

Biomedical Research Activities

University of Tsukuba



Intelligence

Enthusiasm

Strength

Friendliness

Integrity

Creativity



2017



Biomedical Research Activities

University of Tsukuba

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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 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 the Ccr4-Not complex in yeast.
- 2) Regulation of the endoplasmic reticulum stress response by protein kinases.
- 3) Roles of yeast Ataxin-2 ortholog, Pbp1, in the control of mRNA stability and translation.
- 4) Roles of decapping activators in the control of mRNA stability and translation.

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) Molecular biology and biochemistry techniques analyzing gene expression including Northern blotting, RT-PCR, and Western blotting.
- 4) Imaging yeast cells using indirect immunofluorescence and GFP-protein fusions.

Recent Publications

- 1) Duy DL, Suda Y, Irie K. Cytoplasmic Deadenyase Ccr4 is Required for Translational Repression of LRG1 mRNA in the Stationary Phase. PLoS One. 2017 Feb 23;12(2):e0172476.
- 2) Ito Y, Kitagawa T, Yamanishi M, Katahira S, Izawa S, Irie K, Furutani-Seiki M, Matsuyama T. Enhancement of protein production via the strong DIT1 terminator and two RNA-binding proteins in Saccharomyces cerevisiae. Sci Rep. 2016 Nov 15;6:36997.
- 3) Lien PT, Izumikawa K, Muroi K, Irie K, Suda Y, Irie K. Analysis of the Physiological Activities of Scd6 through Its Interaction with Hmt1.. PLoS One. 2016 Oct 24;11(10):e0164773.
- 4) Li X, Ohmori T, Irie K, Kimura Y, Suda Y, Mizuno T, Irie K. Different Regulations of ROM2 and LRG1 Expression by Ccr4, Pop2, and Dhh1 in the Saccharomyces cerevisiae Cell Wall Integrity Pathway. mSphere. 2016 Sep 28;1(5).
- 5) Mizuno T, Masuda Y, Irie K. The Saccharomyces cerevisiae AMPK, Snf1, Negatively Regulates the Hog1 MAPK Pathway in ER Stress Response. PLoS Genet. 2015 Sep 22;11(9):e1005491.
- 6) Kimura Y, Irie K, Irie K. Pbp1 is involved in Ccr4- and Khdl1-mediated regulation of cell growth through association with ribosomal proteins Rpl12a and Rpl12b. Eukaryot Cell. 2013 Jun;12(6):864-74.

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 and reprogramming. In particular, we focus on the studies about the roles of transcription factors and epigenetic changes in regulating iPS cell generation and adipocyte differentiation. We also develop modified vectors and transcription factors to enhance reprogramming and 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 generation.
- 2) Generation of transcription factors with an enhanced reprogramming ability.
- 3) Analyses of epigenetic mechanisms of iPS cell generation.
- 4) Efficient differentiation of iPS cells into neurons.
- 5) Identification and functional analyses of transcription factors involved in adipocyte commitment.

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

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

Recent Publications

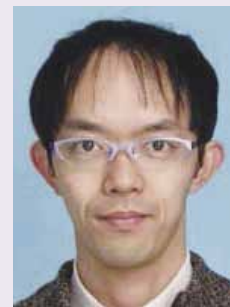
- 1) Nishimura K, Aizawa S, Nugroho FL, Shiomitsu E, Yen THH, Linh BP, Borisova DE, Sakuragi Y, Takada H, Kurisaki A, Hayashi Y, Fukuda A, Nakanishi M, **Hisatake K**. A Role for KLF4 in Promoting the Metabolic Shift via TCL1 during Induced Pluripotent Stem Cell Generation. **Stem Cell Reports**, 2017 (in press)
- 2) Hayashi Y, Hsiao EC, Sami S, Lancero M, Schlieve CR, Nguyen T, Yano K, Nagahashi A, Ikeya M, Matsumoto Y, Nishimura K, Fukuda A, **Hisatake K**, Tomoda K, Asaka I, Toguchida J, Conklin BR, Yamanaka Y. BMP-SMAD-ID Promotes Reprogramming to Pluripotency by Inhibiting p16/INK4A-Dependent Senescence. **Proc Natl Acad Sci USA** 113(46), 13057-13062, 2016
- 3) Nakadai T, Fukuda A, Shimada M, Nishimura K, **Hisatake K**. The RNA-binding Complexes, NF45-NF90 and NF45-NF110, Associate Dynamically with the c-fos Gene and Function as Transcriptional Coactivators. **J Biol Chem** 290(44), 26832-26845, 2015
- 4) Nishimura K, Kato T, Chen C, Oinam L, Shiomitsu E, Ayakawa D, Ohtaka M, Fukuda A, Nakanishi M, **Hisatake K**. Manipulation of KLF4 Expression Generates iPSCs Paused at Successive Stages of Reprogramming. **Stem Cell Reports** 3(5), 915-929, 2014
- 5) Fukuda A, Shimada M, Nakadai T, Nishimura K, **Hisatake K**. Heterogeneous Nuclear Ribonucleoprotein R Cooperates with Mediator to Facilitate Transcription Reinitiation on the c-Fos Gene. **PLoS ONE** 8(8): e72496. doi:10.1371/journal.pone.0072496, 2013

Cellular Reprogramming and Biotechnology

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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) **Nishimura K**, Aizawa S, Nugroho FL, Shiomitsu E, Tran YTH, Bui PL, Borisova E, Sakuragi Y, Takada H, Kurisaki A, Hayashi Y, Fukuda A, Nakanishi M, Hisatake K: A role for KLF4 in promoting the metabolic shift via TCL1 during induced pluripotent stem cell generation. *Stem Cell Reports*, 2017 *in press*
- 2) Bueno C, Sardina JL, Di Stefano B, Romero-Moya D, Muñoz-López A, Ariza L, Chillón MC, Balanzategui A, Castaño J, Herreros A, Fraga MF, Fernández A, Granada I, Quintana-Bustamante O, Segovia JC, **Nishimura K**, Ohtaka M, Nakanishi M, Graf T, Menendez P: Reprogramming human B cells into induced pluripotent stem cells and its enhancement by C/EBPα. *Leukemia*, 30: 674-682, 2016
- 3) **Nishimura K**, Kato T, Chen C, Oinam L, Shiomitsu E, Ayakawa D, Ohtaka M, Fukuda A, Nakanishi M, Hisatake K: Manipulation of KLF4 expression generates iPSCs paused at successive stages of reprogramming. *Stem Cell Reports*, 3: 915-929, 2014
- 4) 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
- 5) **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

Physiological Chemistry

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Major Scientific Interests of the Group

Studies on regulatory mechanisms and physiological functions of membrane trafficking systems through small GTP-binding proteins such as Rab and Arf.

Projects for Regular Students in Doctoral or Master's Programs

- 1) Physiological functions of the small GTP-binding proteins (Rabs and Arf6) and their regulators in tumorigenesis/metastasis, morphogenesis, and neural plasticity.
- 2) Regulatory mechanisms of ubiquitylation of cargo proteins in the recycling system.
- 3) Molecular mechanisms of biogenesis of melanin-containing organelles through Rab small GTP-binding proteins.
- 4) Development of specific agonists/antagonists for certain small GTP-binding proteins.

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

- 1) Enzyme assay and imaging of molecules regulating membrane trafficking systems.
- 2) Assays for cell functions such as cell proliferation, cell motility, focal adhesion, secretion, endocytosis, exocytosis, recycling, etc.

Recent Publications

- 1) Marubashi S, Shimada H, Fukuda M, **Ohbayashi N**. RUTBC1 Functions as a GTPase-activating Protein for Rab32/38 and Regulates Melanogenic Enzyme Trafficking in Melanocytes. **J Biol Chem.** 291, 1427-40, (2016).
- 2) Miura Y, Hongu T, Yamauchi Y, Funakoshi Y, Katagiri N, **Ohbayashi N**, **Kanaho Y**. ACAP3 regulates neurite outgrowth through its GAP activity specific to Arf6 in mouse hippocampal neurons. **Biochem J.** 473, 2591-602, (2016).
- 3) Marubashi S, **Ohbayashi N**, Fukuda M. A Varp-Binding Protein, RACK1, Regulates Dendrite Outgrowth through Stabilization of Varp Protein in Mouse Melanocytes. **J Invest Dermatol.** 136, 1672-80, (2016).
- 4) Okada R, Yamauchi Y, Hongu T, Funakoshi Y, **Ohbayashi N**, Hasegawa H, **Kanaho Y**. Activation of the Small G Protein Arf6 by Dynamin2 through Guanine Nucleotide Exchange Factors in Endocytosis. **Sci Rep.** 27, 14919, (2015).
- 5) Yatsu A, Shimada H, **Ohbayashi N**, Fukuda M. Rab40C is a novel Varp-binding protein that promotes proteasomal degradation of Varp in melanocytes. **Biol Open.** 4, 267-75, (2015).
- 6) Hongu T, Funakoshi Y, Fukuhara S, Suzuki T, Sakimoto S, Takakura N, Ema M, Takahashi S, Itoh S, Kato M, Hasegawa H, Mochizuki N, **Kanaho Y**. Arf6 regulates tumour angiogenesis and growth through HGF-induced endothelial $\beta 1$ integrin recycling. **Nat Commun.** 6, 7925, (2015).
- 7) Ishida M, **Ohbayashi N**, Fukuda M. Rab1A regulates anterograde melanosome transport by recruiting kinesin-1 to melanosomes through interaction with SKIP. **Sci Rep.** 5, 8238, (2015).
- 8) Funakoshi Y, Chou MM, **Kanaho Y**, Donaldson JG. TRE17/USP6 regulates ubiquitylation and trafficking of cargo proteins that enter cells by clathrin-independent endocytosis. **J Cell Sci.** 127, 4750-61, (2014).

