- and loss- of-function approaches in mice.



Mitral cells (magenta) are the major projection neurons in the olfactory bulb, which receive odor information from olfactory sensory neuron axons (green). Dendrites of mitral cells are controlled by Notch signaling, which is activated by olfactory sensory neurons.

◆ Recent Publications

1. Muroyama Y, Baba A, Kitagawa M, Saito T. (2016) Olfactory sensory neurons control dendritic complexity of mitral cells via Notch signaling. *PLoS Genetics* 12, e1006514.
2. Hashimoto M, Sato T, Muroyama Y, Fujimura L, Hatano M, Saito T. (2015) *Nepro* is localized in the nucleolus and essential for preimplantation development in mice. *Develop. Growth Differ.* 57, 529-538.

Allergy and Clinical Immunology



◆ Overview

Pathological conditions of refractory allergic or autoimmune diseases are being clarified on a molecular level due to the recent progress in molecular biology. However, many patients with allergic 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 implemented, and bidirectional interactions from basic research to clinical medicine, and vice versa, are maintained. In our department, we intended to develop new therapeutic strategies for refractory autoimmune diseases and allergic diseases by optimizing the network between basic research and clinical medicine.

Professor :
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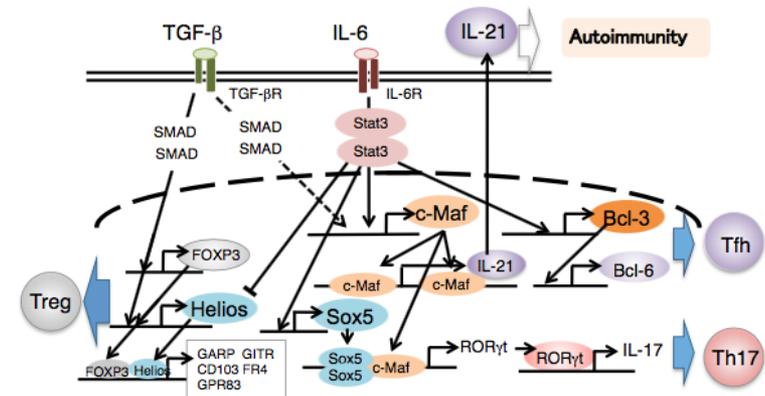


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◆ Research & Education

1. Mechanism underlying allergic inflammation in asthma
 - a) Role of IL-9-ILC2 axis in allergic airway inflammation
 - b) Role of IL-22 signaling in the regulation of allergic airway inflammation
 - c) Role of NF- κ B signaling in allergic airway inflammation
2. Molecular mechanisms of helper T cell differentiation
 - a) Role of Helios in Treg differentiation
 - b) Role of c-Maf and Sox in Th17 cell differentiation
 - c) Role of Ascl2 in Tfh cell differentiation
3. Mechanism underlying autoimmune diseases
 - a) Role of IL-21 in autoimmune myositis
 - b) Mechanism underlying lung abnormalities in patients with MPA
4. Clinical research
 - a) LoVAS study (to evaluate the effects of rituximab in initial treatment of MPA)
 - b) RAXEL study (to evaluate necessity of MTX upon Tofacitinib therapy in RA)
 - c) OPTIWIT (Use of Doppler ultrasonography of joints for drug withdrawal in RA)

Differentiation of Treg, Tfh, and Th17 cells



◆ Recent Publications

1. Tanaka S, Suto A, Iwamoto T, Kashiwakuma D, Kagami S, Suzuki K, Takatori H, Tamachi T, Hirose K, Onodera A, Suzuki J, Ohara O, Yamashita M, Nakayama T, Nakajima H. Sox5 and c-Maf cooperatively induce Th17 cell differentiation via ROR γ t induction as downstream targets of Stat3. *J Exp Med*. 2014;211(9):1857-74.
2. Nakagomi D, Suzuki K, Meguro K, Hosokawa J, Tamachi T, Takatori H, Suto A, Matsue H, Ohara O, Nakayama T, Shimada S, Nakajima H. MMP12 is produced by M2 macrophages and plays important roles in the development of contact hypersensitivity. *J Allergy Clin Immunol*. 2015;135(5):1397-400.
3. Matsuki A, Takatori T, Makita S, Yokota M, Tamachi T, Suto A, Suzuki K, Hirose K, Nakajima H. T-bet inhibits innate lymphoid cell-mediated eosinophilic airway inflammation by suppressing IL-9 production. *J. Allergy Clin Immunol*, in press.

