筑波大学

Summer Research Program in Biomedical Sciences 2014

July 30- August 10, 2014

List of Laboratories
University of Tsukuba

IMAGINE THE FUTURE.

FACULTY OF MEDICINE Med UNIVERSITY OF TSUKUBA

IIIS INTERNATIONAL INSTITUTE FOR INTEGRATIVE SLEEP MEDICINE

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1. International Community Care and Lifespan Development: Empowerment Sciences

Principal Investigator **Tokie Anme**
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Major Scientific Interests

The notion of empowerment is a useful concept and method, which can cross national and cultural boundaries to be utilized in many different situations. Our lab designed such a framework of community empowerment for life span development, and applied to programs in other countries, with special attention to local cultural values.

Participation by and empowerment of the people in areas of health promotion, family caregiving, housing, and community development will be examined. This is offered in the hope that we may be able to create communities that can meet their own needs, in an interdependent manner that draws on many levels of contribution to make lives worth living across the lifespan, regardless of where we live.

Projects for Regular Students in Doctoral or Master's Programs

1) Cross-Cultural Perspectives on Community Care and Health-Social Services
2) Lifespan Development and Environment
3) Health Promotion and Community Empowerment
4) Child and Elderly Abuse Prevention
5) Human Interface with Universal Design: Assistive devices, Housing, and Community Environments

Study Programs for Short Stay Students

1) Leaning skills how to enhance and evaluate empowerment.
2) Field visit on health social settings and implementing empowerment skills.

Recent Publications:

1) Gan-Yadam A, Anme T, et al. Factors Associated with Health Service Utilization in Ulaanbaatar, Mongolia: A Population-Based Survey, Journal of Epidemiology, Jul 6, 2013
2) Mochizuki Y, Anme T, et al. Effects of Wood Education in a Nursery School with a Focus on Changes in Children and Caregivers' Drawings, Journal of Psychology and Behavioral Sciences, 3(6), 2013
3) Sugisawa Y, Anme T, et al. Strengths and Difficulties of 30-month-olds and Features of the Caregiver- Child Interaction, Journal of Health Science, 3(2), 2013
4) Anme T, et al. Validity and Reliability of the Social Skill Scale (SSS) as an Index of Social Competence for Preschool Children, Journal of Health Science, 3(1), 2013
5) Anme T. Kawashima Y et al. Social Interaction and Dementia Prevention : Six-year Follow-up Study, Public Health Frontier, 2(2) , 2013
6) Anme T, et al. Validity and Reliability of the Index of Child Care Environment (ICCE), Public Health Frontier, 2(6), 2013
7) Anme T, et al. Wood products Improve the Quality of Life of Elderly People in Assisted Living, International Multidisciplinary Scientific GeoConference, 6, 2013
8) Anme T, et al. Validity and Reliability of the Index of Active Listening (IAL), Journal of Applied Medical Sciences, 2(2), 2013

2. Hematology

Principal Investigator **Shigeru Chiba**
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Other Faculty Members
Assistant Professor Naoshi Obara
Assistant Professor Mamiko Sakata-Yanagimoto

Major Scientific Interests
We are focusing on molecular mechanisms underlying normal and abnormal hematopoiesis, with particular interests in genetic and epigenetic abnormalities in hematologic malignancies and stromal cell abnormalities in the bone marrow failure syndromes.

Projects for Regular Students in Doctoral or Master's Programs
- Role of Tet2 in normal hematopoiesis and hematologic malignancies
- Identification of stromal cells involved in the bone marrow failure syndromes including myelodyspoastic syndrome

Programs for Short Stay Students (one week ~ one trimester)
- Learn procedures for analyzing progenitor cells from mouse bone marrow by flowcytometry
- Learn blood cell transplantation in mouse model