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
- 3) 3D brain imaging

Recent Publications

- 1) **Masu M**. Proteoglycans and axon guidance: a new relationship between old partners. **J Neurochem** 139: 58-75, 2016.
- 2) Takashima Y, Keino-Masu K, Yashiro H, Hara S, Suzuki T, van Kuppevelt TH, **Masu M**, and Nagata M. Heparan Sulfate 6-O-EndoSulfatases, Sulf1 and Sulf2, Regulate Glomerular Integrity by Modulating Growth Factor Signaling. **Am J Physiol Renal Physiol** 310: F395-408, 2016.
- 3) Freeman SD, Keino-Masu K, **Masu M**, and Ladher RK. Expression of the heparan sulfate 6-O-endosulfatases, Sulf1 and Sulf2, in the avian and mammalian inner ear suggests a role for sulfation in inner ear development. **Dev Dyn** 244: 168-180, 2015.
- 4) 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.
- 5) 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.
- 6) Keino-Masu K, **Masu M**, et al. *Deleted in Colorectal Cancer (DCC)* Encodes a Netrin Receptor. **Cell** 87: 175-185, 1996

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, Maf B, 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) Shichita T, Ito M, Morita R, Komai K, Noguchi Y, Ooboshi H, Koshida R, **Takahashi S**, Kodama T, Yoshimura A. Mafb prevents excess inflammation after ischemic stroke by accelerating clearance of danger signal through MRS1. **Nat Med.** 2017 *in press*.
- 2) Hamada M, Nakamura M, Tran MT, Moriguchi T, Hong C, Ohsumi T, Dinh TT, Kusakabe M, Hattori M, Katsumata T, Arai S, Nakashima K, Kudo T, Kuroda E, Wu CH, Kao PH, Sakai M, Shimano H, Miyazaki T, Tontonz P, **Takahashi S**. MafB promotes atherosclerosis by inhibiting foam-cell apoptosis. **Nat Commun.** 5, 3147, 2014.
- 3) Morito N, Yoh K, Ojima M, Okamura M, Nakamura M, Hamada M, Yamagata K, **Takahashi S**. Mafb plays a protective role in diabetic nephropathy through slit-diaphragm proteins, anti-oxidative enzymes and Notch pathways of podocytes. **J Am Soc Nephrol.** 25, 2546-2557, 2014.
- 4) 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**. Clgalt1-deficient mice exhibit thrombocytopenia due to abnormal terminal differentiation of megakaryocytes. **Blood.** 122, 1649-1657, 2013.
- 5) Takase H, Yamadera R, Matsumoto K, Kubota Y, Ohtsu A, Suzuki R, Kojima T, 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.
- 6) 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.
- 7) 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

Comparative analyses of mouse and human genomes have strongly guided the importance of the pathology of mutant mice for understanding the mechanism of human diseases. Our main task are the development and characterization of new gene-modified mouse models for human diseases. Furthermore, we investigate a new strategy for genome modification in the mouse and develop a novel mouse resource with the genome editing.

Projects for Graduate Students in Doctoral or Master's Programs

- 1) Development of mouse models for human diseases
- 2) Development of genome modification technology for mutant mouse production
- 3) Development of mouse resources such as Cre-driver and Cre-reporter mice

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

- 1) Manipulation of mouse embryos
- 2) Genome manipulation including CRISPR/Cas9
- 3) Manipulation of mouse embryonic stem cells

Recent Publications

- 1) Hasegawa Y, Hoshino Y, Abdelaziz E. Ibrahim, Kato K, Daitoku Y, Tanimoto Y, Ikeda Y, Oishi H, Takahashi S, Yoshiki A, Yagami K, Iseki H, **Mizuno S**, **Sugiyama F**, Generation of CRISPR/Cas9-mediated bicistronic knock-in *Ins1*-cre driver mice. *Exp Anim.* 65:319-327, 2016
- 2) Al-Soudy AS, Nakanishi T, **Mizuno S**, Hasegawa Y, Shawki HH, Katoh MC, Basha WA, Ibrahim AE, El-Shemy HA, Iseki H, Yoshiki A, Hiromori Y, Nagase H, Takahashi S, Oishi H, **Sugiyama F**. Germline recombination in a novel Cre transgenic line, *Prl3b1*-cre mouse. *Genesis.* 2016 54:389-397, 2016.
- 3) **Mizuno S**, Takami K, Daitoku Y, Tanimoto Y, Dinh TT, Mizuno-Iijima S, Hasegawa Y, Takahashi S, **Sugiyama F** (corresponding author), Yagami K. Peri-implantation lethality in mice carrying megabase-scale deletion on 5q3.3 is caused by *Exoc1* null mutation. *Sci Rep.* 5:13632, 2015
- 4) **Mizuno S**, Tra DT, Kato K, Iijima S, Tanimoto Y, Daitoku Y, Hoshino Y, Ikawa M, Takahashi S, **Sugiyama F** (corresponding author), and Yagami K. Simple generation of albino C57BL/6J mice with G291T mutation in the tyrosinase gene by the CRISPR/Cas9 system. *Mamm Genome.* 327-334, 2014
- 5) **Mizuno S**, Tra DT, Mizobuchi A, Iseki H, Iijima S, Kim JD, Ishida J, Matsuda Y, Kunita S, Fukamizu A, **Sugiyama F** (corresponding author), Yagami K. Truncated *Cales1* causes agenesis of the corpus callosum in mice. *Lab Invest.* 94:321-330, 2014

Experimental Pathology

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Major Scientific Interests of the Group

The dynamics and molecular mechanisms how cancer cells grow in our body. The roles of transforming growth factor- β -related molecules in cancer stem cells and cancer progression, and the development of cancer stem cell targeting therapy using non-standard macrocyclic peptides.

Projects for Regular Students in Doctoral or Master's Programs

- 1) Molecular mechanisms of TGF- β -related molecules (TMEPAI, MAF K, GPNMB etc.) in cancer stem cells and cancer progression.
- 2) Molecular mechanisms of a TGF- β related molecule (TSC22D4/THG-1) in squamous cell carcinoma formation
- 3) Establishment of cancer stem cell targeting therapy using non-standard macrocyclic peptides

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 formation, matrigel invasion, etc.)

Recent Publications

- 1) Yoon JH, Sudo K, Kuroda M, **Kato M**, Lee IK, Han JS, Nakae S, Imamura T, Kim J, Ju JH, Kim DK, Matsuzaki K, Weinstein M, Matsumoto I, Sumida T, Mamura M. Phosphorylation status determines the opposing functions of Smad2/Smad3 as STAT3 cofactors in TH17 differentiation. *Nat. Commun.* 6: 7600, 2015.
- 2) Vo Nguyen TT, Watanabe Y, Shiba A, Noguchi M, Itoh S and **Kato M**. TMEPAI/PMEPA1 enhances tumorigenic activities in lung cancer cells. *Cancer Sci.* 105: 334-341, 2014.
- 3) 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.
- 4) 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.
- 5) 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.
- 6) 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.
- 7) 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.
- 8) 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

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) Sato T, Shiba-Ishii A, Kim Y, Dai T, Husni RE, Hong JM, Kano J, Sakashita S, Iijima T, and **Noguchi M.** miR-3941: a novel microRNA that controls IGBP1 expression and is associated with malignant progression of lung adenocarcinoma. **Cancer Sci** (in press)
- 2) Iyama S, Ono M, Kawai-Nakahra H, Husuni RE, Dai T, Shiozawa T, Sakata A, Kohrogi H, and **Noguchi M.** Drebrin: A new oncofetal biomarker associated with prognosis of lung adenocarcinoma. **Lung Cancer** 102:74-81, 2016.
- 3) Husuni RE, Shiba-Ishii A, Iyama S, Shiozawa T, Kim Y, Nakagawa T, Sato T, Kano J, Minami Y, and **Noguchi M.** DNMT3a expression pattern and its prognostic value in lung adenocarcinoma. **Lung Cancer** 97:59-65, 2016.
- 4) Shiozawa T, Iyama S, Toshima S, Sakata A, Usui S, Minami Y, Sato Y, Hizawa N, and **Noguchi M.** Dimethylarginine dimethylaminohydrolase promotes tumor angiogenesis in lung adenocarcinoma. **Virchows Arch** 468:179-190, 2016
- 5) Shiba-Ishii A, Kim Y, Shiozawa T, Iyama S, Satomi K, Kano J, Sakashita S, Morishita Y, and **Noguchi M.** Statfin accelerates progression of lung adenocarcinoma at an early state. **Mol Cancer** 14:142-147, 2015
- 6) Shiba-Ishii A and **Noguchi M.** Aberrant Stratifin overexpression is regulated by tumor-associated CpG demethylation in lung adenocarcinoma. **Am J Pathol** 180:1653-1662, 2012.