Mucosal Immunology



◆ Overview

Our laboratory aims to clarify the whole mechanisms of intestinal immunity, which finely controls the balance between immune activation and tolerance against foreign antigens by analyzing the function of each innate immune cell existed in intestinal mucosa. Since innate immunity initiates systemic immune responses, it is one of good targets for immune regulation. We will develop immunosuppression therapies for inflammatory diseases and allergic diseases, potent cancer immune therapies and effective vaccines by targeting intestinal innate immune cells. Thus, our research goal is to control immune activation and tolerance at will. We will train graduate students to acquire proficiency in analysis of mucosal immunity, to design experiments and to write articles. Finally, we will let graduate students decide the themes by themselves and carry them out. We try to develop professional researchers who can conduct researches independently.

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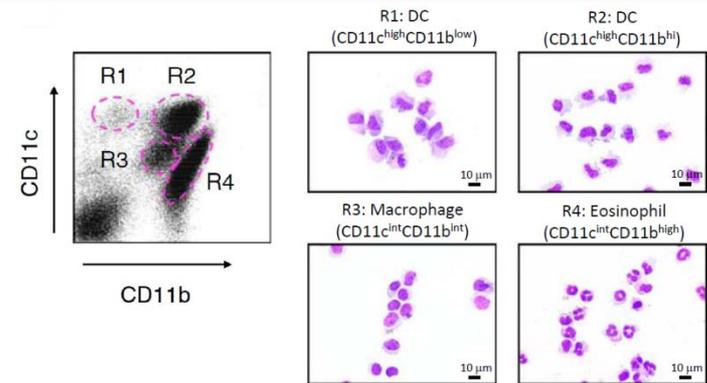
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◆ Research & Education

1. Analysis of the functions of innate immune cells in small intestinal lamina propria
 - CD11c^{high}CD11b^{low} dendritic cells (R1)
 - CD11c^{high}CD11b^{high} dendritic cells (R2)
 - CD11c^{int}CD11b^{int} macrophages (R3)
 - CD11c^{int}CD11b^{high} eosinophils (R4)
2. Investigation of the role of innate immune responses in intestinal disorders
 - Inflammatory bowel diseases
 - Radiation enteropathy
 - Allergic inflammation
3. Development of new therapeutic strategies for infectious diseases and cancer
 - Dendritic cell-based mucosal vaccine
 - Adjuvant-based mucosal vaccine
 - Generation of tumor-specific effector T cells using CRISPR/Cas9 system



We established the method to isolate lamina propria cells from small intestine and reported that innate immune cells in lamina propria are divided into 4 subsets based on the difference in CD11c/CD11b expression (Uematsu S, et al. *Nat Immunol.* 2008;9:769-76.).

◆ Recent Publications

1. Goto Y, Uematsu S, Kiyono H. Epithelial glycosylation in gut homeostasis and inflammation. *Nat Immunol.* 2016;17:1244-1251.
2. Takemura N, Uematsu S. Isolation and Functional Analysis of Lamina Propria Dendritic Cells from the Mouse Small Intestine. *Methods Mol Biol.* 2016;1422:181-8.
3. Takemura N, Kawasaki T, Kunisawa J, Sato S, Lamichhane A, Kobiyama K, Aoshi T, Ito J, Mizuguchi K, Karuppachamy T, Matsunaga K, Miyatake S, Mori N, Tsujimura T, Satoh T, Kumagai Y, Kawai T, Standley DM, Ishii KJ, Kiyono H, Akira S, Uematsu S. Blockade of TLR3 protects mice from lethal radiation-induced gastrointestinal syndrome. *Nat Commun.* 2014;5:3492.

