Biomedical Research Activities

University of Tsukuba

Creativity
Integrity
Friendliness
Strength
Enthusiasm
Intelligence

2014

Biomedical Research Activities
University of Tsukuba

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Anatomy and Embryology

Laboratory Animal Resource Center

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Major Scientific Interests of the Group

We are working on the functional analysis of transcription factors in the body by employing developmental engineering techniques such as the generation of transgenic mice.

Projects for Regular Students in Doctoral or Master's Programs

1) Molecular mechanism of the development of pancreatic endocrine cells and macrophages. We are researching the molecular mechanisms of the development of pancreatic endocrine cells and macrophages. By analyzing the function of the large Maf family of transcription factors. In both human and mouse, four large Maf transcription factors, MafA, MafB, c-Maf and Nrl, have been identified.
2) Analysis about in vivo functions of sugar chains on molecules. In addition to these themes, we are also analyzing functions of sugar chains on molecules in vivo by using genetically manipulated mice.

Study Programs for Short Stay Students (one week ~ one trimester)

1) Histological analysis of genetically manipulated mice.
2) Handling skill for mouse embryos.

Recent Publications

1) Kudo T, Sato T, Hagiwara K, Kozuma Y, Yamagami T, Ikehara Y, Hamada M, Matsumoto K, Ema M, Murata S, Ohkohchi N, Narimatsu H, **Takahashi S.** C1galt1-deficient mice exhibit thrombocytopenia due to abnormal terminal differentiation of megakaryocytes. **Blood.** 122, 1649-1657, 2013.
2) TakaseH, Yamadera R, MatsumotoK, Kubota Y, OhtsuA, Suzuki R, KojimaT, Mochizuki H, Ishitobi H, Takano S, Uchida K, **Takahashi S,** Ema M. Genome-wide identification of vascular endothelial-specific genes during development in the mouse. **Blood.** 120, 914-923, 2012.
3) Kusakabe M, Hasegawa K, Hamada M, Nakamura M, Ohsumi T, Suzuki H, Kudo T, Uchida K, Ninomiya H, Chiba S, **Takahashi S.** c-Maf is indispensable for the microenvironment of definitive erythropoiesis as it forms erythroblastic islands in fetal liver. **Blood.** 118, 1374-1385, 2011.
4) Hishida T, Nozaki Y, Nakachi Y, Mizuno Y, Okazaki Y, Ema M, **Takahashi S,** Nishimoto M, Okuda A. Indefinite self-renewal of ES cells through Myc/Max transcriptional complexes-independent mechanisms. **Cell Stem Cell.** 9, 37-49, 2011.
5) Nishikawa K, Nakashima T, Takeda S, Isogai M, Hamada M, Kimura A, Kodama T, Yamaguchi A, Owen MJ, **Takahashi S,** Takayanagi H. Maf mediates the age-related switch in mesenchymal cell differentiation. ***J Clin Invest.*** 120, 3455-3465, 2010.

Laboratory Animal Science

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Major Scientific Interests of the Group

The aims of our research are development, characterization and quality control of genetically induced animal models for human diseases. We focus on the following research themes:

1) We are creating a variety of mice in which genes regulating blood pressure (BP) are altered. Characterization of these mice allows us to develop hypertension models as well as to evaluate unknown functions of the genes. Additionally, quantitative trait loci (QTL) mapping of BP regulating genes is in progress by using spontaneously hypertensive mice to search novel genes associated with BP regulation.
2) In order to elucidate the molecular mechanisms associated with pathogenesis of infectious agents, such as parvovirus and Helicobacter, we are analyzing the interaction between infectious agents and host genes. Additionally, we continue to develop technology for creating genetically-induced mice and to survey microbiological infection in laboratory animals.

Projects for Regular Students in Doctoral or Master's Programs

1) Development of embryonic stem cells in mice and rats.
2) Development of monoclonal antibody-based antigen detection methods for diagnosing infectious diseases in mice (such as *Helicobacter hepaticus* and murine norovirus infections).

Training Programs for Short Stay Students (one week ~ one trimester)

1) Manipulation of mouse preimplantation embryos.
2) Multiplex serologic tests for infectious diseases in mice and rats by microsphere fluorescent immunoassay.

Recent Publications

1) Feng M, Deerhake ME, Keating R, Thaisz J, Xu L, Tsaih SW, Smith R, Ishige T, **Sugiyama F,** Churchill GA, DiPetrillo K.Genetic analysis of blood pressure in 8 mouse intercross populations. **Hypertension.** 2009 Oct;54(4):802-9. Epub 2009 Aug 3.
2) Tanimoto Y, Iijima S, Hasegawa Y, Suzuki Y, Daitoku Y, Mizuno S, Ishige T, Kudo T, Takahashi S, **Kunita S, Sugiyama F, Yagami K.** Embryonic stem cells derived from C57BL/6J and C57BL/6N mice. **Comp Med.** 2008 Aug;58(4):347-52.
3) Shigematsu Y, Yoshida N, Miwa Y, Mizobuti A, Suzuki Y, Tanimoto Y, Takahashi S, **Kunita S, Sugiyama F, Yagami K.** Novel embryonic stem cells expressing tdKaede protein photoconvertible from green to red fluorescence. (**Int J Mol Med.** 2007 Oct;20(4):439-44)
4) Nishihara E, Tsaih SW, Tsukahara C, Langley S, Sheehan S, DiPetrillo K, **Kunita S, Yagami K,** Churchill GA, Paigen B, **Sugiyama F.** Quantitative trait loci associated with blood pressure of metabolic syndrome in the progeny of NZO/HILtJxC3H/HeJ intercrosses. **Mamm Genome.** 2007 Aug;18(8):573-83.
5) **Kunita S,** Chaya M, Hagiwara K, Ishida T, Takakura A, Sugimoto T, Iseki H, Fuke K, **Sugiyama F, Yagami K.** Development of ELISA using recombinant antigens for specific detection of mouse parvovirus infection. **Exp Anim.** 2006 Apr;55(2):117-24.
6) Shimizu Y, Motohashi N, Iseki H, **Kunita S, Sugiyama F, Yagami K.** A novel subpopulation lacking Oct4 expression in the testicular side population. **Int J Mol Med.** 2006 Jan;17(1):21-8.
7) Iseki H, Shimizukawa R, **Sugiyama F, Kunita S,** Iwama A, Onodera M, Nakauchi H, **Yagami K.** Parvovirus nonstructural proteins induce an epigenetic modification through histone acetylation in host genes and revert tumor malignancy to benignancy. **J Virol.** 2005 Jul;79(14):8886-93.
8) Shimizukawa R, Sakata A, Hirose M, Takahashi A, Iseki H, Liu Y, **Kunita S, Sugiyama F, Yagami K.** Establishment of a new embryonic stem cell line derived from C57BL/6 mouse expressing EGFP ubiquitously. **Genesis.** 2005 May;42(1):47-52.

Physiological Chemistry

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Major Scientific Interests of the Group

Studies on regulatory mechanisms and physiological functions of cell signaling systems, especially through the phospholipid-metabolizing enzymes and the small G protein Arf6.

Projects for Regular Students in Doctoral or Master's Programs

1) Molecular mechanisms through which the small G protein Arf6 regulates each isozyme of the lipid kinase PIP5K.
2) Physiological functions of the phospholipid-metabolizing enzymes, PIP5K and PLD, and of their regulatory protein Arf6 at cellular and whole animal levels.
3) Human diseases caused by the disruption of the signaling systems through the lipid-metabolizing enzymes and the small G protein Arf6.

Study Programs for Short Stay Students (one week ~ one trimester)

1) Enzyme assay, immunohistochemistry, and immunofluorescent staining of signaling molecules
2) Assays for cell functions such as cell proliferation, cell motility, focal adhesion, secretion, endocytosis, exocytosis, etc.

Recent Publications

1) Unoki T., Matsuda S., Kakegawa W., Van TBN., Kohda K., Suzuki A., Funakoshi Y., Hasegawa H., Yuzaki M., and Kanaho Y. NMDA receptor-mediated PIP5K activation to produce PI(4,5)P2 is essential for AMPA receptor endocytosis during LTD. ***Neuron* 73**, 135-148 (2012)
2) Nakano-Kobayashi A., Yamazaki M., Unoki T., Hongu T., Murata C., Taguchi R., Katada T., Frohman M.A., Yokozeki T. and **Kanaho Y**. Role of activation of PIP5Kg661 by AP-2 complex in synaptic vesicle endocytosis. **EMBO J.** 26, 1105-1116 (2007)
3) Suzuki T., Kanai Y., Hara T., Sasaki J., Sasaki T., Kohara M., Maehama T., Taya C., Shitara H., Yonekawa H., Frohaman M.A., Yokozeki T. and **Kanaho Y.** Crucial role of the small GTPase ARF6 in hepatic cord formation during liver development. **Mol. Cell. Biol.** 26, 6149-6156 (2006)
4) Honda A., Nogami M., Yokozeki T., Yamazaki M., Nakamura H., Watanabe H., Kawamoto K., Nakayama K., Morris A.J., Frohman M.A., and **Kanaho Y**. Phosphatidylinositol 4-phosphate 5-kinase a is a downstream effector of the small G protein ARF6 in membrane ruffle formation. **Cell** 99,521-532(1999)

Molecular Cell Biology

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Major Scientific Interests of the Group

Post-transcriptional regulation of gene expression by RNA-binding proteins
Molecular mechanism of mRNA localization and local translation regulating cell polarity, asymmetric cell division, and cell-fate
Regulation of myogenic differentiation by RNA-binding protein
Regulation of the endoplasmic reticulum stress response by protein kinases

Projects for Regular Students in Doctoral or Master's Programs

1) Post-transcriptional regulation of gene expression by Khd1, Ccr4, and Pbp1 in yeast.
2) Stability control of *MTL1* mRNA by the RNA-binding protein Khd1 in yeast.
3) Stau1 negatively regulates myogenic differentiation in C2C12 cells.
4) Regulation of the endoplasmic reticulum stress response by protein kinases

Study Programs for Short Stay Students (one week ~ one trimester)

1) Yeast genetic approaches including the isolation and characterization of mutants, tetrad analysis, complementation, and mitotic recombination.
2) Molecular genetic techniques including yeast transformation, gene knockout, and generation of mutations in cloned genes.
3) Imaging yeast cells using indirect immunofluorescence and GFP-protein fusions.

Recent Publications

1) Pbp1 is involved in Ccr4- and Khd1-mediated regulation of cell growth through association with ribosomal proteins Rpl12a and Rpl12b. Kimura Y, Irie K, **Irie K. Eukaryot Cell.** 2013 June;12(6):864-74.
2) Stau1 regulates Dvl2 expression during myoblast differentiation. Yamaguchi Y, Naiki T, **Irie K. Biochem Biophys Res Commun.** 2012 Jan 6;417(1):427-32.
3) RNA-binding protein Khd1 and Ccr4 deadenylase play overlapping roles in the cell wall integrity pathway in Saccharomyces cerevisiae. Ito W, Li X, Irie K, Mizuno T, **Irie K. Eukaryot Cell.** 2011 Oct;10(10):1340-7.
4) Stability control of MTL1 mRNA by the RNA-binding protein Khd1p in yeast. Mauchi N, Ohtake Y, **Irie K. Cell Struct Funct.** 2010;35(2):95-105.
5) hnRNP K interacts with RNA binding motif protein 42 and functions in the maintenance of cellular ATP level during stress conditions. Fukuda T, Naiki T, Saito M, **Irie K. Genes Cells.** 2009 Feb;14(2):113-28.
6) Distinct roles for Khd1p in the localization and expression of bud-localized mRNAs in yeast. Hasegawa Y, **Irie K, Gerber AP. RNA.** 2008 Nov;14(11):2333-47.
7) Stau1 negatively regulates myogenic differentiation in C2C12 cells. Yamaguchi Y, Oohinata R, Naiki T, **Irie K. Genes Cells.** 2008 Jun;13(6):583-92.