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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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) Honda S, Sato K, Totsuka N, Fujiyama S, Fujimoto M, Miyake K, Nakahashi-Oda C, Tahara-Hanaoka S, Shibuya K, **Shibuya A**. Marginal zone B cells exacerbate endotoxic shock via interleukin-6 secretion induced by Fcα/μR-coupled TLR4 signalling. *Nat Commun*, 7:11498, 2016
- 2) Nakahashi-Oda C, Udayanga KGS, Nakamura Y, Nakazawa Y, Miki H, Iino S, Tahara-Hanaoka S, Shibuya K, **Shibuya A**. Apoptotic epithelial cells control the abundance of Treg cells at barrier surfaces. *Nat Immunol*, 17:441-450, 2016
- 3) Totsuka N, Kim Y, Kanemaru K, Niizuma K, Umemoto E, Nagai K, Tahara-Hanaoka S, Nakahashi-Oda C, Honda S, Miyasaka M, Shibuya K, **Shibuya A**. Toll-like receptor 4 and MAIR-II/CLM-4/LMIR2 immunoreceptor regulate VLA-4-mediated inflammatory monocyte migration. *Nat Commun*, 5:4710, 2014
- 4) Kim Y, Udayanga K G S, Totsuka N, Weinberg J B, Núñez G, **Shibuya A**. Gut Dysbiosis Promotes M2 Macrophage Polarization and Allergic Airway Inflammation via Fungi-Induced PGE2. *Cell Host Microbe*, 15:95–102, 2014
- 5) 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*, 209:1493-1503, 2012
- 6) Hitomi K, Tahara-Hanaoka S, Someya S, Fujiki A, Tada H, Sugiyama T, Shibayama S, Shibuya K, **Shibuya A**. An immunoglobulin-like receptor, Allergin-1, inhibits immunoglobulin E-mediated immediate hypersensitivity reactions. *Nat Immunol*. 11:601-607, 2010

Regenerative Medicine and Stem Cell Biology

Principal Investigator Osamu Ohneda

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Major Scientific Interests of the Group

- 1) Identification and analyses of functional stem cells for cell therapy
- 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

- 1) The role of Hypoxia in Mesenchymal stem cell development
- 2) Neural Differentiation of ES cells

Recent Publications

- 1) Kobayashi S, Yamashita T, Ohneda K, Nagano M, Kimura K, Nakai H, Poellinger L, Ohneda O. Hypoxia-inducible factor-3 α promotes angiogenic activity of pulmonary endothelial cells by repressing the expression of the VE-cadherin gene. **Genes Cells**. 2015; Jan 28. doi: 10.1111/gtc.12215.
- 2) Tsuboi I, Yamashita T, Nagano M, Kimura K, Salazar GT, Ohneda O. Impaired expression of HIF-2 α induces compensatory expression of HIF-1 α for the recovery from anemia. **J Cell Physiol**. 2015; Jan 3. doi: 10.1002/jcp.24899.
- 3) Zhao Y, Matsuo-Takasaki M, Tsuboi I, Kimura K, Salazar GT, Yamashita T, Ohneda O. Dual functions of hypoxia-inducible factor 1 alpha for the commitment of mouse embryonic stem cells toward a neural lineage. **Stem Cells Dev**. 2014; 23: 2143-2155.
- 4) Fukuda S, Nagano M, Yamashita T, Kimura K, Tsuboi I, Salazar G, Ueno S, Kondo M, Kunath T, Oshika T, Ohneda O. Functional endothelial progenitor cells selectively recruit neurovascular protective monocyte-derived F4/80(+) / Ly6c(+) macrophages in a mouse model of retinal degeneration. **Stem Cells**. 2013; 31: 2149-2161.
- 5) 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.
- 6) 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.
- 7) Yamashita T, Ohneda O, Sakiyama A, Iwata F, Ohneda K, and Fujii-Kuriyama Y. The microenvironment for erythropoiesis is regulated by HIF-2 α through VCAM-1 in endothelial cells. **Blood**. 2008; 112: 1482-1492.
- 8) Yamashita T, Ohneda K, Nagano M, Miyoshi C, Kaneko N, Miwa Y, Yamamoto M, Ohneda O, and Fujii-Kuriyama Y. HIF-2 α in endothelial cells regulates tumor neovascularization through activation of ephrin A1. **J Biol. Chem**. 2008; 283: 18926-18936.
- 9) 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.

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**, Morita M, Ohshima N, and Sato C. Expansion of mouse hematopoietic progenitor cells in three-dimensional cocultures on frozen-thawed stromal cell layers formed within porous scaffolds. **Exp Hematol** 43: 115-124, 2015.
- 2) **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.
- 3) **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.
- 4) **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.
- 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.

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 virus and adenovirus. 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

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

Selected Recent Publications

- 1) Asaka MN, Kawaguchi A*, Sakai Y, Mori K, Nagata K*. Polycomb repressive complex 2 facilitates the nuclear export of the influenza viral genome through the interaction with M1. *Sci. Rep.*, 2016;6: 33608.
- 2) Kawaguchi A*, Hirohama M, Harada Y, Osari S, Nagata K. Influenza virus induces cholesterol-enriched endocytic recycling compartments for budzone formation via cell cycle-independent centrosome maturation. *PLoS Pathog.*, 2015; 11(11): e1005284.
- 3) Sugiyama K, Kawaguchi A, Okuwaki M, Nagata K*. pp32 and APRIL are host cell-derived regulators of influenza virus RNA synthesis form cRNA. *eLife*, 2015;4.pii:e08939.
- 4) Imamura K, Imamachi N, Akizuki G, Kumakura M, Kawaguchi A, et al.. Long Noncoding RNA NEAT-1-Dependent SFPQ Relocation from Promoter Region to Paraspeckle Mediates IL8 Expression upon Immune Stimuli. *Mol. Cell*, 2014;53(3):393-406.
- 5) 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.
- 6) 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.

Microbiology

Principal Investigator Kazuya Morikawa

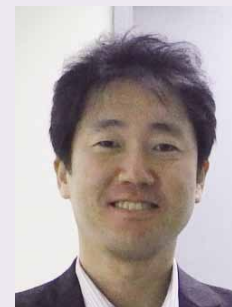
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Major Scientific Interests of the Group

We are studying evolutionary/adaptation strategies of Gram-positive pathogens. Major research interests include the population heterogeneity, and the acquisition of antibiotics resistance. The main research target is the important human pathogen, *Staphylococcus aureus*, that inhabits in our nasal cavity but can cause a variety of diseases.

Projects for Regular Students in Doctoral or Master's Programs

- 1) Natural genetic competence in gram positive pathogens
- 2) Population heterogeneity
- 3) Dynamics of cellular structures: nucleoid and membrane
- 4) Interaction of flora and nasal epithelial cells

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 microscope

Recent Publications

- 1) Medrano Romero V, and **Morikawa K**. *Listeria monocytogenes* σ^H contributes to expression of competence genes and intracellular growth. *J Bacteriol* 198, 1207-1217. 2016
- 2) Cafini F, Nguyen le TT, Higashide M, Román F, Prieto J, and **Morikawa K**. Horizontal Gene Transmission of *cfr* gene to MRSA and *Enterococcus*: role of *S. epidermidis* as reservoir and alternative pathway for the spread of linezolid resistance. *J Antimicrob Chemother* 71, 587-592. 2016
- 3) Ushijima Y, Yoshida O, Villanueva MJ, Ohniwa RL, and **Morikawa K**. Nucleoid clumping is dispensable for the Dps-dependent hydrogen peroxide resistance in *Staphylococcus aureus*. *Microbiol* 162, 1822-1828. 2016
- 4) Maudsdotter L, Imai S, Ohniwa RL, Saito S, and **Morikawa K**. *Staphylococcus aureus* dry stress survivors have a heritable fitness advantage in subsequent dry exposure. *Microb Infect* 17, 456-461. 2015
- 5) Ushijima Y, Ohniwa RL, Maruyama A, Saito S, Tanaka Y, and **Morikawa K**. Nucleoid compaction by MrgA^{Asp56Ala/Glu60Ala} does not contribute to staphylococcal cell survival against oxidative stress and phagocytic killing by macrophage. *FEMS Microbiol Lett* 360, 144-151. 2014
- 6) 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
- 7) 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* 338:141-146. 2013
- 8) **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

Molecular Parasitology

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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 and biosynthesis of hypermethylated cap 4 synthesis in *Trypanosome brucei*.
- 2) Functional characterization of mRNA recapping enzyme.
- 3) Defining the physiological targets for RNA ligase through genome wide screening.