Recent Publications
1) Yoshida K, Sanada M, et al., Obara N, Sakata-Yanagimoto M, et al., **Chiba S**, Nakauchi H, Miyano S, Ogawa S. Frequent pathway mutations of splicing machinery in myelodysplasia. ***Nature*** 478:64-69, 2011
2) Sakata-Yanagimoto M, Sakai T, Miyake Y, Saito TI, et al., Yasutomo K, **Chiba S**. Notch2 signaling is required for proper mast cell distribution and mucosal immunity in the intestine. ***Blood*** 117;128-134, 2011
3) Nakahara F, Sakata-Yanagimoto M, et al., **Chiba S**. Hes1 immortalizes committed progenitors and plays a role in blast crisis transition in chronic myelogenous leukemia. ***Blood*** 115:2872-2881, 2010
4) Sanada M, et al., Sakata-Yanagimoto M, et al., **Chiba S**, et al., Ogawa S. Gain-of-function of mutated c-Cbl tumor suppressor associated with myeloid neoplasms having 11q UPD. ***Nature*** 460:904-908, 2009
4) Yokoyama Y, Suzuki T, Sakata-Yanagimoto M, et al., **Chiba S**. Derivation of functional mature neutrophils from human embryonic stem cells. ***Blood*** 113:6584-6592, 2009
5) Kato M, Sanada M, et al., **Chiba S**, et al., Ogawa S. Frequent inactivation of A20 in B-cell lymphomas. ***Nature*** 459:712-716, 2009
6) Sakata-Yanagimoto M, Nakagami-Yamaguchi E, Saito T, Kumano K, Yasutomo K, Ogawa S, Kurokawa M, **Chiba S**. Coordinated regulation of transcription factors through Notch2 is an important mediator of mast cell fate. ***Proc Natl Acad Sci USA*** 105:7839–7844, 2008

3. Gene Regulation

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

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

Study Programs for Short Stay Students (one week ~ one trimester)
1) Analysis of transcriptional regulation during white and brown adipocyte differentiation.
2) Induction of iPS cells using a Sendai virus-based vector.

Recent Publications
1) **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).
2) Wakao H, Yoshikiyo K, Koshimizu U, Furukawa T, Enomoto K, Matsunaga T, Tanaka T, Yasutomi Y, Yamada T, Minakami H, Tanaka J, Oda A, Sasaki T, Wakao R, Lantz O, Udagawa T, Sekiya Y, Higuchi K, Harada N, **Nishimura K**, Ohtaka M, Nakanishi M, Fujita H: Expansion of Functional Human Mucosal-Associated Invariant T Cells via Reprogramming to Pluripotency and Redifferentiation. **Cell Stem Cell** 12, 546-558 (2013).
3) 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).
4) **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).
5) Shimada M, Nakadai T, **Fukuda A**, **Hisatake K**. cAMP-response element-binding protein (CREB) controls MSK1-mediated phosphorylation of histone H3 at the c-fos promoter in vitro. **J. Biol. Chem.** 285, 9390-9401 (2010).

4. Molecular Parasitology

Principal Investigator **Kiong Ho**
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Major Scientific Interests

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

Projects for Graduate Students

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

Study Programs for Short Stay Students

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

Selected Publications

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

5. Global Public Health

Principal Investigator **Masao Ichikawa**
E-mail address masao@md.tsukuba.ac.jp

Major Scientific Interests

"The existing gross inequality in the health status of the people, particularly between developed and developing countries as well as within countries, is politically, socially, and economically unacceptable and is, therefore, of common concern to all countries." (The Declaration of Alma-Ata, September 1978) With this statement in mind, we have conducted action-oriented researches into global public health problems among socially disadvantaged and vulnerable population. We know that making change happen is difficult but possible through scientifically sound research. Our research interests fall in various aspects of injury prevention and control in Asian countries. To date, we have conducted injury researches in Japan, Thailand, Laos, Cambodia, Vietnam, Nepal and Sri Lanka in cooperation with local researchers.

Projects for Regular Students in Doctoral or Master's Programs

Safe and active transport and outdoor physical activity in Asia
Mobile phone use, motorcycle driving and collisions in Laos
Alcohol intoxication and driving in Nepal
Driving and health in later life in Japan
Health communication in cancer screening

Study Program for Short Stay Students

Data analysis and academic writing

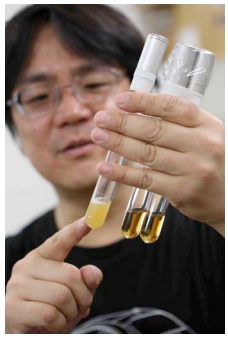
Requirements

For hands-on training, applicants have to possess primary or secondary data for data analysis, with a rough idea on research questions to answer. Basic understanding (undergraduate level) of epidemiological and statistical principles is therefore required.