Immunology



◆ Overview

The basic research focus in the Department is Immunology, particularly the Immunological Memory. We also conduct model studies on various diseases including chronic airway inflammation and cancers, and translational research on allergic disorders and cancers in collaboration with clinical doctors at Chiba University Hospital and researchers from RIKEN. The educational goal of the Department is to “cultivate professional researchers.” We hope to create a global research environment where we can discover principles associated with the control of immunological memory as well as present and verify new treatment concepts in translational research. Thus, we try to contribute to significant developments in immunological research through the international collaboration with the University of California, San Diego and National Institutes of Health (NIH) in the United States, and Deutsches Rheuma-Forschungszentrum Berlin in Germany. Professor Nakayama, as a program leader of the Leading Graduate School at Chiba University titled “Nurture of Creative Research Leaders in Immune System Regulation and Innovative Therapeutics”, has been attempting to cultivate global human resources by providing graduate students with stimulating and innovative programs since 2012.

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◆ Research & Education

1. Generation and Maintenance of Immune system

- 1) Generation and maintenance of memory Th1/Th2 cells
- 2) Induction and maintenance of memory-type “pathogenic” Th2 (Tpath2) cells
- 3) Immune responses and inflammation regulated by CD69
- 4) Epigenetic regulation of memory Th2 cells

2. Regulation of Allergic Airway Inflammation (Asthma, Chronic Rhinosinusitis)

- 1) Regulation of Th2-driven airway inflammation: Molecular studies in mouse models
- 2) Pathophysiology of Eosinophilic chronic rhinosinusitis (ECRS)

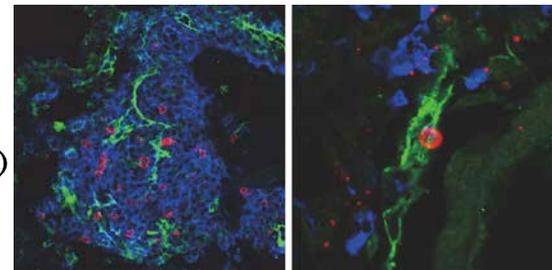
3. Regulation of Cancer by CD4 T cells

- 1) Regulation of Cancer: Molecular studies in mouse models

◆ Recent Publications

- 1) Nakayama, T., Hirahara, K., Onodera, A., et al.: Th2 cells in health and disease. *Annu. Rev. Immunol.* In press (2017).
- 2) Angela, M.,* Endo, Y.,* Asou, HK., et al.: Fatty acid metabolic reprogramming via mTOR-mediated inductions of PPARγ directs early activation of T cells. (* Contributed equally) *Nat. Commun.* 7:13683 (2016).
- 3) Hayashizaki, K.,* Kimura, M. Y.,* Tokoyoda, K.,* et al.: Myosin light chain 9 and 12 are functional ligands for CD69 that regulate airway inflammation. (* Contributed equally) *Sci. Immunol.* 1:pp.eaaf9154 (2016).
- 4) Shinoda, K., Hirahara, K., Iinuma, T., et al.: Thy1⁺IL-7⁺ lymphatic endothelial cells in iBALT provide a survival niche for memory T-helper cells in allergic airway inflammation. *Proc. Natl. Acad. Sci. USA* 113(20):E2842-51 (2016).
- 5) Hosokawa, H., Tanaka, T., Endo, Y., et al.: Akt1-mediated Gata3 phosphorylation controls the repression of IFNγ in memory-type Th2 cells. *Nat. Commun.* 7:11289 (2016).
- 6) Endo, Y., Hirahara, K., Iinuma, T., et al.: The Interleukin-33-p38 kinase axis confers memory T helper 2 cell pathogenicity in the airway. *Immunity* 42(2):294-308 (2015).

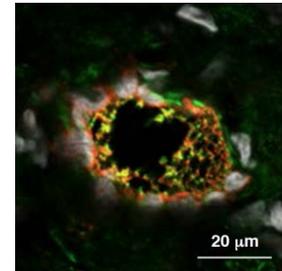
Memory Th2 cells in iBALT



MHC class II, IL-7, memory Th2 cells

Shinoda, K., et al.
Proc. Natl. Acad. Sci. USA (2016).

Polyp (ECRS)



Myl19/12
vWF

Hayashizaki, K., et al.
Sci. Immunol. (2016).