Gene Regulation

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Major Scientific Interests of the Group

Our group studies the regulation of eukaryotic gene expression, focusing on how transcription regulates cell differentiation. In particular, we are studying the roles of transcription factors and epigenetic changes in regulating iPS cell induction and adipocyte differentiation.

Projects for Regular Students in Doctoral or Master's Programs

1) Mechanistic analyses of the roles for Oct4, Sox2, Klf4 and c-myc during iPS cell induction.
2) Analyses of epigenetic mechanisms of iPS cell induction.
3) Identification and functional analyses of transcription factors involved in adipocyte commitment.
4) Role of non-coding RNA in epigenetic regulation during adipocyte differentiation.

Study Programs for Short Stay Students (one week ~ one trimester)

1) Analysis of transcriptional regulation during white and brown adipocyte differentiation.
2) Induction of iPS cells using a Sendai virus-based vector.

Recent Publications

1) Shimada M, Nakadai T, Fukuda A, **Hisatake K**. cAMP-response element-binding protein (CREB) controls MSK1-mediated phosphorylation of histone H3 at the c-fos promoter in vitro. **J. Biol. Chem.** 285, 9390-9401, 2010
2) Chen Y, Yamaguchi Y, Tsugeno Y, Yamamoto J, Yamada T, Nakamura M, **Hisatake K**, Handa H. DSIF, the Paf1 complex, and Tat-SF1 have nonredundant, cooperative roles in RNA polymerase II elongation. **Genes Dev.** 23, 2765-2777, 2009.
3) Fukuda A, Nakadai T, Shimada M, **Hisatake K**. Heterogeneous nuclear ribonucleoprotein R enhances transcription from the naturally configured c-fos promoter in vitro. **J. Biol. Chem.** 284, 23472-23480, 2009.
4) Yamagata K, Daitoku H, Takahashi Y, Namiki K, **Hisatake K**, Kako K, Mukai H, Kasuya Y, Fukamizu A. Arginine methylation of FOXO transcription factors inhibits their phosphorylation by Akt. **Mol. Cell** 32, 221-231, 2008.
5) Fukuda A, Nakadai T, Shimada M, Tsukui T, Matsumoto M, Nogi Y, Meisterernst M, **Hisatake K**. Transcriptional coactivator PC4 stimulates promoter escape and facilitates transcriptional synergy by GAL4-VP16. **Mol. Cell. Biol.** 24, 6525-6535, 2004.

Molecular Cell Physiology / Reproductive Biochemistry

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Major Scientific Interests of the Group

1. Molecular mechanisms involved in the spermatogenesis and sperm maturation in mammals
2. Signal transduction in germ cells
3. Biology of mammogenesis, milkstasis and secretion

Projects for Regular Students in Doctoral or Master's Programs

1) Proteome analysis of calcium-binding proteins expressed in the spermatogenic cells.
2) Molecular mechanisms of the sperm maturation during transit through epididymis.
3) Role of the protein tyrosine phosphorylation in capacitation.

Study Programs for Short Stay Students (one week ~ one trimester)

1) Technology for proteome analysis.
2) Assessment of mammalian sperm fertilizing activities.
3) In vitro studies on functions of monoamines in secretion.

Recent Publications

1) Osman B, **Kawashima A**, Tamba M, Satoh E, Kato Y, Iki A, Konishi K, **Matsuda M** and **Okamura N**. Localization of a Nobel RNA-binding Protein, SKIV2L2, to the Nucleus in the Round Spermatids of Mice. J. Reprod. Develop., 57, 457-467, 2011.
2) Ogushi Y, Akabane G, Hasegawa T, Mochida H, **Matsuda M**, Suzuki M, Tanaka S. Water adaptation strategy in anuran amphibians: molecular diversity of aquaporin. Endocrinology 151(1), 165-173, 2010.
3) **Kawashima A**, Osman B, Takashima M, Kikuchi A, Kohch S, Satoh E, Tamba M, **Matsuda M** and **Okamura N**. CABS1 is a novel calcium-binding protein specifically expressed in elongate spermatids of mice. Biol. Reprod.,80, 1293-1304, 2009.

Molecular Neurobiology

Principal Investigator Prof. Masayuki Masu
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Major Scientific Interests of the Group

Our main research focus is to study the molecular mechanisms that regulate the neural circuit formation and higher brain functions. Using integrative approaches including molecular biology, biochemistry, pharmacology, developmental biology, and neuroanatomy, we have been investigating how complex networks are formed in the developing brain and how the mature brain functions are acquired and regulated. We are particularly interested in the molecules that play a role in neural differentiation, cell migration, axon guidance, and synaptogenesis.

Projects for Regular Students in Doctoral or Master's Programs

1) Molecular study on neural differentiation
2) Molecular study on axon guidance
3) Molecular study on neural cell migration

Training Programs for Short Stay Students (one week ~ one trimester)

1) Immunohistochemistry
2) In situ hybridization

Recent Publications

1) Nagamine S et al. Organ-Specific Sulfation Patterns of Heparan Sulfate Generated by Extracellular Sulfatases Sulf1 and Sulf2 in Mice. **J Biol Chem** 287: 9579-9590, 2012.

2) Koike S, Yutoh Y, Keino-Masu K, Noji S, **Masu M**, and Ohuchi H. Autotaxin is required for the cranial neural tube closure and establishment of the midbrain-hindbrain boundary during mouse development. **Dev Dyn** 240: 413-421, 2011.

3) Koike S, Keino-Masu K, Ohto T, Sugiyama F, Takahashi S, and **Masu M**. Autotaxin/lysophospholipase D-mediated LPA Signaling is Required to Form Distinctive Large Lysosomes in the Visceral Endoderm Cells of the Mouse Yolk Sac. **J Biol Chem** 284: 33561-33570, 2009.

4) Okada T, Keino-Masu K, and **Masu, M**. Migration and nucleogenesis of mouse precerebellar neurons visualized by *in utero* electroporation of a green fluorescent protein gene. **Neurosci Res** 57: 40-49, 2007.

5) Keino-Masu K, **Masu M**, et al. *Deleted in Colorectal Cancer (DCC)* Encodes a Netrin Receptor. **Cell** 87: 175-185, 1996.

Medical Genetics

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Major Scientific Interests of the Group

1) Genetic study of asthma/atopic dermatitis/allergic rhinitis/food allergy. Linkage and association analyses, expression profiles from human and animal tissues
2) Identification of the disease-causing gene by next generation sequencing

Projects for Regular Students in Doctoral or Master's Programs

1) Identification of novel genomic mutations associated with asthma/atopy and development of genetic markers and therapeutic materials for personalized medicine of allergic diseases.
2) Identification of the disease-causing mutation of genetic diseases by next generation sequencers

Study Programs for Short Stay Students (one week ~ one trimester)

1) Genetic testing, genotyping, expression analyses,
2) Bioinformatics

Recent Publications

1) Imoto Y, Tokunaga T, Matsumoto Y, Hamada Y, Ono M, Yamada T, Ito Y, Arinami T, Okano M, **Noguchi E**, Fujieda S Cystatin SN Upregulation in Patients with Seasonal Allergic Rhinitis. **PLoS One** 8:e67057, 2013.
2) Inoue Y, Nakagawara R, Kambara T, Tanaka K, Seki K, Enomoto H, **Noguchi E,** Aihara M, Ikezawa Z Prevalence of atopic dermatitis in Japanese infants treated with moisturizer since birth and its relation to FLG mutations. **Eur J Dermatol** 23:288-9, 2013.
3) Kawaku S, Sato R, Song H, Bando Y, Arinami T, **Noguchi E** Functional analysis of BRCA1 missense variants of uncertain significance in Japanese breast cancer families. **J Hum Genet 2013.**
4) Hirota T, Takahashi A, Kubo M, Tsunoda T, Tomita K, Sakashita M, Yamada T, Fujieda S, Tanaka S, Doi S, Miyatake A, Enomoto T, Nishiyama C, Nakano N, Maeda K, Okumura K, Ogawa H, Ikeda S, Noguchi E, Sakamoto T, Hizawa N, Ebe K, Saeki H, Sasaki T, Ebihara T, Amagai M, Takeuchi S, Furue M, Nakamura Y, Tamari M Genome-wide association study identifies eight new susceptibility loci for atopic dermatitis in the Japanese population. **Nat Genet** 44:1222-6, 2012.
5) **Noguchi E**, Sakamoto H, Hirota T, Ochiai K, Imoto Y, Sakashita M, Kurosaka F, Akasawa A, Yoshihara S, Kanno N, Yamada Y, Shimojo N, Kohno Y, Suzuki Y, Kang MJ, Kwon JW, Hong SJ, Inoue K, Goto Y, Yamashita F, Asada T, Hirose H, Saito I, Fujieda S, Hizawa N, Sakamoto T, Masuko H, Nakamura Y, Nomura I, Tamari M, Arinami T, Yoshida T, Saito H, Matsumoto K Genome-Wide Association Study Identifies HLA-DP as a Susceptibility Gene for Pediatric Asthma in Asian Populations. **PLoS Genet** 7:e1002170, 2011.

Diagnostic Surgical Pathology

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Major Scientific Interests of the Group

1) Molecular pathology of multistep carcinogenesis
2) Studies of the initial genetic alterations of precancerous lesions and early carcinoma
3) Studies of the interactions between cancer cells and interstitial cells

Projects for Regular Students in Doctoral or Master's Programs

1) Analysis for the molecular mechanisms of pulmonary adenocarcinogenesis. Screening of the differentially expressed genes and proteins between early adenocarcinoma of the lung (*in situ* adenocarcinoma) and early advanced tumors.
2) Produce monoclonal antibodies against fetal swine to screen for specific antibodies against human carcinomas.
3) *In vitro* and *in vivo* studies of the molecular mechanisms of the reproduction of liver tissue.

Study Programs for Short Stay Students (one week ~ one trimester)

1) Basic techniques of immunohistochemistry, *in situ* hybridization, and FISH
2) Basic techniques of tissue micro-dissection

Recent Publications

1) Shiba-Ishii A and **Noguchi M**. Aberrant Stratifin overexpression is regulated by tumor-associated CpG demetylation in lung adenocarcinoma. **Am J Pathol** 180:1653-1662, 2012.
2) Tachibana K, Minami Y, Shiba-Ishii A, Kano J, Nakazato Y, Sato Y, Goya T and **Noguchi M.** Abnormality of the hepatocyte growth factor/MET pathway in pulmonary adenocarcinogenesis. **Lung Cancer** 75:181-188, 2012.
3) Satomi K, Morishita Y, Sakashita S, Kondou Y Furuya S, Minami Y and **Noguchi M**. Specific expression of ZO-1 and N-cadherin in rosette structures of various tumor: possible recapitulation of neural tube formation in embryogenesis and utility as a potentially novel immunohistochemical marker of rosette formation in pulmonary neuroendocrine tumors. **Virchow Arch** 459:399-407, 2011.
4) Li D, Sakashita S, Morishita Y, Kano J, Shiba A, Sato T and **Noguchi M**. Binding of lactoferrine to IGBP1 triggers apoptosis in a lung adenocarcinoma cell line. **ANTICANCER RESEARCH** 31:529-534, 2011.
5) Kobayashi H, Minami Y, Anami Y, Kondou Y, Iijima T, Kano J, Morishita Y, Tsuta K, Hayashi S and **Noguchi M**. Expression of the GA733 gene family and its relationship to prognosis in pulmonary adenocarcinoma. **Virchows Arch** 457:69-76, 2010.
6) Nakazato Y, Minami Y, Kobayashi H, Satomi K, Anami Y, Tsuta K, Tanaka R, Okada M, Goya T and **Noguchi M**. Nuclear Grading of Primary Pulmonary Adenocarcinomas -Correlation of nuclear size with prognosis-. **Cancer** 116:2011-2019, 2010.
7) Anami Y, Iijima T, Suzuki K, Yokota J, Minami Y, Kobayashi H, Satomi K, Nakazato Y, Okada M and **Noguchi M**. Bronchioloalveolar carcinoma (lepidic growth) component is a more useful prognostic factor than lymph node metastasis. **J Thorac Oncol** 4:951-8, 2009.