Recent Publications

1) Nakahara S, Tomio J, Takahashi H, Ichikawa M, Nishida M, Morimura N, Sakamoto T. Evaluation of pre-hospital administration of adrenaline (epinephrine) by emergency medical services for patients with out of hospital cardiac arrest in Japan: controlled propensity matched retrospective cohort study. **BMJ** 2013 Dec 10;347:f6829. doi: 10.1136/bmj.f6829.
2) Ichikawa M, Inada H, Kumeji M. Reconsidering the effects of blue-light installation for prevention of railway suicides. **J Affect Disord** 2013 Sep 14. doi:pii: S0165-0327(13)00680-0. 10.1016/j.jad.2013.09.006.
3) Ichikawa M, Nakahara S, Phommachanh S, Mayxay M, Kimura A. Roadside observation of secondary school students' commuting to school in Vientiane, Laos. **Int J Inj Contr Saf Promot** 2013 Oct 18.
4) Southivong B, Ichikawa M, Nakahara S, Southivong C. A cross-sectional community study of post-traumatic stress disorder and social support in Lao People's Democratic Republic. **Bull World Health Organ** 2013;91:765-72.
5) Nakahara S, Ichikawa M. Mortality in the 2011 tsunami in Japan. **J Epidemio**l 2013;23:70-3.

6. Molecular Cell Biology



Principal Investigator Kenji Irie
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Other Faculty Members
Assistant Professor Tomoaki Mizuno: mizuno@md.tsukuba.ac.jp

Major Scientific Interests

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

Projects for Regular Students in Doctoral or Master's Programs

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

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

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

Recent Publications

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

7. Physiological Chemistry

Principal Investigator **Yasunori Kanaho**
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biochem/kanaholab/index.html
Other Faculty Members
Associate Professor Hiroshi Hasegawa: h.hasegawa@md.tsukuba.ac.jp
Assistant Professor Tsunaki Hongu: thongu@md.tsukuba.ac.jp

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

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

Study Programs for Short Stay Students (one week ~ one trimester)
1) Enzyme assay, immunohistochemistry, and immunofluorescent staining of signaling molecules
2) Assays for cell functions such as cell proliferation, cell motility, focal adhesion, secretion, endocytosis, exocytosis, etc.

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

8. Experimental Pathology

Principal Investigator **Mitsuyasu Kato**
E-mail address mit-kato@md.tsukuba.ac.jp
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Assistant Professor Yukihide Watanabe: y-watanabe@md.tsukuba.ac.jp

Major Scientific Interests

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

Projects for Regular Students in Doctoral or Master's Programs

1) Molecular mechanisms of TGF-β related molecules (TMEPAI, MafK etc.) in colonic stem cells maintenance and carcinogenesis using gene-manipulated mice and three dimensional histopathological analysis.
2) Molecular mechanisms of TGF-β related molecules (THG1 etc.) in squamous cell carcinoma formation

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

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

Recent Publications

1) 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.
2) 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.
3) 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.
4) 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.
5) 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.
6) 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.
7) 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.

9. Infection Biology

Principal Investigator Atsushi Kawaguchi
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URL http://www.md.tsukuba.ac.jp/basic-med/infectionbiology/virology/index_english.html
Other Faculty Members
Associate Professor Mitsuru Okuwaki
Assistant Professor Shoko Saito, Kohsuke Kato
(Nagata Special Lab.; Kyosuke Nagata)

Major Scientific Interests

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

Projects for Regular Students in Doctoral or Master's Programs

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

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

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

Selected Recent Publications

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

10. Molecular and Developmental Biology

Principal Investigator **Makoto Kobayashi**
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Major Scientific Interests