Molecular Oncology



◆ Overview

Cells have a store of basic and encrypted information to live on the genomic DNA. Cellular behavior is regulated by this modification on the genome, so-called epigenome, which includes DNA methylation and histone modification and determines genes to be or not to be utilized in each cell type. Environment could alter epigenome aberrantly, which might lead to disruption of physiological cellular function and thus cause diseases e.g. cancer, the leading cause of death in our country. It is seriously requested to accelerate a research and establish a novel strategy for development of innovative diagnostic agents and therapeutic drugs against cancer. Department of Molecular Oncology, formerly 2nd Department of Biochemistry, will therefore promote researches to elucidate critical epigenomic dysfunction and aberrant modifications to cause cancer.

Professor:
Atsushi Kaneda, M.D., Ph.D.

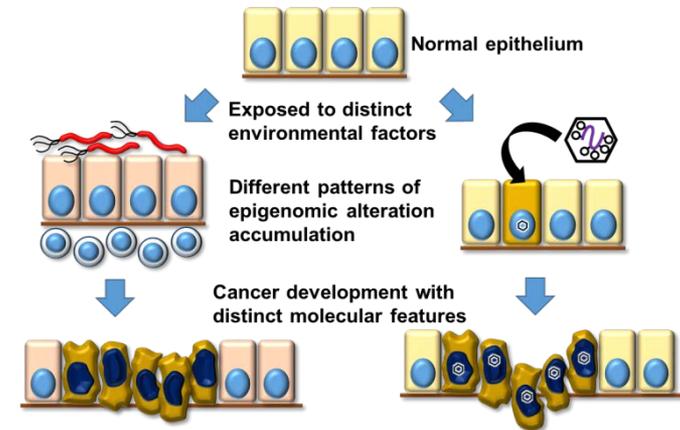


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◆ Research & Education

Cancer arises through accumulation of epigenomic and genomic aberrations, and therefore is stratified into several molecular subtypes using comprehensive epigenomic and genomic information¹. Environment could alter epigenome as Epstein-Barr virus infection induces extensive DNA hypermethylation in gastric cells including critical tumor-related genes, partly due to repression of demethylating enzyme^{2,3}. Epigenomic aberrations accumulated posteriori in apparently normal cells could causally modify tumor risk, so that therapy targeting critical epigenetic aberration would be possible. We promote researches to elucidate environmental and molecular causes for such epigenomic aberrations and genesis of tumor in each subtype, which leads to establishment of novel strategy for epigenetic cancer therapy.

For education, we are responsible for teaching metabolic biochemistry to undergraduate students. As deficiency of α -ketoglutarate interferes processes of histone and DNA demethylation and thus causes aberrant methylation, teaching the physiological pathway of glycolipid metabolism and the responsible enzymes will help medical students to understand normal and pathological cellular states.



◆ Recent Publications

1. Sakai E, Fukuyo M, Ohata K, Matsusaka K, Doi N, Mano Y, Takane K, Abe H, Yagi K, Matsushashi N, Fukushima J, Fukayama M, Akagi K, Aburatani H, Nakajima A, Kaneda A. Genetic and epigenetic aberrations occurring in colorectal tumors associated with serrated pathway. *Int J Cancer*, 138:1634, 2016.
2. Saju P, Murata-Kamiya N, Hayashi T, Senda Y, Nagase L, Noda S, Matsusaka K, Funata S, Kunita A, Urabe M, Seto Y, Fukayama M, Kaneda A, Hatakeyama M. Host SHP1 phosphatase antagonizes Helicobacter pylori CagA and can be downregulated by EBV. *Nat Microbiol*, 1:16026, 2016.
3. Namba-Fukuyo H, Funata S, Matsusaka K, Fukuyo M, Rahmutulla B, Mano Y, Fukayama M, Aburatani H, Kaneda A. TET2 functions as a resistance factor against DNA methylation acquisition during Epstein-Barr virus infection. *Oncotarget*, 7:81512-26, 2016.
4. Matsusaka K, Funata S, Fukuyo M, Seto Y, Aburatani H, Fukayama M, Kaneda A. Epstein-Barr virus infection induces genome-wide *de novo* DNA methylation in non-neoplastic gastric epithelial cells. *J Pathol*, 2017 Apr 18 epub. doi:10.1002/path.4909.