Experimental Pathology

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Major Scientific Interests of the Group

Experimental studies, using murine models and cultured cells, for elucidation of the roles of transforming growth factor-β related molecules in stem cell biology, tissue formation and carcinogenesis. Our aim is to establish novel molecular targeting therapies useful for the prevention of cancer.

Projects for Regular Students in Doctoral or Master's Programs

1) Molecular mechanisms of TGF-β related molecules (TMEPAI, MafK, Gpnmb etc.) in stem cell maintenance and carcinogenesis using gene-manipulated mice and three dimensional histopathological analysis.
2) Molecular mechanisms of TGF-β related molecules (THG-1) in squamous cell carcinoma formation

Study Programs for Short Stay Students (one week ~ one trimester)

1) Pathological tissue preparation, Immunohistochemistry and 3D reconstruction
2) In vitro tumorigenic assays (cell proliferation, sphere forming assay, scratch assay, matrigel invasion assay, 3D culture invasion assay etc.)

Recent Publications

1) Okita Y, Kamoshida A, Suzuki H, Itoh K, Motohashi H, Igarashi K, Yamamoto M Ogami T, Koinuma D, and **Kato M**. Transforming Growth Factor-β induces transcription factors MafK and Bach1 to suppress expression of the heme oxygenase-1 gene. J. Biol Chem, 288: 20658-20667, 2013.
2) Itoh F, Itoh S, Adachi T, Ichikawa K, Matsumura Y, Takagi T, Festing M, Watanabe T, Weinstein M, Karlsson S, and **Kato M**. Smad2/Smad3 in endothelium is indispensable for vascular stability via S1PR1 and N-cadherin expressions. **Blood** 119: 5320-5328, 2012.
3) Watanabe Y, Itoh S, Goto T, Ohnishi E, Inamitsu M, Itoh F, Satoh K, Wiercinska E, Yang W, Shi L, Tanaka A, Nakano N, Mommaas AM, Shibuya H, ten Dijke P and **Kato M**. TMEPAI, a transmembrane TGF-β-inducible protein, sequesters Smad proteins from active participation in TGF-β signaling. **Mol. Cell** 37: 123-134, 2010.
4) Nakano N, Itoh S, Watanabe Y, Maeyama K, Itoh F, and **Kato M**. Requirement of TCF7L2 for TGF-β-dependent transcriptional activation of the TMEPAI gene. **J Biol Chem**. 285: 38023-38033, 2010.
5) Tanaka A, Itoh F, Takezawa T, Itoh S and **Kato M**. bHLH Protein E2-2 inhibits VEGFR2 expression and blocks endothelial cell activation. **Blood**, 115: 4138-4147, 2010.
6) Shi L, Itoh F, Itoh S, Takahashi S, Yamamoto M and **Kato M**. Ephrin-A1 promotes the malignant progression of intestinal tumors in *Apc*$^{min/+}$ mice. **Oncogene** 27(23): 3265-3273, 2008.

Kidney and Vascular Pathology

Principal Investigator Prof. Michio Nagata
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Major Scientific Interests of the Group

Kidney pathology is the main issue in our group.

Current interests include podocyte pathology, pathophysiology of FSGS, systemic vasculitis (ANCA-related) and cystogenesis in polycystic kidney.

Vascular pathology in chronic kidney disease is another focus in our group.

Projects for Regular Students in Doctoral or Master's Programs

1) Pathophysiology and molecular mechanisms of focal segmental glomerulosclerosis from the view of podocyte and parietal cell transdifferentiation.
2) Morphologic investigation in systemic vascular changes and kidney injury.

Training Programs for Short Stay Students (one week ~ one trimester)

1) Diagnosis of human kidney biopsy samples according to the specific interest.
2) Immunohistochemistry and molecular biologic techniques using podocyte-specific transgenic animals.

Recent Publications

1) Aita K, Yamaguchi Y, Horita S, Ohno M, Tanabe K, Fuchinoue S, Teraoka S, Toma H, **Nagata M**. Thickening of the peritubular capillary basement membrane is a useful diagnostic marker of chronic rejection in renal allografts. **Am J Transplant**. 2007 Apr;7(4):923-9.
2) Aita K, Etoh M, Hamada H, Yokoyama C, Takahashi A, Suzuki T, Hara M, **Nagata M**. Acute podocyte loss is the possible mechanism of heavy proteinuria in preeclampsia. **Nephron Clin Prac** 2009;112(2):c65-70.
3) Suzuki T, Matsusaka T, **Nakayama M**, Asano T, Watanabe T, Ichikawa I, Nagata M. Genetic podocyte lineage reveals progressive podocytopenia with parietal cell hyperplasia in a murine model of focal segmental glomerulosclerosis. **Am J Pathol** 2009May;174(5):1675-82.
4) Sekine Y, Nishibori Y, Akimoto Y, Kudo A, Ito N, Fukuhara D, Kurayama R, Higashihara E, Babu E, Kanai Y, Asanuma K, **Nagata M**, Majumdar A, Tryggvason K, Yan K. Amino acid transporter LAT3 is required for podocyte development and function. **J Am Soc Nephrol**. 2009 Jul;20(7):1586-96
5) Kobayashi A, Goto Y, **Nagata M**, Yamaguchi Y Granular swollen epithelial cells: a histological and diagnostic marker for mitochondrial nephropathy **Am J Sur Pathol** 34: 262-70, 2010

Immunology

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Associate Professor: Satoko Tahara, Ph.D (tokothr@md.tsukuba.ac.jp) Chigusa Oda, M.D., Ph.D (chigusano@md.tsukuba.ac.jp)

Major Scientific Interests of the Group

The molecular mechanisms of tumor immunity, autoimmunity, infectious immunity and allergy and clinical applications of our basic research findings

Projects for Regular Students in Doctoral or Master's Programs

1) In vivo and in vitro function of the immunoreceptors DNAM-1, Fcα/mR, MAIR-I, MAIR-II, and Allergin-1, all of which were identified in our laboratory, in immune responses
2) The pathophysiological roles of the immunoreceptors in tumors, autoimmune diseases, allergy and infectious disease

Study Programs for Short Stay Students (one week ~ one trimester)

1) Generation of monoclonal antibodies and their application for expression analyses by flow cytometry and immunohistochemistry
2) Cell separation by sorting on flow cytometry or magnetic beads and analyses of cytokine production or proliferation upon antigen stimulation

Recent Publications

1) Nakahashi-Oda C, Tahara-Hanaoka S, Shoji M, Okoshi Y, Nakano-Yokomizo T, Ohkohchi N, Yasui T, Kikutani H, Honda S, Shibuya K, Nagata S, Shibuya A. Apoptotic cells suppress mast cell inflammatory responses via the CD300a immunoreceptor. ***J. Exp. Med.*** in press (2012)
2) Nakano-Yokomizo T, Tahara-Hanaoka S, Nakahashi-Oda C, Nabekura T, Tchao N K, Kadosaki M, Totsuka N, Kurita N, Nakamagoe K, Tamaoka A, Takai T, Yasui T, Kikutani H, Honda S, Shibuya K, Lanier L L and **Shibuya A**. The immunoreceptor adapter protein DAP12 suppresses B lymphocyte-driven adaptive immune responses. ***J. Exp. Med.*** **208**, 1661-1671, 2011.
3) Hitomi K, Tahara-Hanaoka S, Someya S, Fujiki A, Tada H, Sugiyama T, Shibayama S, Shibuya K and **Shibuya A**. An immunoglobulin-like receptor, Allergin-1, inhibits immunoglobulin E-mediated immediate hypersensitivity reactions. ***Nat Immunol.*** 11: 601-607, 2010
4) Honda S, Miyamoto A, Cho Y, Usui K, Kurita N, Takeshita K, Takahashi S, Kinoshita T, Fujita T, Tahara-Hanaoka S, Shibuya K, **Shibuya A**. Enhanced humoral immune responses against T-independent antigens in Fcα/μR-deficient mice. **Proc Natl Acad Sci USA.** 106:11230-11235, 2009

Regenerative Medicine and Stem Cell Biology

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Dr. Georgina Salazar (Assistant Professor), georgina.salazar@gmail.com

Major Scientific Interests of the Group

1) Identification and analyses of functional stem cells for cell therapy in human tissues
2) Hypoxic responses in stem cell development and tumor development

Projects for Regular Students in Doctoral or Master's Programs

1) Analysis of functional stem cells (MSC and EPC) for clinical application
2) Analysis of how hypoxic inducible factors (HIFs) are involved in stem cell development
3) Analysis of how HIFs are involved in tumor development (tumor itself and tumor endothelial cell)

♦Summer School Course (2012)♦

1) Basic Radiobiology for Mesenchymal stem cells
2) Neural Differentiation of human iPS for clinical use

Recent Publications

1) Tu T, Kimura K, Nagano M, Yamashita T, Ohneda K, Sugimori H, Sato F, Sakakibara Y, Hamada H, Yoshikawa H, Son H , and Ohneda O. Identification of human placenta-derived mesenchymal stem cells involved in re-endothelialization. **J Cell Physiol**. 2011; 226: 224-235.
2) Nagano M, Kimura K, Yamashita T, Ohneda K, Nozawa D, Hamada H, Yoshikawa H, Ochiai N, and Ohneda O. Hypoxia responsive mesenchymal stem cells derived from human umbilical cord blood are effective for bone repair. **Stem Cells and Dev.** 2010; 19: 1195-1210.
3) Yamashita T, Ohneda O, Sakiyama A, Iwata F, Ohneda K, and Fujii-Kuriyama Y. The microenvironment for erythropoiesis is regulated by HIF-2alpha through VCAM-1 in endothelial cells. **Blood** 2008; 112: 1482-1492.
4) Yamashita T, Ohneda K. Nagano M, Miyoshi C, Kaneko N, Miwa Y, Yamamoto M, Ohneda O, and Fujii-Kuriyama Y. HIF-2alpha in endothelial cells regulates tumor neovascularization through activation of ephrin A1. **J Biol Chem** 2008; 283: 18926-18936.
5) Yamashita T, Ohneda O, Nagano M, Iemitsu M, Makino Y, Tanaka H, Miyauchi H, Goto K, Ohneda K, Fujii-Kuriyama Y, Lorenz Poellinger, and Yamamoto M. Abnormal heart development and lung remodeling in mice lacking a HIF-related bHLH-PAS protein NEPAS. **Mol. Cell. Biol.** 2008; 28: 1285-1297.
6) Nagano M, Yamashita T, Hamada H, Ohneda K, Kimura K, Nakagawa T, Shibuya M, Yoshikawa H, and Ohneda O. Identification of functional endothelial progenitor cells suitable for the treatment of ischemic tissue using human umbilical cord blood. **Blood** 2007; 110: 151-160.

Biomedical Engineering

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Major Scientific Interests of the Group

The aims of our researches are development of bioartificial organs, e.g., ex vivo expansion systems of hematopoietic stem/progenitor cells, bioartificial livers, and bioartificial vascular grafts, from the viewpoint of tissue engineering.

Projects for Regular Students in Doctoral or Master's Programs

1) Effects of stromal cells on expansion of hematopoietic stem/progenitor cells in the three-dimensional (3D) cocultures of hematopoietic cells and stromal cells.
2) Effects of 3D cocultures of fetal liver cells with nonparenchymal cells on the growth and functions of fetal liver cells.
3) Influence of the properties of biomaterials on the functions of cultured vascular cells.

Study Programs for Short Stay Students (one week ~ one trimester)

1) Techniques required for 3D cocultures using porous polymer scaffolds.
2) Measurements of numbers and functions of 3D-cultured cells.