Selected Publications

- 1) Gu H, Yoshinari S, Ghosh R, Ignatovich AV, Gollnick PD, Murakami KS and Ho CK. (2016) Structural and Mutational Analysis of Archaeal ATP-dependent RNA ligase Identifies Amino Acid Required for RNA Binding and Catalysis. **Nucleic Acid Res.** 44 (5):2337-2347
- 2) Smith P, Ho CK, Takagi Y, Djaballah H, and Shuman S. (2016) Nanomolar Inhibitors of *Trypanosoma brucei* RNA Triphosphatase. **mBio** 7(1):e00058-16. doi:10.1128/mBio.00058-16.
- 3) Ignatovich AV, Takagi Y, Liu Y, Nagata K, and Ho CK. (2015) The messenger RNA decapping and recapping pathway in *Trypanosoma*. **Proc. Natl. Acad. Sci. USA** 112:6967-6972.
- 4) Torchea C, Takagi Y and Ho CK. (2008) Archaea RNA Ligase is a Homodimeric Protein that Catalyzes Intramolecular Ligation of Single-Stranded RNA and DNA. **Nucleic Acid Res.** 36:6218-6227.
- 5) Takagi Y, Sindkar S, Ekonomidis D, Hall MP and Ho CK. (2007) *Trypanosoma brucei* Encodes a Bifunctional Capping Enzyme Essential for Cap 4 Formation on the Spliced Leader RNA. **J. Biol. Chem.** 282:15995-16005.
- 6) Hall MP and Ho CK. (2006) Characterization of a *Trypanosoma brucei* mRNA Cap (Guanine N-7) Methyltransferase. **RNA** 12:488-497.
- 7) Hall MP and Ho CK. (2006) Functional Characterization of a 48-kDa *Trypanosoma brucei* Cap 2 RNA Methyltransferase. **Nucleic Acid Res.** 34:5594-5602.
- 8) 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. (2005) Identification of the MicroRNAs of the Herpesvirus Family. **Nature Method** 2: 269-276.

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) **Koganezawa T**, Paton JFR Intrinsic chemosensitivity of rostral ventrolateral medullary sympathetic premotor neurons in the in situ arterially perfused preparation of rats. **Exp Physiol**. 99(11), 1453-66 (2014)
- 2) 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)
- 3) **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)
- 4) **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)
- 5) Wang R, **Koganezawa T**, Terui N. Different responses of sympathetic premotor neurons in the rostral ventrolateral medulla to stimulation of the dorsomedial hypothalamus in rabbits. **Brain Res**, 1356, 44-53 (2010)
- 6) 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)
- 7) **Koganezawa T**, Shimomura Y, Teuri N. The role of the RVLM neurons in the viscerosympathetic reflex: A mini review. **Auton Neurosci**, 142(1-2), 17-19. (2008)
- 8) **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)

Cognitive and Behavioral Neuroscience

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

Radiation Biology

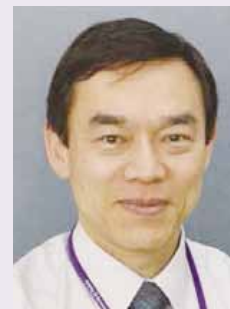
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Major Scientific Interests of the Group

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, **Tsuboi K**: 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, **Tsuboi K**: 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.

Vascular Matrix Biology

Principal Investigator Hiromi Yanagisawa

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Other Faculty Members

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Assistant Professor: Aiko Sada: aisada@tara.tsukuba.ac.jp



Major Scientific Interests of the Group

The maintenance of a proper extracellular environment comprised of extracellular matrices (ECM), ECM degrading enzymes, cytokines/growth factors, and physical factors, is crucial for normal development and stem cell functions. The long-term goal of our research is to investigate the interactions between extracellular environment and various cell types and elucidate how they modulate intracellular signaling, cellular functions, and cell fate. In particular, we focus on the vessel wall and ECM. We aim to identify novel ECM proteins and characterize their biochemical properties, as well as to investigate pathophysiological functions by taking cellular, molecular biological, and genetic engineering approaches.

Projects for Regular Students in Doctoral or Master's Programs

- Molecular mechanism of aortic aneurysm formation
- Characterization of transcriptional cascade in smooth muscle cells induced by increased stiffness and mechanical stress
- Novel ECM and renal calcification
- Identification of novel niche for epidermal stem cells

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

- Genetic and phenotypic identification of mutant mice with defective ECM
- Preparation of histological sections and expression analysis by immunostaining

Recent Publications

- 1) **Y. Yamashiro**, C. L. Papke, J. Kim, L.-J. Ringuette, Q.-J. Zhang, Z.-P. Liu, H. Mirzaei, J. E. Wagenseil, E. C. Davis and **H. Yanagisawa**: Abnormal mechanosensing and cofilin activation promote the progression of ascending aortic aneurysms in mice. *Science Sig.* 8(399):ra105 (2015).
- 2) C. L. Papke and **H. Yanagisawa**: Fibulin-4 and fibulin-5 in elastogenesis and beyond: insights from mouse and human studies. *Invited mini review to Matrix Biology.* 37:142-9. (2014).
- 3) J. Huang, **Y. Yamashiro***, C. L. Papke*, Y. Ikeda*, Y. Lin, M. Patel, T. Inagami, V. P. Le, J. E. Wagenseil and **H. Yanagisawa**: Angiotensin converting enzyme-induced activation of local angiotensin signaling is required for ascending aortic aneurysms in fibulin-4 deficient mice. *Science Transl. Med.* 5, 183ra58 (2013).
- 4) M. Budatha, S. Roshanravan, Q. Zheng, C. Weislander, S. L. Chapman, E. C. Davis, B.C. Starcher, R. A. Word* and **H. Yanagisawa***: Extracellular matrix proteases contribute to progression of pelvic organ prolapse in mice and humans. *J Clin Invest.* 121(5):2048-59 (2011). (Featured in Commentaries in *JCI*, Featured in "Clinical Implication of Basic Research" in *N. Eng. J. Med.*)
- 5) J. Huang, E. C. Davis, S. L. Chapman, L. Y. Budatha, M., Marmorstein, R. A. Word and **H. Yanagisawa**: Fibulin-4 deficiency results in ascending aortic aneurysms: a potential link between abnormal smooth muscle cell phenotype and aneurysm progression. *Circ Res.* 106(3):583-592 (2010).

Molecular and Genetic Epidemiology

Principal Investigator Naoyuki Tsuchiya

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Other Faculty Members

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Major Scientific Interests of the Group

Our laboratory is interested in genetic polymorphisms and their molecular mechanisms involved in the development of human autoimmune rheumatic diseases such as systemic lupus erythematosus, ANCA-associated vasculitis, rheumatoid arthritis and systemic sclerosis.

Projects for Regular Students in Doctoral or Master's Programs

- 1) Identification of polymorphisms associated with autoimmune rheumatic diseases
- 2) Functional analysis of polymorphisms associated with autoimmune rheumatic diseases

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

Genome database (tutorial), SNP typing (laboratory).

Recent Publications

- 1) **Hachiya Y, Kawasaki A, Oka S**, Kondo Y, Ito S, Matsumoto, Kusaoi M, Amano H, Suda A, Setoguchi K, Nagai T, Shimada K, Sugii S, Okamoto A, Chiba N, Suematsu E, Ohno S, Katayama M, Kono H, Hirohata S, Takasaki Y, Hashimoto H, Sumida T, Nagaoka S, Tohma S, **Furukawa H, Tsuchiya N**. Association of HLA-G 3' untranslated region polymorphisms with systemic lupus erythematosus in a Japanese population: a case-control association study. **PLoS ONE** 2016;11:e0158065.
- 2) **Kawasaki A, Hasebe N, Hidaka M**, Hirano F, Sada K-e, Kobayashi S, Yamada H, **Furukawa H**, Yamagata K, Sumida T, Miyasaka N, Tohma S, Ozaki S, Matsuo S, Hashimoto H, Makino H, Arimura Y, Harigai M, **Tsuchiya N**. Protective role of HLA-DRB1*13:02 against microscopic polyangiitis and MPO-ANCA positive vasculitides in a Japanese population: a case-control study. **PLoS ONE** 2016;11:e0154393.
- 3) **Furukawa H, Oka S, Kawasaki A**, Shimada K, Sugii S, Matsushita T, Hashimoto A, Komiya A, Fukui N, Kobayashi K, Osada A, Ihata A, Kondo Y, Nagai T, Setoguchi K, Okamoto A, Okamoto A, Chiba N, Suematsu E, Kono H, Katayama M, Hirohata S, Sumida T, Migita K, Hasegawa M, Fujimoto M, Sato S, Nagaoka S, Takehara K, Tohma S, **Tsuchiya N**. Human leukocyte antigen and systemic sclerosis in Japanese: The sign of the four independent protective alleles, DRB1*13:02, DRB1*14:06, DQB1*03:01, and DPB1*02:01. **PLoS ONE** 2016;11:e0154255.
- 4) Gazal S, Sacre K, Allanore Y, Teruel M, Goodall AH (The CARDIOGENICS consortium), Tohma S, Alfredsson L, Okada Y, Xie G, Constantin A, Balsa A, **Kawasaki A**, Nlicaise P, Amos C, Rodriguez-Rodriguez L, Chiocchia G, Boileau C, Zhang J, Vittecoq O, Barnette T, Gonzalez-Gay MA, **Furukawa H**, Cantagrel A, Le Loet X, Sumida T, Hurtado-Nedelec M, Richez C, Chollet-Martin S, Schaefferbeke T, Combe B, Khoriaty L, Coustet B, El-Benna J, Siminovitch K, Plenge R, Padyukov L, Martin J, **Tsuchiya N**, Dieude P. Identification of secreted phosphoprotein 1 gene as a new rheumatoid arthritis susceptibility gene. **Ann Rheum Dis** 2015;74:e19.
- 5) **Kawasaki A, Furukawa H**, Nishida N, Warabi E, Kondo Y, Ito S, Matsumoto I, Kusaoi M, Amano H, Suda A, Nagaoka S, Setoguchi K, Nagai T, Hirohata S, Shimada K, Sugii S, Okamoto A, Chiba N, Suematsu E, Tokunaga K, Takasaki Y, Hashimoto H, Sumida T, Tohma S, **Tsuchiya N**. Association of functional polymorphisms in Interferon Regulatory Factor 2 (IRF2) with susceptibility to systemic lupus erythematosus: A case-control association study. **PLoS ONE** 2014;9: e109764.
- 6) **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.