Cellular and Molecular Medicine



◆ Overview

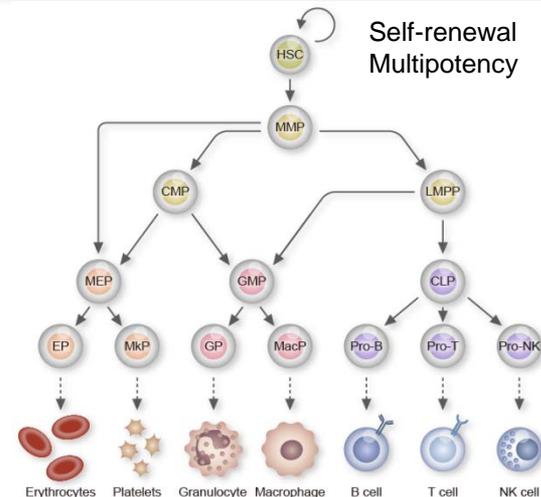
Somatic stem cells are defined as primitive cells that are capable of both self-renewal and differentiation into any of the cell lineages of a given organ. Somatic stem cells undergo cell fate decisions, including self-renewal vs. differentiation. Our main interests are the molecular mechanisms that 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 group complexes.

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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...)
Understanding of the epigenetic machinery operating in normal and cancer stem cells (ex. histone modification by the polycomb group complexes)
- 2. Stem cell-based translational research in regenerative medicine and cancer**
Expansion of cord blood HSCs *ex vivo*
Development of novel epigenetic therapy targeting hematological malignancies



◆ Recent Publications

- Hasegawa N et al. Impact of combinatorial dysfunctions of Tet2 and Ezh2 on the epigenome in the pathogenesis of myelodysplastic syndrome. **Leukemia**. Oct 21. doi: 10.1038/leu.2016.268
- Sashida G, et al. The loss of Ezh2 cooperates with an active JAK2 mutant in the pathogenesis of myelofibrosis and sensitizes tumor-initiating cells to bromodomain inhibition. **J Exp Med** 213:1459-1477, 2016.
- Koide S, et al. Setdb1 maintains hematopoietic stem and progenitor cells by restricting the ectopic activation of non-hematopoietic genes. **Blood** 128:638-649, 2016.
- Sashida G, et al. Ezh2 loss promotes development of myelodysplastic syndrome but attenuates its predisposition to leukemic transformation. **Nat Commun** 5:4177, 2014.
- Mishima Y, et al. Histone acetylation mediated by Brd1/Brpf2 is crucial for *Cd8* gene activation during early thymocyte development. **Nat Commun** 5:5872, 2014.

Bioinformatics

◆ Overview

Department of Bioinformatics was established on 1st January of 2006 with the basic principle, “For smiles of patients and their families.”

As Dr. Kenichi Fukui, a Nobel prize laureate in Chemistry who had fundamental insights into chemical reactivity, keenly indicated: With the development of the computer sciences, chemists became to use mathematical algorithms, statistics, and large databases to integrate chemical theory and modeling with experimental observations. However, chemists have to either advance theoretical methodology or contribute to new discoveries about chemical systems.

We, therefore, are working on “What is life?” by using mathematical science for both the development of basic medicine and the fulfillment of clinical medicine.



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◆ Research & Education

1. Bioinformatics: Sequence Analysis and Genome Annotation

We are working on the precision medicine by gene expression analytical technique using the next-generation sequencer.

2. Bioinformatics: Structural Biology

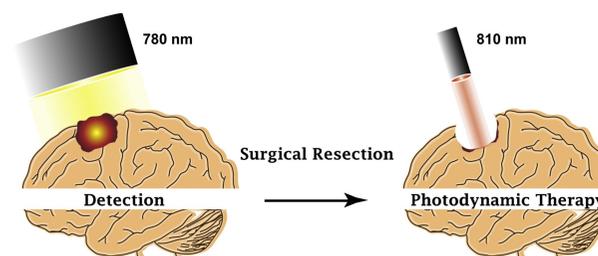
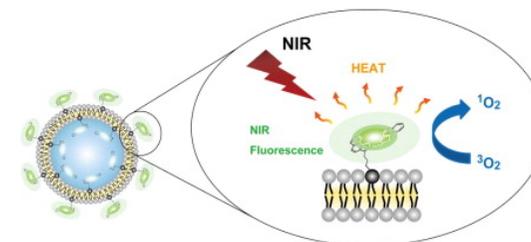
We are employing the computer simulations (molecular dynamics, electrostatic complementary, shape complementary, and quantum chemistry) to approach the elucidation of life phenomena.