Recent Publications

1) Miyoshi H, Ohshima N, and Sato C. Three-dimensional culture of mouse bone marrow cells on stroma formed within a porous scaffold: influence of scaffold shape and cryopreservation of the stromal layer on expansion of haematopoietic progenitor cells. **J Tissue Eng Regen Med** 7: 32-38, 2013.
2) Miyoshi H, Murao M, Ohshima N, and Tun T. Three-dimensional culture of mouse bone marrow cells within a porous polymer scaffold: effects of oxygen concentration and stromal layer on expansion of haematopoietic progenitor cells. **J Tissue Eng Regen Med** 5: 112-118, 2011.
3) Miyoshi H, Ehashi T, Kawai H, Ohshima N, and Suzuki S. Three-dimensional perfusion cultures of mouse and pig fetal liver cells in a packed-bed reactor: effect of medium flow rate on cell numbers and hepatic functions. **J Biotechnol** 148: 226-232, 2010.
4) Miyoshi H, Ehashi T, Ohshima N, and Jagawa A. Cryopreservation of fibroblasts immobilized within a porous scaffold: effects of preculture and collagen coating of scaffold on performance of three-dimensional cryopreservation. **Artif Organs** 34: 609-614, 2010.
5) Koyama T, Ehashi T, Ohshima N, and Miyoshi H. Efficient proliferation and maturation of fetal liver cells in three-dimensional culture by stimulation of oncostatin M, epidermal growth factor, and dimethyl sulfoxide. **Tissue Eng A** 15: 1099-1107, 2009.

Environmental Medicine

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Major Scientific Interests of the Group

This laboratory addresses the mechanisms by which environmental chemicals causing oxidative stress and covalent modification to cellular proteins affect living systems by interacting with sensor proteins with reactive thiols (thiolate ions). The observations obtained by this group regarding environmental electrophiles have lent new insight into mechanisms of redox-dependent cellular signal transduction pathways that are negatively regulated by reactive sulfur species (e.g., hydrogen sulfide anions, persulfide and polysulfide).

Projects for Regular Students in Doctoral or Master's Programs

1) Activation of electrophilic signal transduction pathways associated with cell survival, cell proliferation and cell damage during exposure to environmental electrophiles.
2) Search for such cellular systems regulating sensor proteins covalently modified by the environmental electrophiles.

Study Programs for Short Stay Students (one week ~ one trimester)

1) Detection of cellular proteins modified by environmental electrophiles by Western blot analysis with specific antibodies against the electrophiles.
2) Proteomics analysis by using 2D-SDS/PAGE and MALDI-TOF/MS.

Recent Publications

1) Nishida M, Sawa T, Kitajima N, Ono K, Inoue H, Ihara H, Motohashi H, Yamamoto M, Suematsu M, Kurose H, Van der Vliet A, Freeman BA, Shibata T, Uchida K, **Kumagai Y**, Akaike T. Hydrogen sulfide anion regulates redox signaling via electrophile sulfhydration. **Nature Chem Biol** 8: 714-724, 2012.
2) **Kumagai Y**, Shinkai Y, Miura T, Cho AK. The chemical biology of naphthoquinones and its environmental implications. **Annu Rev Pharmacol Toxicol** 52: 221-247, 2012.
3) Toyama T, Shinkai Y, Yasutake A, Uchida K, Yamamoto M, **Kumagai Y.** Isothiocyanates reduce mercury accumulation via an Nrf2-dependent mechanism during exposure of mice to methylmercury. **Environ Health Perspect** 119: 1117-1121, 2011.
4) Yoshida E, Toyama T, Shinkai Y, Sawa T, Akaike T, **Kumagai Y.** Detoxification of methylmercury by hydrogen sulfide producing enzyme in mammalian Cells. **Chem Res Toxicol** 24: 1633-1635, 2011.
Iwamoto N, Sumi D, Ishii T, Uchida K, Cho AK, Froines JR, **Kumagai Y**. Chemical knockdown of protein tyrosine phosphatase 1B by 1,2-naphthoquinone through covalent modification causes persistent transactivation of epidermal growth factor receptor. **J Biol. Chem**. 282: 33396-33404, 2007.

Molecular and Genetic Epidemiology/ Public Health Medicine

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Major Scientific Interests of the Group

1) Genetics of human autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis and microscopic polyangiitis (Dr. Naoyuki Tsuchiya, Dr. Aya Kawasak)
2) Genetics of obesity in Oceanic islanders (Dr. Jun Ohashi)
3) Epidemiology and prevention of lifestyle-related diseases (Dr. Kazumasa Yamagishi)

Projects for Regular Students in Doctoral or Master's Programs

1) Polymorphisms associated with autoimmune diseases in Japanese (Dr. Naoyuki Tsuchiya, Dr. Aya Kawasak)
2) Polymorphisms associated with obesity in Oceanic populations (Dr. Jun Ohashi)

Study Programs for Short Stay Students (one week ~ one trimester)

Genome database (tutorial), SNP typing (laboratory), Preventive medicine activity in the community (a field trip)

Recent Publications

1) Furukawa H, Oka S, Shimada K, RA-ILD Study Consortium, **Tsuchiya N**, Tohma S. *HLA-A*31:01* and methotrexate-induced interstitial lung disease in Japanese rheumatoid arthritis patients: a multi-drug hypersensitivity marker? **Ann Rheum Dis** 2013;72:153-155.
2) Hasebe N, **Kawasaki A**, Ito I, Kawamoto M, Hasegawa M, Fujimoto M, Furukawa H, Tohma S, Sumida T, Takehara K, Sato S, Kawaguchi Y, **Tsuchiya N**. Association of *UBE2L3* polymorphisms with diffuse cutaneous systemic sclerosis in a Japanese population. **Ann Rheum Dis** 2012;71:1259-1260.
3) Hikami K, **Kawasaki A**, Ito I, Koga M, Ito S, Hayashi T, Matsumoto I, Tsutsumi A, Kusaoi M, Takasaki Y, Hashimoto H, Arinami T, Sumida T, **Tsuchiya N**. Association of a functional polymorphism in the 3' untranslated region of *SPI1* with systemic lupus erythematosus. **Arthritis Rheum** 2011;63:755-763.
4) **Ohashi J**, Naka I, **Tsuchiya N**. The impact of natural selection on an *ABCC11* SNP determining earwax type. **Mol Biol Evol** 2011;28:849-857.
5) Chei CL, **Yamagishi K**, Kitamura A, Kiyama M, Imano H, Ohira T, et al. C-reactive protein levels and risk of stroke and its subtype in Japanese: the Circulatory Risk in Communities Study (CIRCS). **Atherosclerosis** 2011;217:187-193.
6) Ito I, Kawaguchi K, **Kawasaki A**, Hasegawa M, **Ohashi J**, Kawamoto M, Fujimoto M, Takehara K, Sato S, Hara M, **Tsuchiya N**. Association of the *FAM167A-BLK* region with systemic sclerosis. **Arthritis Rheum** 2010;62:890-895.

Occupational Psychiatry / Space Medicine [#1]
Longevity medicineEndowed Chair [#2]

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Assistant Professor:Satoshi Yoshino [#1], satoshi-yoshino.gm@u.tsukuba.ac.jp

Major Scientific Interests of the Group

Environmental and occupational prevention of work-related diseases.
Empirical and epidemiological study on risk factors for work-related diseases and prevention.

Projects for Regular Students in Doctoral or Master's Programs

1) Various mental disorder patients' treatment in occupational health.
Training of psychiatric clinical ability demanded on site of industrial medicine.
2) Techniques for managing working people's mental/physical health (industrial physicians).
3) Research by use of epidemiological techniques.

Training Programs for Short Stay Students (one week ~ one trimester)

1) Health care for workers focusing on their mental health
2) Clinical psychiatry (major depressive disorder, adjustment disorder etc.)
3) Return-to-work support

Recent Publications

1) **I.Matsuzaki**, T. Sagara, Y. Ohshita, H. Nagase, K. Ogino, A. Eboshida, **S. Sasahara**, H. Nakamura : Psychological factors including sense of coherence and some lifestyles are related to General Health Questionnaire-12 (GHQ-12) in elderly workers in Japan. Environ. **Health Prev. Med**., Vol.12, 71-77, 2007

2) **S. Yoshino**, **S. Sasahara**, T. Maeno, K. Kitaoka-Higashiguchi, Y. Tomotsune, K. Taniguchi, E. Tomita, K. Usami , T. Haoka, H. Nakamura, **I. Matsuzaki**: Relationship between mental health of Japanese residents and the quality of medical service. **Journal of Physical Fitness, Nutrition and Immunology**, Vol. 17(1), 3-11, 2007

3) H. Tatsukawa, **S. Sasahara**, **S. Yoshino**, Y Tomotsune, K Taniguchi, H. Nakamura, **I. Matsuzaki**: Influence of the stress coping ability of supervisors on the stress situation of their subordinates. Journal of Physical Fitness, **Nutrition and Immunology**, Vol.15(2), 82-87, 2005

4) **Sasahara S**, **Matsuzaki I**, Nakamura H, Ozasa K, Endo T, Imai T, Honda Y, Hatta K, Ide T, Motohashi Y, Eboshida A : Environmental factors and lifestyles as risk factors for Japanese cedar pollinosis in recent urban areas. **Arch Complex Environ Studies Arch. Com. Eff. Study**, 15,20-25,2003

Radiation Biology

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Major Scientific Interests of the Group

Radiation biology is a field of medical sciences dealing with research on the biological actions of ionizing radiation on life or living things. In this field, it is essential to establish robust methods to evaluate and measure biological phenomena by physical parameters. The mission of this group is to clarify the biological characteristics of x-rays and proton beams and to improve the safety and efficacy of x-rays and proton beam radiotherapy.

Projects for Regular Students in Doctoral or Master's Programs

1) Particle beam induced DNA damage and repair,
2) Radiation induced tumor immunological reactions,
3) Biological effects of x-ray micro beams,

Study Programs for Short Stay Students (2 weeks – 6 months)

1) Cell culture techniques and basic in vitro radio sensitivity assays
2) Methods to evaluate DNA damage in cells and tissues
3) Studies on physical parameters to evaluate biological effects

Recent Publications

1) Abei M, Okumura T, Fukuda K, Hashimoto T, Araki M, Ishige K, Hyodo I, Kanemoto A, Numajiri H, Mizumoto M, Sakae T, Sakurai H, Zenkoh J, Ariungerel G, Sogo Y, Ito A, Ohno T, Tsuboi K. A phase I study on combined therapy with proton-beam radiotherapy and in situ tumor vaccination for locally advanced recurrent hepatocellular carcinoma. Radiat Oncol. 2013 Oct 16;8(1):239.
2) Suzuki K, Gerelchuluun A, Hong Z, Sun L, Zenkoh J, Moritake T, Tsuboi K. Celecoxib enhances radiosensitivity of hypoxic glioblastoma cells through endoplasmic reticulum stress. Neuro Oncol. 2013 Sep;15(9):1186-99.
3) Sun L, Moritake T, Zheng YW, Suzuki K, Gerelchuluun A, Hong Z, Zenkoh J, Taniguchi H, TsuboiK: In vitro stemness characterization of radioresistant clones isolated from a medulloblastoma cell line ONS-76. J Radiat Res. 2013 Jan;54(1):61-9.
4) Hong Z, Kase Y, Moritake T, Gerelchuluun A, Sun L, Suzuki K, Terunuma T, Yasuoka K, Kumada H, Anzai K, Sakurai H, Sakae T, TsuboiK: Lineal energy-based evaluation of oxidative DNA damage induced by proton beams and X-rays. Int J Radiat Biol. 2013 Jan;89(1):36-43.
5) Gerelchuluun A, Hong Z, Sun L, Suzuki K, Terunuma T, Yasuoka K, Sakae T, Moritake T, Tsuboi K. Induction of in situ DNA double-strand breaks and apoptosis by 200 MeV protons and 10 MV X-rays in human tumour cell lines. Int J Radiat Biol. 2011 Jan;87(1):57-70.

Infection Biology

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Assistant Professor; Shoko SAITO, Kohsuke KATO
(President Special Lab.; President Kyosuke NAGATA)

Major Scientific Interests of the Group

The research aim of this group is to understand the molecular mechanism of replication and pathogenicity of animal viruses such as influenza viruses, measles virus, adenovirus, human cytomegalovirus, etc. The structure and function of virus-encoded factors and host cell-derived factors involved in the above processes are being studied at the atomic, molecular, cellular, and body levels. In addition, we are particularly interested in clarifying the physiological function of identified host factors such as chromatin regulators, molecular chaperones, etc. as well as their roles in infection.