Public Health Medicine

Principal Investigator Kazumasa Yamagishi

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Major Scientific Interests of the Group

Epidemiology and prevention of lifestyle-related diseases in communities

Recent Publications

- 1) **Yamagishi K**, Ikeda A, Chei CL, Noda H, Umesawa M, Cui R, Muraki I, Ohira T, Imano H, Sankai T, Okada T, Tanigawa T, Kitamura A, Kiyama M, Iso H; for the CIRCIS Investigators. Serum α -linolenic and other ω -3 fatty acids, and risk of disabling dementia: community-based nested case control study. *Clin Nutr* in press
- 2) Sairenchi T, Iso H, **Yamagishi K**, Irie F, Nagao M, Umesawa M, Haruyama Y, Kobashi G, Watanabe H, Ota H. Impact and burden of each obesity-related cardiovascular risk factor in combination with abdominal obesity on total health expenditures in adult Japanese National Health Insurance beneficiaries: the Ibaraki Prefectural Health Study. *J Epidemiol* in press.
- 3) Saito I, **Yamagishi K**, Kokubo Y, Yatsuya H, Iso H, Sawada N, Inoue M, Tsugane S. Association between mortality and incidence rates of coronary heart disease and stroke: The Japan Public Health Center-based Prospective (JPHC) Study. *Int J Cardiol* 2016; 222:281-286.
- 4) Sata M, **Yamagishi K**, Sairenchi T, Ikeda A, Irie F, Watanabe H, Iso H, Ota H. Impact of caregiver type for 3-year-old children on subsequent between-meal eating habits and being overweight from childhood to adulthood: A 20-year follow-up of the Ibaraki Children's Cohort (IBACHIL) Study. *J Epidemiol* 2015; 25:600-607

Environmental Medicine

Principal Investigator Yoshito Kumagai

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Other Faculty Members

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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) Unoki T, Abiko Y, Toyama T, Uehara T, Tsuboi K, Nishida M, Kaji T, **Kumagai Y**. Methylmercury, an environmental electrophile capable of activation and disruption of the Akt/CREB/Bcl-2 signal transduction pathway in SH-SY5Y cells. *Sci Rep* **6**: 28944, 2016.
- 2) Ida T, Sawa T, Ihara H, Tsuchiya Y, Watanabe Y, **Kumagai Y**, Suematsu M, Motohashi H, Fujii S, Matsunaga T, Yamamoto M, Ono K, Devarie-Baez NO, Xian M, Fukuto JM, Akaike T. Reactive cysteine persulfides and S-polythiolation regulate oxidative stress and redox signaling. *Proc Natl Acad Sci USA* **111**: 7606-7611, 2014.
- 3) 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 sulf hydration. *Nature Chem Biol* **8**: 714-724, 2012.
- 4) 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.
- 5) 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.

Occupational Psychiatry / Space Medicine ^{#1}

Longevity medicine Endowed Chair ^{#2}

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Other Faculty Members

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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

Molecular and Developmental Biology

Principal Investigator Makoto Kobayashi

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Major Scientific Interests of the Group

- 1) Gene regulation in the cellular defense mechanisms against a variety of stresses
- 2) Gene regulation in the cell-fate determination especially in hematopoiesis

Projects for Graduate Students in Doctoral or Master's Programs

- 1) Stress sensors in the Keap1-Nrf2 system
- 2) Gene regulation of Nrf2-dependent cytoprotective genes
- 3) Determination of hematopoietic and endothelial cell fate
- 4) Determination of erythropoietic and myelopoietic cell fate
- 5) Relationship between cell differentiation and energy pathways

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

- 1) Gene expression analyses using zebrafish embryos by whole-mount *in situ* hybridization
- 2) Examination of toxicity/medicinal effects of oxidants and/or anti-oxidants using zebrafish embryos

Recent Publications

- 1) Nguyen TV, Fuse Y, Tamaoki J, Akiyama S, Muratani M, Tamaru Y, **Kobayashi M**. Conservation of the Nrf2-mediated gene regulation of proteasome subunits and glucose metabolism in zebrafish. *Oxid Med Cell Longev*, 2016:5720574,2016
- 2) Fuse Y, Nguyen VT, **Kobayashi M**. Nrf2-dependent protection against acute sodium arsenite toxicity in zebrafish. *Toxicol Appl Pharmacol*, 305:136-142,2016
- 3) Takeuchi M, Fuse Y, Watanabe M, Andrea CS, Takeuchi M, Nakajima H, Ohashi K, Kaneko H, Kobayashi-Osaki M, Yamamoto M, **Kobayashi M**. LSD1/KDM1A promotes hematopoietic commitment of hemangioblasts through downregulation of Etv2. *Proc Natl Acad Sci USA*, 112: 13922-13927,2015
- 4) Fuse Y, Nakajima H, Nakajima-Takagi Y, Nakajima O, **Kobayashi M**. Heme-mediated inhibition of Bach1 regulates the liver specificity and transience of the Nrf2-dependent induction of zebrafish heme oxygenase 1. *Genes Cells*, 20:590-600,2015
- 5) Mukaigasa K, Nguyen LTP, Li L, Nakajima H, Yamamoto M, **Kobayashi M**. Genetic evidence of an evolutionarily conserved role for Nrf2 in the protection against oxidative stress. *Mol Cell Biol*, 32: 4455-4461,2012
- 6) Nakajima H, Nakajima-Takagi Y, Tsujita T, Akiyama S, Wakasa T, Mukaigasa K, Kaneko H, Tamaru Y, Yamamoto M, **Kobayashi M**. Tissue-restricted induction of Nrf2 and its target genes in zebrafish with gene-specific variations in the induction profiles. *PLoS ONE*, 6:e26884,2011
- 7) Tsujita T, Li L, Nakajima H, Iwamoto N, Nakajima-Takagi Y, Ohashi K, Kawakami K, Kumagai Y, Freeman BA, Yamamoto M, **Kobayashi M**. Nitro-fatty acids and cyclopentenone prostaglandins share strategies to activate the Keap1-Nrf2 system: a study using green fluorescent protein transgenic zebrafish. *Genes Cells*, 16:46-57,2011
- 8) **Kobayashi M**. Harnessing the antioxidant power with ARE-inducing compounds. *Chem Biol*, 17: 419-420,2010

Medical Genetics

Principal Investigator Emiko Noguchi

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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.

Legal Medicine

Principal Investigator Katsuya Honda

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Other Faculty Members

Assistant Professor Yukiko Sugano

Research assistant Fujio Ishizawa



Major Scientific Interests of the Group

- 1) Development of innovative DNA profiling
- 2) Pathology of the cardiac sudden death
- 3) Development of a hypersensitive toxicological test
- 4) Study of the social aspect of the medical history

Projects for Regular Students in Doctoral or Master's Programs

Mitochondrial polymorphisms associated with fetal diseases in Japanese
Forensic DNA analysis using next generation sequencing

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

Forensic DNA typing, LC/MS/MS and GC analysis, ICP- AES analysis, Microscopic Analysis

Recent Publications

- 1) **K Honda**. DNA analysis overturns the death sentence of a condemned criminal held in custody for 8 years. **Forensic Sci Int Genet**. 2015;16:e5-e6.
- 2) **K Honda**, Muramatsu H, Hashimoto R, Iwabichi Y, Tatsuzawa C, Yano S, **Sugano Y**. The mitochondrial DNA polymorphisms in chromosomal aberration detected by next generation sequence. **Forensic Sci Int Genet SS**. 2015;5:e375–e377.
- 3) Yano S, **Honda K**, Kaminiwa J, Nishi T, **Sugano Y**. DNA extraction for short tandem repeat typing from mixed samples using anti-human leukocyte CD45 and ABO blood group antibodies. **Forensic Sci Int Genet**. 2014;10:17-22.
- 4) Nishi T, Kurosu A, **Sugano Y**, Kaminiwa J, Sekine Y, Yano S, **Honda K**. Application of a novel multiplex polymerase chain reaction system for 12 X-chromosomal short tandem repeats to a Japanese population study. **Legal Med**. 2013;15:43-46.
- 5) **Honda K**. The Ashikaga case of Japan—Y-STR testing used as the exculpatory evidence to free a convicted felon after 17.5 years in prison. **Forensic Sci Int Genet**. 2012;6:e1-e2.
- 6) **Sugano Y**, **Honda K**. The Succession of the Hippocratic Corpus in Modern Greece. **J Japan Society of Med History**. 2010;56:67-76.