3. Molecular Target Drug Discovery

- Antibody Drugs: Immunoadhesins for IL-10
- Peptide Drugs: Peptide Mimetics for NKG2D, MICA, MICB

4. Photo Induced Immunotherapy: Non-Invasive Medicine

We are trying to improve QOL and elongation of survival times of patients by the combination of LP-iDOPE, a clinically translatable fluorescent nanoparticle, with NIR fluorescence (detection and resection) and a beam (PDT) system.



◆ Recent Publications

- “Human DP and EP2 prostanoid receptors take on distinct forms depending on the diverse binding of different ligands.” Suganami A, Fujino H, Okura I, Yanagisawa N, Sugiyama H, Regan JW, Tamura Y, Murayama T. *FEBS J.* 2016 Nov;283(21):3931-3940.
- “Liposomally formulated phospholipid-conjugated indocyanine green for intra-operative brain tumor detection and resection.” Suganami A, Iwadata Y, Shibata S, Yamashita M, Tanaka T, Shinozaki N, Aoki I, Saeki N, Shirasawa H, Okamoto Y, Tamura Y. *Int J Pharm.* 2015 Dec 30;496(2):401-6.
- “Structure based functional distinction between Cln1 and Cln2 depends on the ubiquitin-proteasome pathway.” Suganami A, Takase N, Sugiyama H, Virtudazo EV, Kawamoto S, Tamura Y. *J. Proteomics Bioinform.* 2014 May; 7:102-107.

Clinical Cell Biology and Medicine



◆ Overview

Our department was formerly called the Second Department of Internal Medicine. It 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. We carry out the basic science and clinical studies covering 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. Molecular mechanism of diabetic complications: the role of transcription factors.
3. Insulin action in the liver and brain.
4. Obesity research: from molecular mechanisms to clinical trials.
5. Dyslipidemia and atherosclerosis.
6. Intracellular signaling in regulation of proliferation and apoptosis of endocrine cells.
7. Advanced research for osteoporosis and bone metabolism.
8. Generation of endocrine cells from ES/iPS cells.
9. Molecular pathogenesis and treatment of adrenal diseases.
10. Molecular mechanism of aging: pathogenesis and treatment of progeric Werner syndrome.

Hematology

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

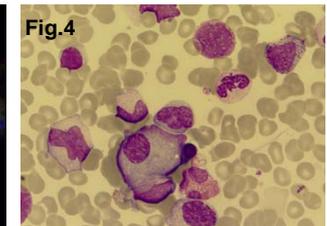
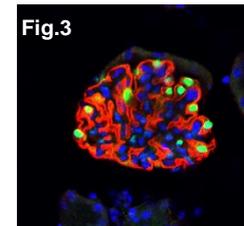
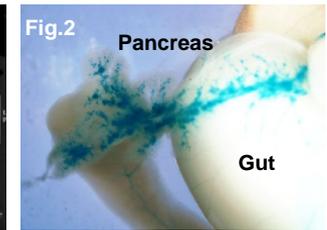
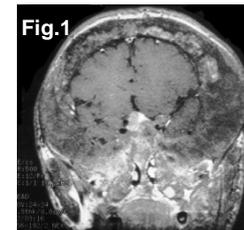


Fig.1. GH-producing pituitary adenoma in McCune-Albright syndrome.
Fig.2. Newly identified pancreatic islet gene.
Fig.3. Identification and characterization of a novel podocyte gene.
Fig.4. Bone marrow plasma cell in POEMS syndrome.

◆ Recent Publications

1. Sakuma I et al. Cushing Syndrome Due to ACTH-Secreting Pheochromocytoma, Aggravated by Glucocorticoid-Driven Positive-Feedback Loop. *J Clin Endocrinol Metab.* 2016; 101:841-846.
2. Ishibashi R et al. A novel podocyte gene, semaphorin 3G, protects glomerular podocyte from lipopolysaccharide-induced inflammation. *Sci Rep.* 2016; 6:25955.
3. Shimizu R et al. Possible role of intragenic DNA hypermethylation in gene silencing of the tumor suppressor gene NR4A3 in acute myeloid leukemia. *Leuk Res.* 2016;50:85-94.
4. Yokote et al. WRN Mutation Update: Mutation Spectrum, Patient Registries, and Translational Prospects. *Hum Mutat.* 2017;38:7-15.