Projects for Regular Students in Doctoral or Master's Programs

1) Identification and characterization of novel factors in virus replication
2) Control of virus diseases based on the knowledge of host defense systems, or through development of novel anti-viral drugs
3) Regulatory mechanism for the structure and function of chromatin
4) Leukemogenic mechanism by chromosomal translocation

Study Programs for Short Stay Students (one week ~ one trimester)

1) Molecular mechanism of host factors involved in influenza virus replication
2) Action mechanism of an anti-virus drug
3) *Cell-free* reconstitution of a nucleus
4) Molecular function of a fusion gene product(s) in oncogenesis

Selected Recent Publications

1) Kawaguchi A, Matsumoto K, Nagata K. YB-1 functions as a porter to lead influenza virus ribonucleoprotein complexes to microtubules. ***J. Virol.***, 2012; 86: 11086-11095.
2) Kato K, Okuwaki M, Nagata K. Involvement of Template Activating Factor-I as a chaperone in linker histone dynamics. ***J. Cell Sci.***, 2011; 124: 3254-3265.
3) Sugiyama K, Obayashi E, Kawaguchi A, Tame J R H, Nagata K, Park S-Y. Structural insight into a novel subunit contact within influenza virus RNA polymerase. ***EMBO J.***, 2009; 28: 1803-1811.
4) Obayashi E, Yoshida H, Kawai F, Shibayama N, Kawaguchi A, Nagata K, Tame J R H, Park S-Y. The structural basis for an essential subunit interaction in influenza virus RNA polymerase. ***Nature***, 2008; 454: 1127-1131.
5) Naito T, Kiyasu Y, Sugiyama K, Kimura A, Nakano R, Matsukage A, Nagata K. A novel influenza virus replicon system in yeast identified Tat-SF1 as a stimulatory host factor for viral RNA synthesis. ***Proc. Natl. Acad. Sci. USA***, 2007; 104: 18235-18240.
6) Kawaguchi A, Nagata K. *De novo* replication of the influenza virus RNA genome is regulated by a DNA replicative helicase, MCM. ***EMBO J.***, 2007; 26: 4566-4575.

Microbiology

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Major Scientific Interests of the Group

The research aim of our lab is to understand how *Staphylococcus aureus* and other pathogens have evolved to cope with bactericidal factors from host and environment.

Projects for Regular Students in Doctoral or Master's Programs

1) Dynamics of cellular structures: nucleoid and membrane
2) Population heterogeneity: stochastic gene expression
3) Natural genetic competence in gram positive pathogens
4) Host-pathogen interaction *in vitro*

Study Programs for Short Stay Students (one week ~ one trimester)

1) Molecular genetic and biochemical techniques in bacteria
2) Single molecule analysis using atomic force microscopy

Recent Publications

1) **Ohniwa RL**, Muchaku H, **Saito S**, Wada C and **Morikawa K**. "Atomic force microscopy analysis of the role of major DNA-binding proteins in organization of the nucleoid in *Escherichia coli*." ***PLoS ONE*. 8**, e72954 (2013)
2) **Ohniwa RL**, Kitabayashi K, **Morikawa K**. Alternative cardiolipin synthase Cls1 compensates for stalled Cls2 function in *Staphylococcus aureus* under conditions of acute acid stress. ***FEMS Microbiol Lett.* 338**:141-6 (2013)
3) **Morikawa K**, Takemura A, Inose Y, Tsai M, Nguyen Thi le T, Ohta T and Msadek T. "Expression of a cryptic secondary sigma factor gene unveils natural competence for DNA transformation in *Staphylococcus aureus*". ***PLoS Pathog*, 8**:e1003003. (2012)
4) **Ohniwa RL**, Ushijima Y, **Saito S** and **Morikawa K**, "Proteomic Analyses of Nucleoid-Associated Proteins in *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Staphylococcus aureus*." ***PLoS ONE*, 6**, e19172 (2011)
5) Tsai M, **Ohniwa RL**, Kato Y, Takeshita SL, Ohta T, **Saito S**, Hayashi H and **Morikawa K** "*Staphylococcus aureus* requires cardiolipin for survival under high salinity conditions." ***BMC Microbiology*, 11**:13 (2011)
6) **Morikawa K**, **Ohniwa RL**, Ohta T, Tanaka Y, Takeyasu K and Msadek T. "Adaptation beyond the Stress Response: Cell Structure Dynamics and Population Heterogeneity *in Staphylococcus aureus*." ***Microbes Environ*, 25(2)**,75-82 (2010)

Neurophysiology

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Major Scientific Interests of the Group

We are studying mechanisms of cardiovascular and respiratory regulation by the central nervous system. Especially, we are paying attention to the autonomic nervous system for the circulatory and respiratory system.

Projects for Regular Students in Doctoral or Master's Programs

Cardiovascular and respiratory regulation by the central nervous system plays crucial roles in homeostasis. Disorder of this system causes serious problems in a living body. Despite this, it has been remained that lots of unknown mechanisms in the cardiovascular and respiratory center. Now, we are studying cardiovascular and respiratory regulation by the autonomic nervous system using electrophysiological methods *in situ* and *in vivo*, and trying to investigate relationship between disorder of the neurogenic regulation and cardiovascular and respiratory diseases.

Study Programs for Short Stay Students (one week ~ one trimester)

1) Recording of cardiovascular and respiratory parameters in human and rodent.
2) Physiological analysis of cardiovascular and respiratory parameters in human and rodent.

Recent Publications

1) Sabino-Silva R, Ceroni A, **Koganezawa T**, Michelini LC, Machado UF, Antunes VR Baroreceptor-mediated activation of sympathetic nerve activity to salivary glands. **Physiol Behav**, 107(3), 390-396 (2012)
2) **Koganezawa T**, Okada Y, Terui N, Paton JF, Oku Y A μ-opioid receptor agonist DAMGO induces rapid breathing in the arterially perfused in situ preparation of rat. **Respir Physiol Neurobiol,** 177(2), 207-211 (2011)
3) **Koganezawa T**, Shimomura Y, Terui N. The viscerosympathetic response in rabbits is mediated by GABAergic and glutamatergic inputs into the sympathetic premotor neurons of the rostral ventrolateral medulla. **Exp Physiol**, 95(11), 1061-1070 (2010)
4) Wang R, **Koganezawa T**, Terui N. Different responses of symapthetic premotor neurons in the rostral ventrolateral medulla to stimulation of the dorsomedial hypothalamus in rabbits. **Brain Res**, 1356, 44-53 (2010)
5) Nishimaru H, **Koganezawa T**, Kakizaki M, Ebihara T, Yanagawa Y. Inhibitory synaptic modulation of Renshaw cell activity in the lumbar spinal cord of neonatal mice. **J Neurophysiol**, 103(6), 3437-3447. (2010)
6) **Koganezawa T**, Shimomura Y, Teuri N. The role of the RVLM neurons in the viscero-sympathetic reflex: A mini review. **Auton Neurosci**, 142(1-2), 17-19. (2008)
7) **Koganezawa T**, Terui N. Differential responsiveness of RVLM sympathetic premotor neurons to hypoxia in the rabbit. **Am J Physiol Heart Circ Physiol**., 292, H408-414 (2007)

Molecular Parasitology

Principal Investigator Kiong Ho
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Major Scientific Interests of the Group

Our primary research interest is to understand the gene expression of eukaryotic parasites with a goal in identifying parasite-specific processes that can be exploited as targets for novel therapeutic interventions. We have focused on how messenger RNA acquire 5' cap in the protozoan parasites that responsible for malaria and sleeping sickness. The structure and mechanism of protozoan capping enzyme is completely different from human host, and thus, capping is an attractive target for anti-protozoal drug discovery. We are also investigating the mechanism of RNA repair and recombination. RNA ligase is the key enzyme that joins the broken RNAs together. We are characterized three separate types of RNA ligases from various species and our immediate goal is to define how these ligases recognize the breaks in the RNA and to identify what types of RNA are repaired in the cell.

Projects for Graduate Students

1) Dissecting the mechanism of hypermethylated cap 4 synthesis in Trypanosome brucei.
2) Characterization of T.brucei capping enzyme complex with transcription and RNA processing factors.
3) Defining the physiological targets for RNA ligase through genome wide screening.

Study Programs for Short Stay Students

1) Screening of small molecule inhibitor against malaria and sleeping sickness.
2) Biochemical characterization of novel RNA capping activities.
3) Defining the optimal RNA substrates for RNA ligase.

Selected Publications

1) Torchea C, Takagi Y and Ho CK. Archaea RNA Ligase is a Homodimeric Protein that Catalyzes Intramolecular Ligation of Single-Stranded RNA and DNA. ***Nucleic Acid Res.*** 2008; 36: 6218 - 6227.
2) Takagi Y, Sindkar S, Ekonomidis D, Hall MP and Ho CK. *Trypanosoma brucei* Encodes a Bifunctional Capping Enzyme Essential for Cap 4 Formation on the Spliced Leader RNA. ***J. Biol. Chem.*** 2007; 282: 15995-16005.
3) Hall MP and Ho CK. Functional Characterization of a 48-kDa *Trypanosoma brucei* Cap 2 RNA Methyltransferase. ***Nucleic Acid Res.*** 2006 34: 5594 - 5602.
4) Pfeffer S, Sewer A, Lagos-Quintana M, Sheridan R, Sander C, Grässer FA, van Dyk LF, Shuman S, Ho CK, Chien M, Russo JJ, Ju J, Randall G, Lindenbach BD, Rice CM, Simon V, Ho DD, Zavolan M, and Tuschl T. Identification of the MicroRNAs of the Herpesvirus Family. ***Nature Method*** 2005; 2: 269-276.
5) Ho CK, Wang LK, Lima CD and Shuman S. Structure and Mechanism of RNA Ligase. ***Structure*** 2004;12:327-339.
6) Chiu YL, Ho CK, Saha N, Schwer B, Shuman S, and Rana TM. Tat Stimulates Cotranscriptional Capping of HIV-1 mRNA. ***Molecular Cell*** 2002; 10: 585-597.
7) Ho CK and Shuman S. A Yeast-like mRNA Capping Apparatus in *Plasmodium falciparum*. ***Proc. Natl. Acad. Sci. USA*** 2001; 98: 3050-3055
8) Ho CK and Shuman S. Distinct Roles for CTD Ser2 and Ser5 Phosphorylation in the Recruitment and Allosteric Activation of Mammalian mRNA Capping Enzyme. ***Molecular Cell*** 1999; 3: 405-411.

Cellular Reprogramming and Biotechnology

Principal Investigator Ken Nishimura
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Major Scientific Interests of the Group

Our group studies the molecular mechanism of the cell reprogramming to establish an efficient method of the production of well-reprogrammed iPS cells by using our unique gene transfer system (SeVdp vectors). We are also trying to apply these vector to establish safe cell-differentiation systems.

Projects for Regular Students in Doctoral or Master's Programs

1) Molecular mechanism of iPS cell production by analyzing series of partially reprogrammed cells induced by SeVdp vectors.
2) Establishment of iPS cell production methods with novel factors which improve cell reprogramming.
3) Development of SeVdp vector-based methods to produce differentiated tissues without contaminating undifferentiated cells.

Study Programs for Short Stay Students (one week ~ one trimester)

1) Production of mouse and human iPS cells using SeVdp vectors.
2) Cell biology and molecular biology experiments for analysis of gene expression.