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

Projects for Regular 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

Study 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) Mukaigasa, K., Nguyen, L.T.P., Li, L., Nakajima, H., Yamamoto, M. and Kobayashi, M. (2012) Genetic evidence of an evolutionarily conserved role for Nrf2 in the protection against oxidative stress. ***Mol. Cell. Biol.*** 32: 4455-4461.
2) Nakajima, H., Nakajima-Takagi, Y., Tsujita, T., Akiyama, S., Wakasa, T., Mukaigasa, M., Kaneko, H., Tamaru, Y., Yamamoto, M. and Kobayashi, M. (2011) Tissue-restricted induction of Nrf2 and its target genes in zebrafish with gene-specific variations in the induction profiles. ***PLoS ONE*** 6: e26884.
3) Tsujita, T., Li, L., Nakajima, H., Iwamoto, N., Nakajima-Takagi, Y., Ohashi, K., Kawakami, K., Kumagai, Y., Freeman, B. A., Yamamoto, M. and Kobayashi, M. (2011) 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.
4) Takeuchi, M., Kaneko, H., Nishikawa, K., Kawakami, K., Yamamoto, M. and Kobayashi, M. (2010) Efficient transient rescue of hematopoietic mutant phenotypes in zebrafish using *Tol2*-mediated transgenesis. ***Dev. Growth Differ.*** 52: 245-250.
5) Kobayashi, M., Li, L., Iwamoto, N., Nakajima-Takagi, Y., Kaneko, H., Nakayama, Y., Eguchi, E., Wada, Y., Kumagai, Y. and Yamamoto, M. (2009) The antioxidant defense system Keap1-Nrf2 comprises a multiple sensing mechanism for responding to a wide range of chemical compounds. ***Mol. Cell. Biol.*** 29: 493-502.

11. Environmental Biology

Principal Investigator **Yoshito Kumagai**
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Major Scientific Interests

This laboratory addresses the mechanisms by which chemicals causing oxidative stress and environmental electrophiles such as polycyclic aromatic hydrocarbon quinones, methylmercury and arsenic affect living systems by interacting with sensor proteins with reactive thiols (thiolate ions) through chemical modification. The observations obtained by this group regarding environmental electrophiles have lent new insight into mechanisms of redox-dependent signal transduction pathways that are regulated by reactive sulfur species in the body.

Projects for Regular Students in Doctoral or Master's Programs

1) Activation of electrophilic signal transduction pathways (e.g., PTP1B/EGFR-, Keap1/Nrf2-, HSP/HSF-1-signalings) during exposure to environmental electrophiles such as 1,2-naphthoquinone and methylmercury.
2) Search for 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) 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** in press, 2014.
2) Nishida M, Sawa T, Kitajima N, Ono K, Inoue H, Ihara H, Motohashi H, Yamamoto M, Suematsu M, Kurose H, Van der Vliet A, Freeman BA, Shibata T, Uchida K, **Kumagai Y**, Akaike T. Hydrogen sulfide anion regulates redox signaling via electrophile sulfhydration. **Nature Chem Biol** 8: 714-724, 2012.
3) **Kumagai Y**, Shinkai Y, Miura T, Cho AK. The chemical biology of naphthoquinones and its environmental implications. **Annu Rev Pharmacol Toxicol** 52: 221-247, 2012.
4) Yoshida E, Toyama T, Shinkai Y, Sawa T, Akaike T, **Kumagai Y**. Detoxification of methylmercury by hydrogen sulfide producing enzyme in mammalian Cells. **Chem Res Toxicol** 24: 1633-1635, 2011.
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.

12. Molecular Neurobiology

Principal Investigator **Masayuki Masu**
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Lecturer: Kazuko Keino-Masu: kazumasu@md.tsukuba.ac.jp
Assistant Professor: Takuya Okada: okada.takuya.gw@u.tsukuba.ac.jp

Major Scientific Interests

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, microscopy, and 3D imaging of neural network
2) In situ hybridization