Genome Biology

Principal Investigator Masafumi Muratani

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Major Scientific Interests

We develop methods for genome and epigenome analysis of limited samples. Main area of application is characterization of clinical tissue samples from Tsukuba Human Tissue Bank. We try to link histopathological features of human diseases to regulatory status of the genome.

Projects for Regular Students in Doctoral or Master's Programs

- 1) Clinical sample analysis using chromatin immunoprecipitation combined with 2nd generation sequencing (ChIPseq) and RNAseq, data analysis and validation of potential disease biomarkers.
- 2) Genomics and epigenomics analysis of human and experimental mouse samples at single-cell resolution.

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

- 1) Access to genomics databases, integrative analysis of regulatory regions, gene expression and genetic variations.
- 2) Genomics and epigenomics assays, chromatin immunoprecipitation, RNA assays and genotyping.

Selected Publications

- 1) Kumar V*, Rayan NA*, **Muratani M***, Lim S, Elanggovan B, Lixia X, Lu T, Makhija H, Poschmann J, Lufkin T, Ng HH, Prabhakar S. Comprehensive benchmarking reveals H2BK20 acetylation as a distinctive signature of cell-state-specific enhancers and promoters. *Genome Res.* pii: gr.201038.115, 2016. (*Equal contribution)
- 2) Kakran M*, **Muratani M***, Tng WJ, Liang H, Trushina DB, Sukhorukov GB, Ng HH, Antipina MN. Layered polymeric capsules inhibiting the activity of RNases for intracellular delivery of messenger RNA. *J. Mater. Chem. B.* Vol.3, 5842-5848, 2015. (*Equal contribution)
- 3) **Muratani M**, Deng N, Ooi WF, Lin SJ, Xing M, Xu C, Qamra A, Tay ST, Malik S, Wu J, Lee MH, Zhang S, Tan LL, Chua H, Wong WK, Ong HS, Ooi LL, Chow PK, Chan WH, Soo KC, Goh LK, Rozen S, Teh BT, Yu Q, Ng HH, Tan P. Nanoscale chromatin profiling of gastric adenocarcinoma reveals cancer-associated cryptic promoters and somatically acquired regulatory elements. *Nat Commun.* 5:4361, 2014.
- 4) V. Kumar, **M. Muratani**, N.A. Rayan, P. Kraus, T. Lufkin, H.H. Ng, S. Prabhakar. Uniform, optimal signal processing of mapped deep-sequencing data. *Nature Biotechnology*, Vol.31(7), 615-22, 2013
- 5) J.H. Ng*, V. Kumar*, **M. Muratani***, P. Kraus, J.C. Yeo, L.P. Yaw, K. Xue, T. Lufkin, S. Prabhakar, H.H. Ng: In vivo epigenomic profiling of germ cells reveals germ cell molecular signatures, *Developmental Cell*, Vol.24(3), 324-33, 2013 (*Equal contribution)

Behavioral Neuroscience

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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 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 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) 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.
- 2) 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.
- 3) 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.
- 4) Lee, I.T., Chang, A.S., Manandhar, M., Shan, Y., Fan, J., Izumo, M., Ikeda, Y., Motoike, T., Dixon, S., Seinfeld, E.J., Takahashi, S.J., Yanagisawa, M. Neuromedin S-Producing Neurons Act as Essential Pacemakers in the Suprachiasmatic Nucleus to Couple Clock Neurons and Dictate Circadian Rhythms. *Neuron* **85**:1086-1102, 2015
- 5) Nagahara, T., Saitoh, T., Kutsumura, N., Irukayama-Tomobe, Y., Ogawa, Y., Kuroda, D., Gouda, H., Kumagai, H., Fujii, H., Yanagisawa, M., Nagase, H. Design and synthesis of non-peptide, selective orexin receptor 2 agonists. *J. Med. Chem.* **58**: 7931-7937, 2015.
- 6) Funato, H., Miyoshi, C., Fujiyama, T., Kanda, T., Sato, M., Wang, Z., Ma, J., Nakane, S., Tomita, J., Ikkyu, A., Kakizaki, M., Hotta, N., Kanno, S., Komiya, H., Asano, F., Honda, T., Kim, J.S., Harano, K., Muramoto, H., Yonezawa, T., Mizuno, S., Miyazaki, S., Connor, L., Kumar, V., Miura, I., Suzuki, T., Watanabe, A., Abe, M., Sugiyama, F., Takahashi, S., Sakimura, K., Hayashi, Y., Liu, Q., Kume, K., Wakana, S., Takahashi, J.S., Yanagisawa, M. Forward genetic analysis of sleep in randomly mutagenized mice. *Nature* **539**: 378-383, 2016
- 7) Ogawa, Y., Irukayama-Tomobe, Y., Murakoshi, N., Kiyama, M., Ishikawa, Y., Hosokawa, N., Tominaga, H., Uchida, S., Kimura, S., Kanuka, M., Morita, M., Hamada, M., Takahashi, S., Hayashi, Y., Yanagisawa, M. Peripherally administered orexin improves survival of mice with endotoxin shock. *eLife* DOI: 10.7554/eLife.21055, 2016
- 8) Irukayama-Tomobe, Y., Ogawa, Y., Tominaga, H., Ishikawa, Y., Hosokawa, N., Ambai, S., Kawabe, Y., Uchida, S., Nakajima, R., Saitoh, T., Kanda, T., Vogt, K., Sakurai, T., Nagase, H., Yanagisawa, M. A non-peptide orexin type-2 receptor agonist ameliorates narcolepsy-cataplexis symptoms in mouse models. *Proc. Natl. Acad. Sci. USA*, in press

Functional neuroanatomy

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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) Hiromasa Funato*, Chika Miyoshi, Tomoyuki Fujiyama, Takeshi Kanda, Makito Sato, Zhiqiang Wang, Jing Ma, Shin Nakane, Jun Tomita, Aya Ikkyu, Miyo Kakizaki, Noriko Hotta-Hirashima, Satomi Kanno, Haruna Komiya, Fuyuki Asano, Takato Honda, Staci J. Kim, Kanako Harano, Hiroki Muramoto, Toshiya Yonezawa, Seiya Mizuno, Shinichi Miyazaki, Linzi Connor, Vivek Kumar, Ikuo Miura, Tomohiro Suzuki, Atsushi Watanabe, Manabu Abe, Fumihiko Sugiyama, Satoru Takahashi, Kenji Sakimura, Yu Hayashi, Qinghua Liu, Kazuhiko Kume, Shigeharu Wakana, Joseph S Takahashi, Masashi Yanagisawa*.
Forward-genetics analysis of sleep in randomly mutagenized mice
Nature, 539, 378-383, 2016 (* corresponding author)
DOI: 10.1038/nature20142

- 2) Mohammad Sarowar Hossain, Fuyuki Asano, Tomoyuki Fujiyama, Chika Miyoshi, Makito Sato, Aya Ikkyu, Satomi Kanno, Noriko Hotta, Miyo Kakizaki, Takato Honda, Staci J. Kim, Haruna Komiya, Ikuo Miura, Tomohiro Suzuki, Kimio Kobayashi, Hideki Kaneda, Vivek Kumar, Joseph S. Takahashi, Shigeharu Wakana, Hiromasa Funato*, Masashi Yanagisawa* (*corresponding author)
Identification of mutations through dominant screening for obesity using C57BL/6 substrains
Scientific Reports 6:32453, 2016
DOI: 10.1038/srep32453

- 3) Kenkichi Takase, Yousuke Tsuneoka, Satoko Oda, Masaru Kuroda, Hiromasa Funato High-fat diet feeding alters olfactory-, social- and reward-related behaviors of mice independent of obesity
Obesity (Silver Spring) 24:886-894, 2016
doi: 10.1002/oby.21441

- 4) Takeshi Kanda, Natsuko Tsujino, Eriko Kuramoto, Yoshimasa Koyama, Etsuo A. Susaki, Sachiko Chikahisa, Hiromasa Funato
Sleep as a biological problem: an overview of frontiers in sleep research
Journal of Physiological Sciences 66:1-13, 2016
doi: 10.1007/s12576-015-0414-3

Medicinal Chemistry, Organic Chemistry

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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

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Researcher: Makito Sato, Ph.D.; Researcher: Daniela Klewe-Nebenius



Major Scientific Interests of the Group

- 1) RNA Interference and MicroRNAs
- 2) Molecular Mechanism of Sleep/Wake Regulation
- 3) Molecular Mechanism of Innate Fear

Projects for Regular Students in Doctoral or Master's Programs

- 1) We combine forward genetic screen and classical biochemical fractionation & reconstitution approaches to identify novel factors (e.g. R2D2, C3PO, and etc.) and characterize their precise function in the RNA Interference (RNAi) and microRNA pathways.
- 2) We will understand the fundamental mechanism of Sleep/Wake control by integrating mouse genetic screen, quantitative proteome/phosphor-proteome analysis of Sleepy mutant brains, classical biochemistry and modern neuroscience approaches.
- 3) We will understand the fundamental mechanism of innate fear (of predator) and the molecular principles of human emotions by conducting the first forward genetic screen in mice in search of the “fearless” mutants and the core molecular pathways underlying the fear response.