Recent Publications

1) Wakao H, Yoshikiyo K, Koshimizu U, Furukawa T, Enomoto K, Matsunaga T, Tanaka T, Yasutomi Y, Yamada T, Minakami H, Tanaka J, Oda A, Sasaki T, Wakao R, Lantz O, Udagawa T, Sekiya Y, Higuchi K, Harada N, **Nishimura K**, Ohtaka M, Nakanishi M, Fujita H: Expansion of Functional Human Mucosal-Associated Invariant T Cells via Reprogramming to Pluripotency and Redifferentiation. ***Cell Stem Cell***, 12: 546-558, 2013
2) Nishimura T, Kaneko S, Kawana-Tachikawa A, Tajima Y, Goto H, Zhu D, Nakayama -Hosoya K, Iriguchi S, Uemura Y, Shimizu T, Takayama N, Yamada D, **Nishimura K**, Ohtaka M, Watanabe N, Takahashi S, Iwamoto A, Koseki H, Nakanishi M, Eto K, Nakauchi H: Generation of rejuvenated antigen-specific T cells by reprogramming to pluripotency and redifferentiation. ***Cell Stem Cell***, 12: 114-126, 2013
3) **Nishimura K**, Sano M, Ohtaka M, Furuta B, Umemura Y, Nakajima Y, Ikehara Y, Kobayashi T, Segawa H, Takayasu S, Sato H, Motomura K, Uchida E, Kanayasu-Toyoda T, Asashima M, Nakauchi H, Yamaguchi T, Nakanishi M: Development of Defective and Persistent Sendai Virus Vector: a Unique Gene Delivery/Expression System Ideal for Cell Reprogramming. ***J. Biol. Chem.***, 286: 4760-4771, 2011
4) **Nishimura K**, Segawa H, Goto T, Morishita M, Masago A, Takahashi H, Ohmiya Y, Sakaguchi T, Asada M, Imamura T, Shimotono K, Takayama K, Yoshida Y, Nakanishi M: Persistent and stable gene expression by a cytoplasmic RNA replicon based on a noncytopathic variant Sendai virus. ***J. Biol. Chem.***, 282: 27383-27391, 2007

Cognitive and Behavioral Neuroscience

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Other Faculty Members
Assistant Professor Hiroshi Yamada: h-yamada@md.tsukuba.ac.jp

Major Scientific Interests of the Group

The goal of our research is to understand neural mechanisms underlying cognition such as attention, memory, prediction, learning and decision making. In particular, we are investigating the role of monoamine systems, such as dopamine and serotonin, in cognitive functions. Experiments in our laboratory center on the brain of awake behaving monkeys as a model for similar systems in the human brain. Using electrophysiological and pharmacological techniques, we examine what signals monoamine neurons convey while monkeys are performing cognitive tasks and how the signals, released monoamine, work in targeted brain areas to achieve the tasks. These studies will provide more mechanistic accounts of cognitive disorders.

Projects for Graduate Students in Doctoral or Master's Programs

1) Electrophysiological studies on roles of monoamine systems in cognitive functions
2) Pharmacological studies on roles of monoamine systems in cognitive functions
3) Optogenetical manipulations of monoamine systems in awake monkeys

Training Programs for Short Stay Students (one week – one trimester)

1) Analysis of cognitive performance in monkeys
2) Recording of neuron activity in awake monkeys

Recent Publications

1) MatsumotoM, Takada M, Distinct representations of cognitive and motivational signals in midbrain dopamine neurons. **Neuron**, Vol.79, 1011-24, 2013
2. MatsumotoM, Hikosaka O, Electrical stimulation of the primate lateral habenula suppresses saccadic eye movement through a learning mechanism. **PLoS ONE**, Vol.6, e26701, 2011
3. MatsumotoM, Hikosaka O, Two types of dopamine neuron distinctly convey positive and negative motivational signals. **Nature**, Vol.459, 837-41, 2009
4. MatsumotoM, Hikosaka O, Representation of negative motivational value in the primate lateral habenula. **Nature Neuroscience**, Vol.12, 77-84, 2009
5. MatsumotoM, Hikosaka O, Lateral habenula as a source of negative reward signals in dopamine neurons. **Nature**, Vol.447, 1111-5, 2007

Molecular Pharmacology

Principal Investigator Masashi Yanagisawa, M.D., Ph.D.
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Other Faculty Member
Professor, Hiromasa Funato

Major Scientific Interests of the Group

1) Exploring genes regulating sleep/wake
2) Real-time visualization and manipulation of neuronal mechanisms controlling sleep/wake
3) Finding new drugs for sleep disorders

Projects for Regular Students in Doctoral or Master's Programs

1) Large-scale, forward genetic screening of genes responsible for sleep/wake regulation in mutagenized mice
2) Screening for orexin receptor agonists
3) Analysis of sleep and wakefulness in genetically modified mice
4) in vivo real-time imaging of neuronal activities in hypothalamus and other deep brain structures in freely behaving mice

Training Programs for Short Stay Students (one week ~ one trimester)

1) EEG/EMG electrode implantation and recording in mice
2) patch clamp recording in cells and brain slices
3) imaging of nerve cell activities in brain slices

Recent Publications

1) Matsuki, T., Nomiyama, M., Takahira, H., Hirashima. N., Kunita, S., Takahashi, S., Yagami, K., Kilduff, T.S., Bettler, B., Yanagisawa, M., Sakurai, T. Selective loss of GABAB receptors in orexin-producing neurons results in disrupted sleep/wakefulness architecture. *Proc. Natl. Acad. Sci. USA* **106**:4459-4464, 2009.
2) Funato, H., Tsai, A.L., Willie, J.T., Kisanuki, Y., Williams, S.C., Sakurai, T., Yanagisawa, M. Enhanced orexin receptor-2 signaling prevents diet-induced obesity and improves leptin sensitivity. *Cell Metab.* **9**:64-76, 2009.
3) Funato, H., Sato, M., Sinton, C.M., Gautron, L., Williams, S.C., Skach, A., Elmquist, J.K., Skoultchi, A.I., Yanagisawa, M. Loss of Goosecoid-like and DiGeorge syndrome critical region 14 in interpeduncular nucleus results in altered regulation of rapid eye movement sleep. *Proc. Natl. Acad. Sci. USA* **107**:18155-18160, 2010.
4) Chang, L., Bramall, N.A., Baynash, G.A., Rattner, A., Rakheja, D., Post, M., McKerlie, J.S., Stewart, J.D., McInnes, R.R., Yanagisawa, M. Endothelin-2 deficiency causes growth retardation, hypothermia, and emphysema in mice. *J.Clin. Invest.* **123**:2643-2653, 2013.
5) Suzuki, A., Sinton, M.C., Green, W.R., Yanagisawa, M. Behavioral and biochemical dissociation of arousal and homeostatic sleep need influenced by prior wakeful experience in mice. *Proc. Natl. Acad. Sci. USA* **110**:10288-10293, 2013.
6) Ikeda, Y., Kumagai, H., Skach, A., Sato, M., Yanagisawa, M. Modulation of circadian glucocorticoid oscillation through adrenal opioid-CXCR7 signaling alters emotional behavior. *Cell* **155**: 1323-1336, 2013.

Functional neuroanatomy

Principal Investigator Hiromasa Funato
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Major Scientific Interests of the Group

1) Identification of novel genes that regulate sleep/wakefulness behavior using forward genetic approach.
2) Molecular mechanism underlying feeding and body weight homeostasis, anxiety and depressive behavior

Projects for Regular Students in Doctoral or Master's Programs

1) Functional characterization of novel sleep-regulating genes
2) Combined approaches using viral vectors and gene-modified mice to uncover neural circuits underlying sleep/wakefulness behavior, feeding and body weight homeostasis, and anxiety and depressive behavior

Training Programs for Short Stay Students (one week ~ one trimester)

1) Basic skills for EEG/EMG-based sleep analysis
2) Histological analysis using immunohistochemistry and *in situ* hybridization
3) Behavioral analysis of viral vector-injected mice.

Recent Publications

1) Kenkichi Takase, Satoko Oda, Masaru Kuroda, *Hiromasa Funato. Monoaminergic and neuropeptidergic neurons have distinct expression profiles of histone deacetylases. PLoS One 8:e58473, 1-15, 2013.
2) Hiromasa Funato, Makito Sato, Christopher M. Sinton, Laurent Gautron, S. Clay Williams, Amber Skach, Joel K. Elmquist, Arthur I. Skoultchi, Masashi Yanagisawa. Loss of Goosecoid-like and DiGeorge syndrome critical region 14 in interpeduncular nucleus results in altered regulation of rapid eye movement sleep. Proceedings of the National Academy of Sciences of the United States of America 107:18155-18160, 2010.
3) Hiromasa Funato, Allen L. Tsai, Jon T. Willie, Yasushi Kisanuki, S. Clay Williams, Takeshi Sakurai, Masashi Yanagisawa. Enhanced orexin receptor-2 signaling prevents diet-induced obesity and improves leptin sensitivity. Cell Metabolism 9:64-76, 2009.

Medicinal Chemistry, Organic Chemistry

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Assistant Prof. Tsuyoshi Saitoh, Ph.D.: tsuyoshi-saito.gf@u.tsukuba.ac.jp

Major Scientific Interests of the Group

1) Design and Synthesis of Orexin Agonists
2) Design and Synthesis of Opioid Receptor Agonists and Antagonists
3) Clarification of Mechanism of Drug Resistance and Dependence

Projects for Regular Students in Doctoral or Master's Programs

1) Study of Medicinal Chemistry 2) Study of Organic Chemistry
3) Research Development of New Drugs

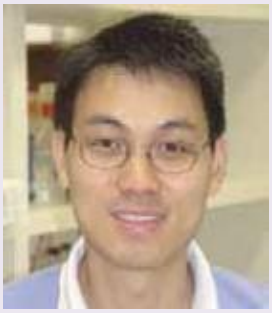
Training Programs for Short Stay Students (one week ~ one trimester)

1) Organic Synthesis of Opioid Compounds 2) Organic Synthesis of Orexin Ligands
3) Purification and Separation Technique 4) Basic Drug Design

Selected Recent Publications

1) Watanabe, Y.; Kitazawa, S.; Nemoto, T.; Hirayama, S.; Iwai, T.; Fujii, H.; **Nagase, H.**, Design and synthesis of novel opioid ligands with an azabicyclo[2.2.2]octane skeleton having a 7-amide chain and their pharmacologies, *Bioorg. Med. Chem.* **2013**, *21*, 3032-3050.
2) **Kutsumura, N**.; Matsubara, Y.; Niwa, K.; Ito, A.; Saito, T., Novel One-pot Method for Regioselective Bromination and Sequential Carbon−Carbon Bond-forming Reactions of Allylic Alcohol Derivatives, *Eur. J. Org. Chem.* **2013**, 3337-3346.
3) Nemoto, T.; Yamamoto, N.; Wada, N.; Harada, Y.; Tomatsu, M.; Ishihara, M.; Hirayama, S.; Iwai, T.; Fujii, H.; **Nagase, H**., The effect of 17-N substituents on the activity of the opioid κ receptor in nalfurafine derivatives, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 268-272.
4) **Nagase, H**.; Imaide, S.; Hirayama, S.; Nemoto, T.; Fujii, H., Essential structure of opioid κ receptor agonist nalfurafine for binding to the κ receptor 2: Synthesis of decahydro(iminoethano) phenanthrene derivatives and their pharmacologies, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5071-5074.
5) **Nagase, H**.; Akiyama, J.; Nakajima, R.; Hirayama, S.; Nemoto, T.; Gouda, H.; Hirono, S.; Fujii, H., Synthesis of new opioid derivatives with a propellane skeleton and their pharmacology. Part 2: Propellane derivatives with an amide side chain, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2775-2779.
6) **Kutsumura, N**.; Kiriseko, A.; Saito, T., Total Synthesis of (+)-Heteroplexisolide E, *Heterocycles* **2012**, *86*, 1367-1378.
7) **Kutsumura, N**; Kiriseko, A.; Saito, T., First total synthesis of (+)-heteroplexisolide E, *Tetrahedron Lett.* **2012**, *53*, 3274-3276.
8) **Nagase, H**.; Imaide, S.; Yamada, T.; Hirayama, S.; Nemoto, T.; Yamaotsu, N.; Hirono, S.; Fujii, H., Essential Structure of Opioid κ Receptor Agonist Nalfurafine for Binding to κ Receptor 1: Synthesis of Decahydroisoquinoline Derivatives and Their Pharmacologies, *Chem. Pharm. Bull.* **2012**, *60*, 945-948.