Recent Publications

1) Nagamine S et al. Organ-Specific Sulfation Patterns of Heparan Sulfate Generated by Extracellular Sulfatases Sulf1 and Sulf2 in Mice. **J Biol Chem** 287: 9579-9590, 2012.
2) Koike S, Yutoh Y, Keino-Masu K, Noji S, **Masu M**, and Ohuchi H. Autotaxin is required for the cranial neural tube closure and establishment of the midbrain-hindbrain boundary during mouse development. **Dev Dyn** 240: 413-421, 2011.
3) Koike S, Keino-Masu K, Ohto T, Sugiyama F, Takahashi S, and **Masu M**. Autotaxin/lysophospholipase D-mediated LPA Signaling is Required to Form Distinctive Large Lysosomes in the Visceral Endoderm Cells of the Mouse Yolk Sac. **J Biol Chem** 284: 33561-33570, 2009.
4) Okada T, Keino-Masu K, and **Masu, M**. Migration and nucleogenesis of mouse precerebellar neurons visualized by *in utero* electroporation of a green fluorescent protein gene. **Neurosci Res** 57: 40-49, 2007.
5) Keino-Masu K, **Masu M**, et al. *Deleted in Colorectal Cancer* (*DCC*) Encodes a Netrin Receptor. **Cell** 87: 175-185, 1996.

13. 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) 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
2) 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)
3) X. Wang, M. Muratani, W.P. Tansey, M. Ptashne: Proteolytic instability and the action of nonclassical transcriptional activators, *Current Biology*, Vol.20(9), 868-71, 2010
4) Daulny, F. Geng, M. Muratani, J.M. Geisinger, S.E. Salghetti, W.P. Tansey: Modulation of RNA polymerase II subunit composition by ubiquitylation, *Proceedings of National Academy of Sciences U S A*, Vol.105(50), 19649-54, 2008
5) M. Muratani, C. Kung, K.M. Shokat, W.P. Tansey: The F box protein Dsg1/Mdm30 is a transcriptional coactivator that stimulates Gal4 turnover and cotranscriptional mRNA processing, *Cell*, Vol.120(6), 887-99, 20056.
6) M. Muratani*, D. Gerlich*, S.M. Janicki, M. Gebhard, R. Eils, D.L. Spector: Metabolic-energy-dependent movement of PML bodies within the mammalian cell nucleus, *Nature Cell Biology*, Vol.4(2), 106-10, 2002 (*Equal contribution)

14. Medical Genetics

Principal Investigator **Emiko Noguchi**
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Major Scientific Interests
Genetic study of asthma/atopic dermatitis/allergic rhinitis/food allergy. Linkage and association analyses, expression profiles from human and animal tissues
Identification of the disease-causing gene by next generation sequencing

Projects for Regular Students in Doctoral or Master's Programs
Identification of novel genomic mutations associated with asthma/atopy and development of genetic markers and therapeutic materials for personalized medicine of allergic diseases.
Identification of the disease-causing mutation of genetic diseases by next generation sequencers

Study Programs for Short Stay Students (one week ~ one trimester)
Genetic testing, genotyping, expression analyses,
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.

15. Diagnostic Surgical Pathology

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Major Scientific Interests
Molecular pathology of multistep carcinogenesis
Studies of the initial genetic alterations of precancerous lesions and early carcinoma
Studies of the interactions between cancer cells and interstitial cells

Projects for Regular Students in Doctoral or Master's Programs
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.
Produce monoclonal antibodies against fetal swine to screen for specific antibodies against human carcinomas.
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)
Basic techniques of immunohistochemistry, *in situ* hybridization, and FISH
Basic techniques of tissue micro-dissection

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

16. Surgery

Principal Investigator **Nobuhiro Ohkohchi, MD, PhD**
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Major Clinical Activities

1) Surgical resection of esophageal, gastrointestinal, hepatobiliary and pancreatic tumor
2) Computer-assisted 3D-CT hepatectomy simulation
3) Chemoradiation of Esophageal cancer
4) Neoadjuvant chemoradiation of rectal cancer
5) Surgical treatment of Inflammatory bowel disease
6) Living donor liver transplantation
7) Cadaveric donor kidney transplantation

Major Scientific Interests

1) Liver regeneration and prevention of liver cirrhosis by platelet
2) Hepatic ischemia reperfusion injury
3) Anatomy of liver
4) DDS of anti-cancer drug
5) sense/anti sense RNA of cancer and liver disease
6) Mechanism of wound healing