Pediatrics



◆ Overview

At present there are 7 subspecialty groups in the Department of Pediatrics. We are mainly conducting research related to immunological/allergic diseases, with a central focus on clarifying the pathogenic mechanisms of allergy and therapeutic intervention, hedgehog signaling pathway and patients with its disorder, pathogenesis and epidemiology of invasive bacterial infection due to *Haemophilus influenzae* and *Pneumococcus*, clinical and basic studies of Kawasaki disease, pediatric tumors and hematological diseases, endocrinological disorders such as mineral and glucose metabolism, and all aspects of neonatology, fetal medicine and developmental biology. Intergroup collaboration is encouraged to promote research activities in our department. Collaboration with basic scientists in Chiba University and companies is one of the characteristics of our department.

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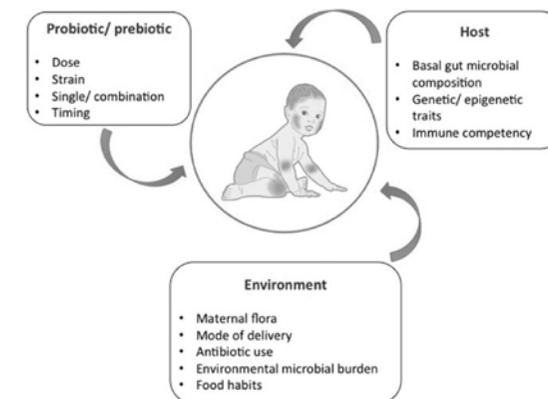


◆ Research & Education

We are doing clinical and basic research. Main research themes are;

1. Mechanism and risk factors for development of allergy
 - 1) cytokines (in blood, breast-milk, etc.), function of lymphocytes
 - 2) signal transduction and regulation of gene expression.
 - 3) birth cohort studies, viruses and environmental factors
2. Prevention and early intervention for allergic diseases
pre, pro-biotics, clinical trials of drugs, immunotherapy
3. Analysis of hedgehog signaling pathway and patients with its disorder
4. Pathogenesis and epidemiology of pneumonia and meningitis in children.
5. Kawasaki disease, congenital heart diseases and heart failure
6. Pediatric tumors and hematological diseases
7. Endocrinological disorders such as mineral and glucose metabolism
8. Neonatology, fetal medicine and developmental biology

Elucidation of factors affecting efficacy of pre/probiotics for prevention of atopic dermatitis



◆ Recent Publications

- Dissanayake E, et al. Probiotics and prebiotics in prevention and treatment of atopic dermatitis. *Pediatr Allergy Immunol Pulmonol* s2016;29:174.
- Shiohama T, et al. Brain morphology in children with basal cell carcinoma syndrome. *Am J Med Genet* 2017 in press
- Nagasawa K, et al. Congenital Rubella Syndrome: A Case Report on Changes in Viral Load and Rubella Antibody Titers. *Pediatrics*. 2016;137:e20153333
- Iwakura H, et al. Ellis-van Creveld syndrome associated with chronic intestinal pseudo-obstruction. *Pediatr Int*. 2016;58:64
- Aoki T, et al. Low Frequency of Programmed Death Ligand 1 Expression in Pediatric Cancers. *Pediatr Blood Cancer*. 2016;63:1461
- Onouchi Y, et al. Variations in ORAI1 Gene Associated with Kawasaki Disease. *PLoS One*. 2016;20:e0145486
- Takatani R, et al. Similar frequency of paternal uniparental disomy involving chromosome 20q (patUPD20q) in Japanese and Caucasian patients affected by sporadic pseudohypoparathyroidism type 1b (sporPHP1B). *Bone*. 2015;79:15

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.