Biochemistry and Molecular Genetics



Principal Investigator Qinghua Liu, Ph.D.
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Other Faculty Member: None

Major Scientific Interests of the Group

1) RNA Interference and MicroRNAs
2) Sleep Research
3) Odor-induced Innate Fear

Projects for Regular Students in Doctoral or Master's Programs

1) We use genetic screen and biochemical fractionation to identify novel factors (e.g. R2D2, C3PO, and others) and characterize their precise functions in the RNA Interference (RNAi) and MicroRNA pathways.
2) We will understand the molecular circuits of Sleep/Wake control, a fundamental mystery in neuroscience, by integrating mouse genetic screen, quantitative mass spectrometry, and biochemical reconstitution.
3) We are conducting the first genetic screen in mice in search of the "fearless" mutants to understand the molecular circuits of odor-induced innate fear (of predator).

Training Programs for Short Stay Students (one week ~ one trimester)

1) Molecular cloning
2) Fear screen
3) Sleep recording

Recent Publications

1) C. Liang et al. and **Q. Liu**. Sjogren Syndrome Antigen B (SSB)/La promotes global microRNA expression by binding microRNA precursors through stem-loop recognition. ***J Biol Chem***, 288:723-36 (2013)
2) Y. Liu, H. Tan, H. Tian, C. Liang, S. Chen, **Q. Liu**. Autoantigen La promotes RNAi, antiviral response, and transposon silencing by facilitating multi-turnover RISC catalysis, ***Molecular Cell*** 44:502-8 (2011).
3) X. Ye, N. Huang, Y. Liu, Z. Paroo, C. Huerta, P. Li, S. Chen, **Q. Liu***, H. Zhang* (co-corresponding authors). Structure of C3PO and mechanism of human RISC activation. ***Nat Struct Mol Biol***. 18:650-657 (2011)
4) Paroo, X. Ye, S. Chen, and **Q. Liu**. Phosphorylation of the human micro-RNA generating complex mediates MAPK/Erk signaling. ***Cell*** 139:112-122 (2009)
5) Y. Liu, X. Ye, F. Jiang, C. Liang, D. Chen, J. Peng, L.N. Kinch, N.V. Grishin, and **Q. Liu.** C3PO, an endoribonuclease that promotes RNAi by facilitating RISC activation. ***Science***,325:750-753 (2009)

Memory, Adult Neurogenesis, and Sleep

Principal Investigator Masanori Sakaguchi
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Major Scientific Interests of the Group

After receiving my medical degree from the University of Tsukuba in 2001, I continued to pursue a research-oriented career in neuroscience, focusing on regenerative medicine, adult neurogenesis and memory in particular. My experience abroad and career thereafter provided me with a firm grasp of world-class techniques (optogenetics, neuronal tracing, behavioral neuroscience, etc.) but furthermore, with an open-mindedness in understanding both Western and Eastern cultures and sufficient communication abilities (fluent English and intermediate-level Chinese) all so vital in scientific research today.

Currently, at IIIS our group strives to investigate the relation between sleep, adult neurogenesis and memory. Our group consist of Dr. Sakaguchi, one technician (English native speaker) and four undergrad students. We hope to clarify the still unanswered questions regarding sleep and its significance towards memory and adult neurogenesis. I welcome motivated and self-driven students and researchers anytime for lab visiting.

Projects for Regular Students in Doctoral or Master's Programs

1) Function of sleep in memory consolidation
2) Activation of adult born neurons in sleep and its significance in memory
3) Mapping brain regions activated in each sleep stages

Training Programs for Short Stay Students (one week ~ one trimester)

1) Optogenetic stimulation of the target neurons during sleep
2) Behavioral examination of learning&memory using mouse
3) Visualization of memory trace using CAT-FISH analysis

Recent Publications

1) SakaguchiM and Hayashi Y, Catching the engram: strategies to examine the memory trace, **Mol. Brain** 2012, 5:32(359 viewed in the first 10days, 6th best viewed during the 1st month)
2) SakaguchiM and Okano H. Neural stem cells, adult neurogenesis and galectins: from bench to bedside, **Dev. Neurobiol.**, 2012, 72(7):1059-67.
3) Arruda-Carvalho M*., SakaguchiM*, Akers KG., Josselyn SA., Frankland PW., Post-training ablation of adult-generated neurons degrades previously-acquired memories., J. Neurosci. 2011, 31(42):15113-27., *The authors contributed equally
4) SakaguchiM, Imaizumi Y, Shingo T, Tada H, Hayama K, Yamada O, Morishita T, Kadoya T, Uchiyama N, Shimazaki T, Kuno A, Poirier F, Hirabayashi J, Sawamoto K, Okano H., Regulation of adult neural progenitor cells by Galectin-1/beta1 Integrin interaction., **J. Neurochem.**, 2010, 113(6):1516-24.
5) SakaguchiM., Shingo T., Shimazaki T., Okano H.J., Shiwa M., Ishibashi S., Oguro H., Ninomiya M., Kadoya T., Horie H., Shibuya A., Mizusawa H., Poirier F., Nakauchi H., Sawamoto K., Okano H. A carbohydrate binding protein, Galectin-1, promotes proliferation of adult neural stem cells. **PNAS**, 2006, 103:pp7112-7117 (Track II direct submission)

Systems Sleep Biology

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Other Faculty Members
Researcher Yo Oishi,
Ph.D. Researcher Yoko
Takata, Ph.D.

Major Scientific Interests of the Group

1) Role of adenosine and dopamine in sleep-wake regulation
2) Motivational state as fundamental regulator of sleep and wake
3) Exploring methamphetamine-sensitive circadian oscillation

Projects for Regular Students in Doctoral or Master's Programs

1) Neuronal mechanisms of dopamine in sleep-wake regulation
2) Characterization of neuronal firing in the nucleus accumbens during sleep-wake states
3) Role of cannabinoid or opioid receptors in the striatum for sleep-wake regulation

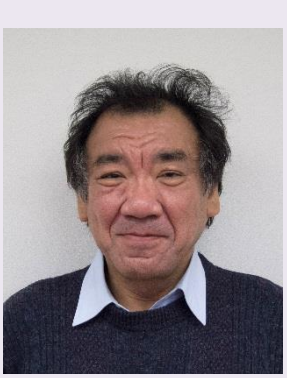
Training Programs for Short Stay Students (one week ~ one trimester)

1) EEG/EMG electrode implantation and recording in mice
2) Engineering and production of adeno-associated viruses
3) Opto-/pharmacogenetic modulation of neural circuitry by using stereotaxic microinjections of viral vectors
4) Immunohistochemistry and in situ hybridization of brain tissue

Recent Publications

1) Lazarus M, Chen J-F, Urade Y, Huang Z-L. Role of the basal ganglia in the control of sleep and wakefulness. Curr Opin Neurobiol 2013, 23: 780-785.
2) Lazarus M, Huang Z-L, Lu J, Urade Y, Chen J-F. How do the basal ganglia regulate sleep-wake behavior? Trends Neurosci 2012, 35: 723-732.
3) Lazarus M, Shen HY, Cherasse Y, Qu WM, Huang ZL, Bass C, Winsky-Sommerer R, Semba K, Fredholm B, Boison D, Hayaishi O, Urade Y, Chen JF. Arousal effect of caffeine depends on adenosine A2A receptors in the shell of the nucleus accumbens. J Neurosci 2011, 31: 10067-10075.
4) Gautron L*, Lazarus M* (Co-first author), Scott MM, Saper CB, Elmquist JK. Identifying the efferent projections of leptin-responsive neurons in the dorsomedial hypothalamus using a novel conditional tracing approach. J Comp Neurol 2010, 518: 2090-2108.
5) Lazarus M, Yoshida K, Coppari R, Bass CE, Mochizuki T, Lowell BB, Saper CB. EP3 prostaglandin receptors in the median preoptic nucleus are critical for fever responses. Nat Neurosci 10(9), 1131-3 (2007).

Name of the Field: Molecular Sleep Biology



Principal Investigator Yoshihiro Urade, PhD
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URL
Other Faculty Member
Associate Professor Kosuke Aritake, PhD

Major Scientific Interests of the Group

1) Role of prostaglandin D_2 in sleep-wake regulation
2) Role of Sox5 in controlling sleep cycle
3) Relationship between sleep and neurodegenerative diseases

Projects for Regular Students in Doctoral or Master's Programs

1) Involvement of glutamatergic neurons in sleep regulation
2) Relationship between sleep and memory in gene-manipulated animals
3) Screening of new sleep-regulatory natural compounds

Training Programs for Short Stay Students (one week ~ one trimester)

1) Basic and advanced molecular biology and biochemistry experiments
2) Sleep recording and analysis
3) Mouse brain surgery and gene manipulation
4) Screening of new sleep-regulatory natural compounds

Recent Publications

1) Mahesh K Kaushik; **Kosuke Aritake**; Shinya Kamauchi; Osamu Hayaishi; Zhi-Li Huang; **Yoshihiro Urade**, Prostaglandin D_2 is crucial for seizure suppression and postictal sleep, Exp. Neurol., in Press
2) Murata T, **Aritake K**, Matsumoto S, Kamauchi S, Nakagawa T, Hori M, Momotani E, **Urade Y**, Ozaki H. Prostagladin D_2 is a mast cell-derived antiangiogenic factor in lung carcinoma. Proc Natl Acad Sci U S A. **108**(49):19802-7, 2011
3) **Urade Y**, Hayaishi O. Prostaglandin D_2 and sleep/wake regulation. Sleep Med Rev. **15**(6):411-8, 2011
4) Lazarus M, Shen HY, Cherasse Y, Qu WM, Huang ZL, Bass CE, Winsky-Sommerer R, Semba K, Fredholm BB, Boison D, Hayaishi O, **Urade Y**, Chen JF. Arousal effect of caffeine depends on adenosine A_{2A} receptors in the shell of the nucleus accumbens. J Neurosci. **31**(27):10067-75, 2011
5) Nagata N, Kusakari Y, Fukunishi Y, Inoue T, **Urade Y**. Catalytic mechanism of the primary human prostaglandin $F_{2\alpha}$ synthase, aldo-keto reductase 1B1--prostaglandin D_2 synthase activity in the absence of NADP(H). FEBS J. **278**(8):1288-98, 2011
6) Qu WM, Xu XH, Yan MM, Wang YQ, **Urade Y**, Huang ZL. Essential role of dopamine D_2 receptor in the maintenance of wakefulness, but not in homeostatic regulation of sleep, in mice. J Neurosci. **30**(12):4382-9, 2010

Functional Genomics

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Major Scientific Interests of the Group

Transcriptional control is a key step for development, stress response, and various diseases in human beings. We focus on understanding the molecular mechanisms of transcription control. Our lab has three groups (molecular biology, mouse, and Drosophila), which are using different methods, but focus on the same transcriptional regulators.

Projects for Regular Students in Doctoral or Master's Programs

1) Role of nuclear oncogene products Myb and Ski in cancer
2) Epigenetic regulation by ATF-2 family transcription factors
3) Mechanism of iPSC generation

Training Programs for Short Stay Students (one week ~ one trimester)

1) Molecular biology experiments for studying transcriptional control
2) Genetic experiments using Drosophila and mice

Recent Publications

1) Seong KH, Li D, Shimizu H, Nakamura R and **Ishii S.** Inheritance of stress-induced, ATF-2-dependent epigenetic change. ***Cell*** in press, 2011.
2) Maekawa T, Kim S, Nakai D, Makino C, Takagi T, Ogura H, Yamada K, Chatton B and **Ishii S.** Social isolation stress induces ATF-7 phosphorylation and impairs silencing of the 5-HT 5B receptor gene. **EMBO J.** 29: 196-208, 2010.
3) Yamauchi T, Ishidao T, Nomura T, Shinagawa T, Tanaka Y, Yonemura S and **Ishii S.** A B-Myb complex containing clathrin and filamin is required for mitotic spindle function. **EMBO J.** 27: 1852-1862, 2008.
4) Jin W, Takagi T, Kanesashi S, Kurahashi T, Nomura T, Harada J and **Ishii S.** Schnurri-2 controls BMP-dependent adipogenesis via interaction with Smad proteins. **Dev. Cell** 10: 461-471, 2006.
5) Kanei-Ishii C, Ninomiya-Tsuji J, Tanikawa J, Nomura T, Ishitani T, Kishida S, Kokura K, Kurahashi T, Ichikawa-Iwata E, Kim Y, Matsumoto K and **Ishii S.** Wnt-1 signal induces phosphorylation and degradation of c-Myb protein via TAK1, HIPK2, and NLK. **Genes Dev.** 18, 816-829, 2004.