Projects for Regular Students in Doctoral or Master's Programs

1) Research on platelet effects on liver regeneration and fibrosis
2) Research on prevention of hepatic ischemia reperfusion injury
3) Research on DDS of anti-cancer drug of gastrointestinal tract
4) Research on function of anti-sense RNA in cancer
5) Research on mechanism of wound healing of intestine

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

1) Handling of abdominal organs of small animals
2) Handling of cell culture
3) Techniques of molecular biology

Recent Publications

1) Matsuo R, Nakano Y, Ohkohchi N. Platelet administration via the portal vein promotes liver regeneration in rats after 70% hepatectomy. Annals of surgery. 235;1-5.2011
2) Kobayashi A, Oda T, Fukunaga K, Sasaki R, Minami M, Ohkohchi N. MR Imaging of Reactive Lymphoid Hyperplasia of the liver. Journal of Gastrointestinal Surgery. Epub ahead of print.Feb
3) Hisakura K, Murata S, Matsuo R, Paku S, Ikeda N, Kawasaki T, Kohno K, Myronovych A, Nakano Y, Ikeda O, Watanabe M, Ohkohchi N. Platelets Prevent Acute Hepatitis Induced by Anti-Fas Antibody. Journal of Gastroenterology and Hepatology. 26(2);348-355.2011
4) Ohkohchi N. Platelets play an important role in the recovery of liver dysfunction after hepatic resection. Annals of surgery. 252(4);708-709.2010
5) Yamaguchi R, Terashima H, Yoneyama S, Tadano S, Ohkohchi N. Effects

of Platelet-Rich Plasma on Intestinal Anastomotic Healing in Rats: PRP Concentration is a Key Factor. Journal of Surgical Research. Epub ahead of print. 2-Nov.2010

6) Kohno K, Chiba M, Murata S, Pak S, Nagai K, Yamamoto M, Yanagisawa K, Kobayashi A, Yasue H, Ohkohchi N. Identification of natural antisense transcripts involved in human colorectal cancer development. International Journal of Oncology. 37(6);1425-1432.2010
7) Murata S, Yanagisawa K, Fukunaga K, Oda T, Kobayashi A, Sasaki R, Ohkohchi N. Fatty acid synthase cerulenin suppresses liver metastasis of colon cancer in mice. Cancer Science. 101(8);1861-1865.2010
8) Kawasaki T, Murata S, Takahashi K, Nozaki R, Ohshiro Y, Ikeda N, Paku S, Myronovych A, Hisakura K, Fukunaga K, Oda T, Sasaki R, Ohkohchi N. Activation of human liver sinusoidal endothelial cell by human platelets induces hepatocyte proliferation. Journal of Hepatology. 53(4);648-654.2010
9) Matsuda A, Kuno A, Kawamoto T, Ohkohchi N, Shoda J, Hirabayashi J, Naarimatsu H. Wisteria floribunda agglutinin-positive mucin 1 is a sensitive biliary marker for human cholangiocarcinoma. Hepatology. 52(1);174-182.2010
10) Hashimoto S, Oda T, Yamada K, Takagi M, Enomoto T, Ohkohchi N, Takagi T, Kanamori T, Ikeda H, Yanagihara H, Kita E, Tasaki A. The measurement of small magnetic signals from magnetic nanoparticles attached to the cell surface and surrounding living cells using a general-purpose SQUID magnetometer. Physics in Medicine and Biology. 54(8);2571-2583.2009
11) Nakano Y, Kondo T, Matsuo R, Murata S, Fukunaga K, Ohkohchi N. Prevention of leukocyte activation by the neutrophil elastase inhibitor, sivelestat, in the hepatic microcirculation after ischemia-reperfusion. Journal of Surgical Research. 155(2);311-317.2009
12) Watanabe M, Murata S, Hashimoto I, Nakano Y, Ikeda O, Aoyagi Y, Matsuo R, Fukunaga K, Yasue H, Ohkohchi N. Platelets contribute to the reduction of liver fibrosis in mice. Journal of Gastroenterology and Hepatology. 24(1);78-89.2009

17. Regenerative Medicine and Stem Cell Biology

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Dr. Masumi Kuma Nagano (Assistant Professor) naganom@md.tsukuba.ac.jp