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

- 1) Molecular cloning (e.g. for constructing CRISPR knockout and knockin mice/cell lines)
- 2) “Fearless” screen
- 3) Sleep (EEG/EMG) recording

Recent Publications

- 1) Z. Wang, S. Liu, M. Kakizaki, Y. Hirose, Y. Ishikawa, H. Funato, M. Yanagisawa, Y. Yu, **Q. Liu**, Orexin/Hypocretin activates mTOR complex 1 (mTORC1) via an Erk/Akt-independent and calcium-stimulated lysosome v-ATPase pathway. *J Biol Chem*, 289: 31950-31959 (2014)
- 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)

Manipulation of memory during sleep

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Major Scientific Interests of the Group

Our group strives to investigate the function of sleep in memory. We have recently discovered that fear memory can be unlearned by exposing subject to a sound which is associated with the memory (Sci. Rep, in minor revision). Also, we found that fear memory can be manipulated by silencing the adult-born neurons during sleep using optogenetics (in prep). Our hope is that these findings will contribute to the development of new therapeutic strategy for memory related disorders including PTSD. We welcome motivated and self-driven students and researchers anytime for lab visiting.

Projects for Regular Students in Doctoral or Master's Programs

- 1) Optogenetic manipulation of memory during sleep
- 2) Imaging neuronal activity using miniaturized end-microscope
- 3) Molecular mechanisms of memory processing during sleep

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

- 4) Sleep-stage specific intervention of memory
- 5) Learning basic of optogenetics

Recent Publications (10 first/correspondent, 28 international publications)

- 1) **Sakaguchi M** 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) **Sakaguchi M** 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*, **Sakaguchi M***, 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) **Sakaguchi M**, 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) **Sakaguchi M.**, 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

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Researcher Yoko Takata, Ph.D.



Major Scientific Interests of the Group

- 1) Motivated behavior as a major sleep-regulating factor
- 2) Optopharmacology to regulate sleep
- 3) REM sleep and the links to the desire for sugary and fatty foods (<http://www.asahi.com/ajw/articles/AJ201701160072.html>)

Projects for Regular Students in Doctoral or Master's Programs

- 1) Use of genetically engineered systems to dissect neural circuitry regulating sleep and wakefulness
- 2) Development of optopharmacologic tools to control sleep
- 3) Living in space: hypothermia as risk factor for memory consolidation (Collaborative project with Satoshi Furukawa/ JAXA)
- 4) Role of brainstem neurons in linking REM sleep to the consumption of weight promoting foods

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) Optogenetic and chemogenetic modulation of neural circuitry by using stereotaxic microinjections of viral vectors
- 4) Immunohistochemistry and in situ hybridization of brain tissue

Recent Publications

- 1) McEown K, Takata Y, Cherasse Y, Nagata N, Aritake K, Lazarus M. Chemogenetic inhibition of the medial prefrontal cortex reverses the effects of REM sleep loss on sucrose consumption. *eLife*, 5: e20269, 2016
- 2) Oishi Y, Suzuki Y, Takahashi K, Yonezawa T, Kanda T, Takata Y, Cherasse Y, Lazarus M. Activation of ventral tegmental area dopamine neurons produces wakefulness through dopamine D2-like receptors in mice. *Brain Struct Funct*, doi: 10.1007/s00429-017-1365-7
- 3) 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.
- 4) 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.
- 5) 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.
- 6) 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.
- 7) 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).

Molecular Sleep Biology

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Researcher Olga Malyshevskaya, Ph.D.

Researcher Nanae Nagata



Major Scientific Interests of the Group

- 1) Role of prostaglandin D2 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) **Kaushik MK**, Kaul SC, Wadhwa R, Yanagisawa M, **Urade Y** Triethylene glycol, an active component of Ashwagandha (*Withania somnifera*) leaves, is responsible for sleep induction. *PLoS One*. 2017 *in press*
- 2) Saito H, **Cherasse Y**, Suzuki R, Mitarai M, Ueda F, **Urade Y**. Zinc-rich oysters as well as zinc yeast- and astaxanthin-enriched food improved sleep efficiency and sleep onset in a randomized controlled trial of healthy individuals. *Mol Nutr Food Res*. 2017 *in press*
- 3) Zhang BJ, Shao SR, **Aritake K**, Takeuchi A, **Urade Y**, Huang ZL, Lazarus M, Qu WM. Interleukin-1 β induces sleep independent of prostaglandin D2 in rats and mice. *Neuroscience*. 6;340:258-267. 2017
- 4) Kida T, Ayabe S, Omori K, Nakamura T, Maehara T, **Aritake K**, **Urade Y**, Murata T. Prostaglandin D2 Attenuates Bleomycin-Induced Lung Inflammation and Pulmonary Fibrosis. *PLoS One*. 19;11(12): e0167729. 2016
- 5) Nakamura Y, Midorikawa T, Monoi N, Kimura E, Murata-Matsuno A, Sano T, Oka K, Sugafuji T, Uchiyama A, Murakoshi M, Sugiyama K, Nishino H, **Urade Y**. Oral administration of Japanese sake yeast (*Saccharomyces cerevisiae* sake) promotes non-rapid eye movement sleep in mice via adenosine A2A receptors. *J Sleep Res*. 25(6):746-753. 2016
- 6) Nakamura T, Maeda S, Horiguchi K, Maehara T, **Aritake K**, Choi BI, Iwakura Y, **Urade Y**, Murata T. PGD2 deficiency exacerbates food antigen-induced mast cell hyperplasia. *Nat Commun*. 10;6:7514. 2015
- 7) **Cherasse Y**, Saito H, **Nagata N**, **Aritake K**, Lazarus M, **Urade Y**. Zinc-containing yeast extract promotes nonrapid eye movement sleep in mice. *Mol Nutr Food Res*. 59(10):2087-93. 2015
- 8) Trimarco A, Forese MG, Alfieri V, Lucente A, Brambilla P, Dina G, Pieragostino D, Sacchetta P, **Urade Y**, Boizet-Bonhoure B, Martinelli Boneschi F, Quattrini A, Taveggia C. Prostaglandin D2 synthase/GPR44: a signaling axis in PNS myelination. *Nat Neurosci*. 17(12):1682-92. 2014
- 9) Moniot B, Ujjan S, Champagne J, Hirai H, **Aritake K**, Nagata K, Dubois E, Nidelet S, Nakamura M, **Urade Y**, Poulat F, Boizet-Bonhoure B. Prostaglandin D2 acts through the Dp2 receptor to influence male germ cell differentiation in the foetal mouse testis. *Development*. 141(18):3561-71. 2014
- 10) **Kaushik MK**, **Aritake K**, Kamauchi S, Hayaishi O, Huang ZL, Lazarus M, **Urade Y**. Prostaglandin D2 is crucial for seizure suppression and postictal sleep, *Exp. Neurol*. 253:82-90. 2014

Sleep Neuroscience

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Major Scientific Interests of the Group

- 1) Cortical networks underlying sleep rhythms
- 2) The neural basis of sleep homeostasis
- 3) In-vivo functional imaging of neural activity

Projects for Regular Students in Doctoral or Master's Programs

- 1) The role of cortical neurons in the generation of sleep patterns
- 2) Cortical circuits as regulators of sleep homeostasis
- 3) Optogenetic control of sleep rhythms and its effects on sleep quality

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

- 1) Local field potential and EEG recordings
- 2) Basic neurophysiology (patch-clamp and field recordings in-vitro)
- 3) Functional imaging of neural activity
- 4) Generation and use of viral vectors

Recent Publications

- 1) Vogt K. Diversity in GABAergic signaling. *Adv Pharmacol.* 2015;73:203-22.
- 2) Willadt S, Canepari M, Yan P, Loew LM, Vogt KE. Combined optogenetics and voltage sensitive dye imaging at single cell resolution. *Front Cell Neurosci.* 2014;8:311.
- 3) Canepari M, Vogt KE, De Waard M, Zecevic D. Combining Ca²⁺ and membrane potential imaging in single neurons. *Cold Spring Harb Protoc.* 2013 Dec 1;2013(12):1161-4.
- 4) Willadt S, Nenniger M, Vogt KE. Hippocampal feedforward inhibition focuses excitatory synaptic signals into distinct dendritic compartments. *PLoS One.* 2013;8(11):e80984.
- 5) Baudouin SJ, Gaudias J, Gerharz S, Hatstatt L, Zhou K, Punnakal P, Tanaka KF, Spooren W, Hen R, De Zeeuw CI, Vogt K, Scheiffele P. Shared synaptic pathophysiology in syndromic and nonsyndromic rodent models of autism. *Science.* 2012 Oct 5;338(6103):128-32.
- 6) Vogt KE, Gerharz S, Graham J, Canepari M. High-resolution simultaneous voltage and Ca²⁺ imaging. *J Physiol.* 2011 Feb 1;589(Pt 3):489-94.