International Medicine

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Major Scientific Interests of the Group

The objectives of our research group are to develop appropriate medical technologies that are transferable to developing countries, in order to promote their primary health status. The following two subjects are our biggest research targets.

1) Research on controlling emerging and re-emerging infectious diseases of international importance.
2) Research on international medical cooperation.

Projects for Regular Students in Doctoral or Master's Programs

1) Biology and pathophysiology of re-emerging infectious diseases
   (a) Basic and clinical research on malaria
   (b) Research on the development of malaria vaccine
2) Social technology development for controlling diseases in developing countries
   (a) Researches on global malaria and parasite control strategy
   (b) Evaluation of international health cooperation projects

Training Programs for Short Stay Students (one week ~ one trimester)

1) *In vitro* culture of *Plasmodium falciparum* and its drug susceptibility assay
2) Discrimination of parasite species by PCR and other methods, including drug resistant DNA marker detection.

Recent Publications

1) Kimura R, Komaki-Yasuda K, Kawazu S, Kano S. 2-Cys peroxiredoxin of *Plasmodium falciparum* is involved in resistance to heat stress of the parasite. **Parasitol Int** 62:137-43, 2013
2) Iwagami M, Fukumoto M, Hwang SY, Kim SH, Kho WG, Kano S: Population structure and transmission dynamics of *Plasmodium vivax* in the Republic of Korea based on microsatellite DNA analysis. **PLoS Negl Trop Dis**, 6(4):e1592, 2012
3) Culleton R, Coban C, Zeyrek FY, et al: The origins of African *Plasmodium vivax*; Insights from mitochondrial genome sequencing. **PLoS ONE** 6(12): e29137, 2011
4) Okudaira N, Goto M, Yanobu-Takanashi R, et al.: Involvement of retrotransposition of long interspersed nucleotide element-1 in skin tumorigenesis induced by 7,12-dimethylbenz[a]anthracene and 12-O-tetradecanoylphorbol-13-acetate. **Cancer Scienc**e 102(11): 2000-6, 2011

Functional Genomics

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Major Scientific Interests of the Group

Elucidation of the pathogenesis of dengue fever and dengue hemorrhagic fever.

Projects for Regular Students in Doctoral or Master's Programs

1) Establishment of animal models of dengue fever.
2) Role of immune responses in the pathogenesis of dengue hemorrhagic fever.

Training Programs for Short Stay Students (one week ~ one trimester)

None

Recent Publications

1) Moi, M.L., Lim,C.K., Kotaki, A., Takasaki, T. and **Kurane, I**.: Detection of higher levels of dengue viremia using Fc{gamma}R-expressing BHK-21 cells than Fc{gamma}R-negative cells in secondary infection but not in primary infection. Journal of Infectious Diseases. 203(10): 1405-1414, 2011.
2) Fujii, K., Matsutani, T., Kitaura, K., Suzuki, S., Itoh, T., Takasaki, T., Suzuki, R. and **Kurane, I**.: Comprehensive analysis and characterization of the TCR alpha chain sequences in the common marmoset. **Immunogenetics,** 62(6): 383-385, 2010.
3) Tajima, S., Nerome, R., Nukui, Y., Kato, F, Takasaki, T. and **Kurane, I**.: A single mutation in the Japanese encephalitis virus E protein (S123R) increases its growth rate in mouse neuroblastoma cells and its pathogenicity in mice. **Virology** 396(2): 298-304, 2010.
4) Moi, M.L., Lim, C.K., Takasaki, T. and **Kurane, I**.: Involvement of the Fc gamma receptor IIA cytoplasmic domain in antibody-dependent enhancement of dengue virus infection. **Journal of General Virology** 91(Pt 1): 103-111, 2010.
5) Moi, M.L., Lim, C.K., Kotaki, A., Takasaki, T. and **Kurane, I**.: Discrepancy in neutralizing antibody titers between plaque reduction neutralizing tests with Fcgamma receptor (Fcgamma R)-negative and FcgammaR-expressing BHK-21 cells. **Clinical and Vaccine Imunology** 17(3): 402-7,2010.
6) Lim, C.K., Nishibori, T., Watanabe, K., Ito, M., Kotaki, A., Tanaka, K., **Kurane, I.** and Takasaki, T.: Chikungunya virus isolated from a returnee to Japan from Sri Lanka: isolation of two sub-strains with different characteristics. **American Journal of Tropical Medicine and Hygiene** 81(5): 865-8, 2009.
7) Moi, M.L., Lim, C.K., Kotaki, A., Takasaki, T. and **Kurane, I**.: Development of an antibody-dependent enhancement assay for dengue virus using stable BHK-21 cell lines expressing Fc gammaRIIA. **Journal of Virological Methods** 163(2)205-9, 2010.

Experimental Hematology

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Major Scientific Interests of the Group

In vitro production of red blood cells (RBCs) able to be used in the clinic. For this purpose, we are attempting to establish immortalized human RBC progenitor cell lines from various cell sources such as hematopoietic stem cells, ES cells and iPS cells. In addition, we are studying the mechanisms of enucleation of RBC progenitor cells so as to improve the efficiency of in vitro enucleation.

Projects for Regular Students in Doctoral or Master's Programs

1) Cell culture of human ES and iPS cells. Induction of hematopoietic cells from human ES and iPS cells. Establishment of immortalized human hematopoietic cell lines from various cell sources such as hematopoietic stem cells, ES cells and iPS cells.
2) Molecular mechanisms of enucleation of RBC progenitor cells.

Training Programs for Short Stay Students (one week ~ one trimester)

1) Cell culture of mouse ES or iPS cells.
2) Cell analysis by flow cytometer.

Recent Publications

1) Kurita, R., Suda, N., Sudo, K., Miharada, K., Hiroyama, T., Miyoshi, H., Tani, K., and Nakamura,Y. Establishment of immortalized human erythroid progenitor cell lines able to produce enucleated red blood cells. ***PLoS ONE*** 8: e59890 (2013)
2) Fujitani, N., Furukawa, J., Araki, K., Fujioka, T., Takegawa, Y., Piao, J., Nishioka, T., Tamura, T., Nikaido, T., Ito, M., Nakamura,Y., and Shinohara, Y. Total cellular glycomics allows characterizing cells and streamlining the discovery process for cellular biomarkers. ***Proc. Natl. Acad. Sci. U.S.A.*** 110: 2105-2110 (2013)
3) Masters, J. R., Alston-Roberts, C., Barrett, T., Burnett, E. C., Cooper, J. R., Dirks, W. G., Freshney, R. I., Healy, L., Kerrigan, L., Kohara, A., Korch, C., MacLeod, R. A. F., Nakamura,Y., Nims, R. W., Reid, Y. A., Storts, D. R., and Capes-Davis, A. (The International Cell Line Authentication Committee) End the scandal of false cell lines. ***Nature*** 492: 186 (2012)
4) Hiroyama, T., Miharada, K., Sudo, K., Danjo, I., Aoki, N., and Nakamura,Y. Establishment of mouse embryonic stem cell-derived erythroid progenitor cell lines able to produce functional red blood cells. ***PLoS ONE*** 3: e1544 (open access journal) (2008)
5) Miharada, K., Hiroyama, T., Sudo, K., Nagasawa, T., and Nakamura,Y. Efficient enucleation of erythroblasts differentiated in vitro from hematopoietic stem and progenitor cells. ***Nat. Biotechnol.*** 24: 1255-1256 (2006)

Biochemistry and Molecular Cell Biology

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Other Faculty Members
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Major Scientific Interests of the Group

In-depth analyses of ubiquitin-, proteasome-, and autophagy-mediated regulatory proteolysis.

Projects for Graduate Students

1) Molecular mechanisms for assembly and diversity in eukaryotic proteasomes.
2) Physiological and Pathological roles of the autophagy system.
3) Control of mitochondrial homeostasis by PINK1/Parkin whose impairment causes Parkinson's disease.

Study Programs for Short Stay Students (one week ~ one trimester)

1) Enzymatic assays and affinity purification of eukaryotic proteasomes.
2) Ubiquitylation assays directed by Parkin and SCFFbs ubiquitin E3 ligases.
3) Assays for monitoring autophagy based on genetically engineered mice.

Recent Publications

1) Pack, Chan-Gi., Yukii, H., Toh-e, A., Kudo, T., Tsuchiya, H., Kaiho, A., Sakata, E., Murata, S., Yokosawa, H., Sako, Y., Baumeister, W., Tanaka, K., and Saeki, Y. (2014) Quantitative live-cell imaging reveals molecular dynamics and cytoplasmic assembly of the 26S proteasome. ***Nat Commun.*** in press.
2) Ichimura, Y., Waguri, S., Sou, Y., Kageyama, S., Hasegawa, J., Ishimura, R., Saito, T., Yang, Y., Kouno, T., Fukutomi, T., Hoshii, T., Atsushi, H., Takagi, K., Mizushima, T., Motohashi, H., Lee, M-S., Yoshimori, T., Tanaka, K. *, Yamamoto, M. *, and Komatsu, K. * (2013) Phosphorylation of p62 activates the Keap1-Nrf2 pathway during selective autophagy. *cocorespondences ***Mol Cell*** 51, 618-631.
3) Okatsu K, Oka T, Iguchi M, Imamura K, Kosako H, Tani N, Kimura M, Go E, Koyano F, Funayama M, Shiba-Fukushima K, Sato S, Shimizu H, Fukunaga Y, Taniguchi H, Komatsu M, Hattori N, Mihara K, Tanaka K, and Matsuda N. (2012) PINK1 autophosphorylation upon membrane potential dissipation is essential for Parkin recruitment to damaged mitochondria. ***Nat Commun.*** 2012; 3: 1016. doi: 10.1038/ncomms2016.
4) Sakata, E., Stengel, F., Fukunaga, K., Zhou, M., Saeki, Y., Förster, F., Baumeister, W.*, Tanaka, K.*, and Robinson, CV.* (2011) The catalytic activity of Ubp6 enhances maturation of the proteasomal regulatory particle. *correspondences ***Mol. Cell*** 42, 637-649.
5) Matsuda, N., Sato, S., Shiba, K., Okatsu, K., Saisho, K., Gautier, CA Sou, Y., Saiki, S., Kawajiri, S., Sato, F., Kimura, M., Komatsu, M., Hattori, N., and Tanaka, K. (2010) PINK1 stabilized by depolarization recruits Parkin to damaged mitochondria and activates latent Parkin for mitophagy. ***J Cell Biol.*** 189, 211-221
6) Saeki, Y., Toh-e, A., Kudo, T., Kawamura, H., and Tanaka, K. (2009) Multiple proteasome-interacting proteins assist the assembly of the yeast 19S regulatory particle. ***Cell*** 137, 900-913
7) Murata, S., Sasaki, K., Kishimoto, T., Niwa, S., Hayashi, H., Takahama, Y., and Tanaka, K. (2007) Regulation of CD8+ T cell development by thymus-specific proteasomes. ***Science*** 316, 1349-1353
8) Komatsu, M., Waguri, S., Chiba, T., Murata, S., Iwata, J., Ueno, T., Koike, M., Uchiyama, Y., Kominami, E., and Tanaka, K. (2006) Loss of autophagy in the central nervous system causes neurodegeneration. ***Nature*** 441, 880-884
9) Hirano, Y., Hendil, K.B., Yashiroda, H., Iemura, S., Nagane, R., Hioki, Y., Natsume, T., Tanaka, K., and Murata, S. (2005) A heterodimeric complex that promotes the assembly of mammalian 20S proteasomes. ***Nature*** 437, 1381-1385.