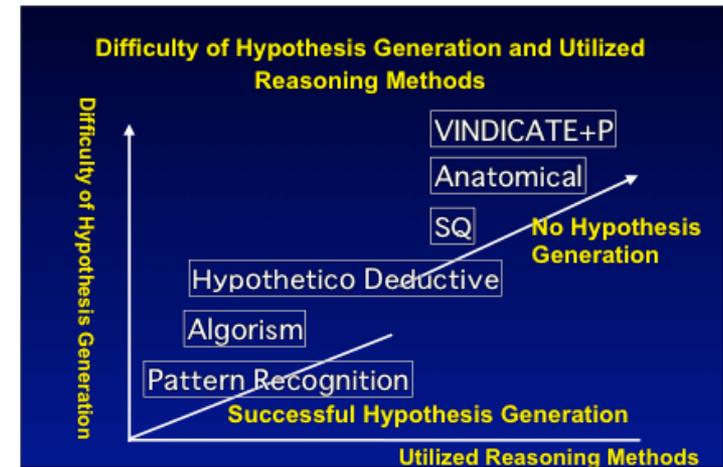
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◆ Research & Education

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 with remote diagnosis



◆ Recent Publications

Takada T, Ikusaka M, Ohira Y, et.al. Diagnostic usefulness of Carnett's test in psychogenic abdominal pain. Intern Med 2011; 50 (3) : 213-217.

Ohira Y, Ikusaka M, Noda K, et.al. Consultation behaviour of doctor-shopping patients and factors that reduce shopping. J Eval Clin Pract 2011; 18 : 433-440.

Ohta M, Ohira Y, Uehara T, et.al. How Accurate Are First Visit Diagnoses Using Synchronous Video Visits with Physicians? Telemed J E Health 2016; DOI: 10.1089/tmj.2015.0245.

Innovative Medicine



◆ Overview

The Laboratory of Innovative Medicine was founded on December 2016 through the Ministry of Education, Culture, Sports, Science and Technology's (MEXT) Leading Initiative for Excellent Young Researchers (LEADER).

Our researchers at the Laboratory of Innovative Medicine explore the roles of mucosal mesenchymal cells, including stromal cells and fibroblasts. We aim revolutionize the way the world views mesenchymal cells and discover innovative treatments for intestinal allergic and inflammatory disorders.

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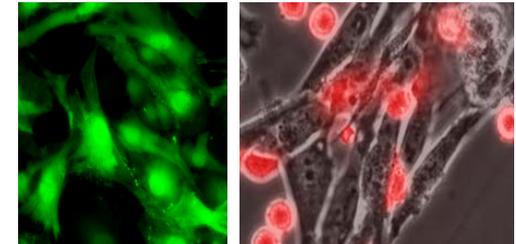
◆ Research & Education

Located at the outermost layer of the body, epithelial cells are essential our body's physical and chemical barrier against pathogens and antigens alike. However, epithelial cells require a complex support system located beneath them. **Mesenchymal cells**, traditionally known solely for their role in the production of the extracellular matrix and the support of epithelial cells, is one of these supporting cells, or structural cells.

Recently, our lab has found that these multifaceted cells are not merely just support cells, but are responsible for **peripheral education of immune cells** as well as **regulation of epithelial cell differentiation**.

In addition, alterations in these mesenchymal cell function can lead to **organ dysfunction (e.g., fibrosis)**. We hope to further elucidate these complex functions and their relation to diseases to develop a deeper understanding of mesenchymal cells.

Mesenchymal cells and immune cells interaction



Kurashima Y. et al., **Immunity**, 2014

◆ Recent Publications

Kurashima Y., Kiyono H. Mucosal ecological network of epithelium and immune cells for gut homeostasis and tissue healing. **Annual Review Immunology**. *In press*. (2017)

Nelson S., Kiyono H., Kurashima Y. Epithelial extracellular ATP: an initiator of immunity to parasitic infections. **Immunology and Cell Biology**. doi: 10.1038/icc.2016.106. (2016)

Kurashima Y., Amiya T., Fujisawa K., Shibata N., Suzuki Y., Kogure y., Hashimoto E., Otsuka A., Kabashima K., Sato S., Sato T., Kubo M., Akira S., Miyake K., Kunisawa J., and Kiyono H. Skin-barrier homeostasis through Cyp26b1-mediated inhibition of ATP-dependent mast-cell activation by fibroblasts. **Immunity**. 40(4):530-541. (2014)