Brain Maturation/Evolution

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Major Scientific Interests of the Group

- 1) Elucidating the function of sleep
- 2) Revealing the evolutionary origin of REM and non-REM sleep
- 3) Developing new therapeutics for neural disorders

Projects for Regular Students in Doctoral or Master's Programs

- 1) Search for the function of REM sleep using mouse genetics
- 2) Search for the function of sleep using *C. elegans* genetics
- 3) Comparison of sleep-regulating neuron in animals with & without REM sleep
- 4) Development of novel therapeutics focusing on sleep-regulating neurons

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

- 1) Viral vector-mediated gene transfection in mice
- 2) Sleep analyses in roundworms in *C. elegans*

Recent Publications

- 1) Funato H, Miyoshi C, Fujiyama T, Kanda T, Sato M, Wang Z, Ma J, Nakane S, Tomita J, Ikkyu A, Kakizaki M, Hotta-Hirashima N, Kanno S, Komiya H, Asano F, Honda T, Kim SJ, Harano K, Muramoto H, Yonezawa T, Mizuno S, Miyazaki S, Connor L, Kumar V, Miura I, Suzuki T, Watanabe A, Abe M, Sugiyama F, Takahashi S, Sakimura K, Hayashi Y, Liu Q, Kume K, Wakana S, Takahashi JS, Yanagisawa M, "Forward-genetics analysis of sleep in randomly mutagenized mice," *Nature* 539, 378–383 (2016)
- 2) Hayashi Y, Kashiwagi M, Yasuda K, Ando R, Kanuka M, Sakai K, Itohara S, "Cells of a common developmental origin regulate REM/non-REM sleep and wakefulness in mice," *Science* 350, 957-961 (2015)
- 3) Hayashi Y, *Hirotsu T (*equal contribution), *Iwata R (*equal contribution), Kage-Nakadai E, Kunitomo H, Ishihara T, Iino Y, Kubo T, "A trophic role for Wnt-Ror kinase signaling during developmental pruning in *Caenorhabditis elegans*," *Nature Neuroscience* 12, 981-987 (2009)
- 4) *Kage E (*equal contribution), *Hayashi Y (*equal contribution), Takeuchi H, Hirotsu T, Kunitomo H, Inoue T, Arai H, Iino Y, Kubo T, "MBR-1, a novel helix-turn-helix transcription factor, is required for pruning excessive neurites in *Caenorhabditis elegans*," *Current Biology* 15, 1554-1559 (2005)

Molecular Behavioral Physiology

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Major Scientific Interests of the Group

- 1) To seek out novel factors that regulate emotion, feeding, and sleep/wakefulness states.
- 2) To define roles of neuropeptides in regulation of animals' behavior.
- 3) To explore neural circuits that play a prominent role in regulation of animals' behavior

Projects for Regular Students in Doctoral or Master's Programs

- 1) Input and output tracings of neuron populations that play important roles in regulation of animals' behavior
- 2) Optogenetic/pharmacogenetic manipulation of these circuits.
- 3) Comprehensive behavioral analyses of genetically-modified mice.
- 4) Developing new optogenetic/pharmacogenetic tools.

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

- 1) Behavioral experiments on genetically-modified mice
- 2) EEG/EMG electrode implantation and recording in mice
- 3) Patch clamp recording in brain slices
- 4) Optogenetic manipulations on behavior in mice

Recent Publications

- 1) Mieda, M., Ono, D., Hasegawa, E., Okamoto, H., Honma, K., Honma, S., Sakurai, T. Cellular Clocks in AVP Neurons of the SCN Are Critical for Interneuronal Coupling Regulating Circadian Behavior Rhythm. *Neuron*, 2015, 85(5): 1103–1116.
- 2) Sakurai T. The role of orexin in motivated behaviours. *Nat Rev Neurosci.* 2014;15(11):719-31.
- 3) Matsuki, T., Nomiyama, M., Takahira, H., Hirashima, N., Kilduff, T.S., Kunita, S., Takahashi, S., Yagami, K., Bettler, B., Yanagisawa, M., Sakurai, T. Selective loss of GABAB receptors in orexin/hypocretin-producing neurons results in disrupted sleep/wakefulness architecture. *Proc. Natl. Acad. Sci., USA.*, 106(11), 4459–64, 2009
- 4) Sakurai T. Neural Circuit of Orexin (Hypocretin): Maintaining Sleep and Wakefulness. *Nat. Rev. Neurosci.* 8, 171–181, 2007.
- 5) Sakurai T, et al. Input of Orexin/Hypocretin Neurons Revealed by a Genetically Encoded Tracer in Mice. *Neuron* 46(2):297-308, 2005
- 6) Yamanaka A. Beuckmann CT. Willie JT. Hara J. Tsujino N. Mieda M. Tominaga M. Yagami K. Sugiyama F. Goto K. Yanagisawa M. and Sakurai T. Hypothalamic Orexin neurons regulate arousal according to energy balance in mice. *Neuron.* 38:701-713, 2003
- 7) Hara J, Beuckmann CT, Nambu T, Willie JT, Chemelli RM, Sinton CM, Sugiyama F, Yanagi K, Goto K, Yanagisawa M, Sakurai T. Genetic Ablation of Orexin Neurons in Mice Results in Narcolepsy, Hypophagia and Obesity. *Neuron* 30:345-354, 2001
- 8) Sakurai T, et al. Orexins and orexin receptors: A family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell* 92:573-585, 1998

Functional Genomics

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Other Faculty Member

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Major Scientific Interests of the Group

Regulation of transcription, a process of mRNA synthesis from DNA, is a basis of biological phenomena. Our group aims to solve the mechanism of transcriptional control via analyzing transcriptional regulators, which are involved in development, immunity, and various diseases, using whole animal body system. Recently, we are focusing on epigenetic regulation of transcription.

Projects for Regular Students in Doctoral or Master's Programs

- 1) Epigenetic memory induced by environmental factors
- 2) Epigenetic state of totipotent cells

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) Yoshida K, Maekawa T, Zhu Y, Renard-Guillet C, Chatton B, Inoue K, Uchiyama T, Ishibashi K, Yamada T, Ohno N, Shirahige K, Okada-Hatakeyama M and **Ishii S**. The transcription factor ATF7 mediates lipopolysaccharide-induced epigenetic changes in macrophages involved in innate immunological memory. *Nat. Immunol.* 16, 1034-1043, 2015.
- 2) Shinagawa T, Huynh ML, Takagi T, Tsukamoto D, Tomaru C, Kwak HG, Dohmae N, Noguchi J and **Ishii S**. Disruption of *Th2a* and *Th2b* genes causes defects in spermatogenesis. *Development* 142, 1287-1292, 2015.
- 3) Shinagawa T, Takagi T, Tsukamoto D, Tomaru C, Huynh LM, Sivaraman P, Kumarevel T, Inoue K, Nakato R, Katou Y, Sado T, Takahashi S, Ogura A, Shirahige K and **Ishii S**. Histone variants enriched in oocytes enhance reprogramming to induced pluripotent stem cells. *Cell Stem Cell* 14, 217-227, 2014.
- 4) Seong KH, Li D, Shimizu H, Nakamura R and **Ishii S**. Inheritance of stress-induced, ATF-2-dependent epigenetic change. *Cell* 145, 1049-1061, 2011.
- 5) 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.

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) Masuda, T., Wang, X., Maeda, M., Canver, M.C., Sher, F., Funnell, A.P.W., Fisher, C., Suciu, M., Martyn, G.E., Norton, L.J., Zhu, R., Kurita, R., **Nakamura, Y.**, Xu, J., Higgs, D.R., Crossley, M., Bauer, D.E., Orkin, S.H., Kharchenko, P., and Maeda, T. Transcription factors LRF and BCL11A independently repress expression of fetal hemoglobin. *Science* 351: 285-289 (2016)
- 2) Canver, M.C., Smith, E.C., Sher, F., Pinello, L., Sanjana, N.E., Shalem, O., Chen, D.D., Schupp, P.G., Vinjamur, D.S., Garcia, S.P., Luc, S., Kurita, R., **Nakamura, Y.**, Fujiwara, Y., Maeda, T., Yuan, G.C., Zhang, F., Orkin, S.H., and Bauer, D.E. BCL11A enhancer dissection by Cas9-mediated in situ saturating mutagenesis. *Nature* 527: 192-197 (2015)
- 3) 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)
- 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 (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

Project leader, Noriyuki Matsuda; Chief Researcher, Yasushi Saeki; Senior Researcher, Yukiko Yoshida; Senior Researcher; Kei Okatsu



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. **coco*responedences *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.

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 Science** 102(11): 2000-6, 2011

Virology

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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 Immunology* 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.

Notes