Major Scientific Interests

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

Projects for Regular Students in Doctoral or Master's Programs:

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

♦Summer School Course (2014)♦

1) Analysis of Mesenchymal Stem Cells
2) Neural Differentiation of human iPS

Recent Publications:

1) Akimoto K, Kimura K, Nagano M, Takano S, Salazar G, Yamashita T, and Ohneda O. Umbilical cord blood-derived mesenchymal stem cells inhibit, but adipose tissue-derived mesenchymal stem cells promote, glioblastoma multiforme proliferation. **Stem Cells and Dev.** 2013; 22: 1370-1386.
2) 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.
3) 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.
4) Yamashita T, Ohneda O, Sakiyama A, Iwata F, Ohneda K, and Fujii-Kuriyama Y. The microenvironment for erythropoiesis is regulated by HIF-2alpha through VCAM-1 in endothelial cells. **Blood** 2008; 112: 1482-1492.
5) Yamashita T, Ohneda K. Nagano M, Miyoshi C, Kaneko N, Miwa Y, Yamamoto M, Ohneda O, and Fujii-Kuriyama Y. HIF-2alpha in endothelial cells regulates tumor neovascularization through activation of ephrin A1. **J Biol Chem** 2008; 283: 18926-18936.
6) Nagano M, Yamashita T, Hamada H, Ohneda K, Kimura K, Nakagawa T, Shibuya M, Yoshikawa H, and Ohneda O. Identification of functional endothelial progenitor cells suitable for the treatment of ischemic tissue using human umbilical cord blood. **Blood** 2007; 110: 151-160.

18. Molecular Cell Physiology / Reproductive Biochemistry

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Other Faculty Members
Assistant Professor Manabu Matsuda, Akihiro Kawashima

Major Scientific Interests

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

Projects for Regular Students in Doctoral or Master's Programs

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

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

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

Recent Publications

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

19. Bacteriology, Molecular Biology

Princial Investigators **Ryosuke Ohniwa**
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Major Scientific Interests
We study how pathogenic bacteria (especially, *Staphylococcus aureus*) cope with bactericidal factors form host and environment.

Study Programs for Short Stay Students
1) Basic techniques of bacteriology
2) Basic techniques of molecular genetics in bacteria
3) AFM analysis of DNA-protein interaction.

Academic Publications
1) Ryosuke L. Ohniwa, Hiroki Muchaku, Shinji Saito, Chieko Wada and Kazuya Morikawa. Atomic force microscopy analysis of the role of major DNA-binding proteins in organization of the nucleoid in *Escherichia coli*. **PLoS One**. 8:e72954. 2013
2) Ryosuke L. Ohniwa, Kana Kitabayashi, and Kazuya Morikawa. Alternative cardiolipin synthase Cls1 compensates for stalled Cls2 function in *Staphylococcus aureus* under conditions of acute acid stress. **FEMS Microbiol Lett** 388, 141-146. 2012.
3) Kazuya Morikawa, Aya J Takemura, Yumiko Inose, Melody Tsai, Le Thuy Nguyen Thi, Toshiko Ohta, and Tarek Msadek. Expression of a cryptic secondary sigma factor gene unveils natural competence for DNA transformation in *Staphylococcus aureus*. **PLoS Pathogen** 8:e1003003. 2012.
4) Melody Tsai, Ryosuke L. Ohniwa, Yusuke Kato, Sayaka L. Takeshita, Toshiko Ohta, Shinji Saito, Hideo Hayashi, and Kazuya Morikawa. *Staphylococcus aureus* requires cardiolipin for survival under conditions of high salinity. **BMC Microbiol.** 11, 13. 2011.
5) Ryosuke L. Ohniwa, Yuri Ushijima, Shinji Saito, and Kazuya Morikawa Proteomic Analyses of Nucleoid-Associated Proteins in *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis,* and *Staphylococcus aureus*. **PLoS One** 6:e19172. 2011.
6) Kazuya Morikawa, Ryosuke L. Ohniwa, Toshiko Ohta, Yoshikazu Tanaka, Kunio Takeyasu, and Tarek Msadek. Adaptation beyond the Stress Response: Cell Structure Dynamics and Population Heterogeneity in *Staphylococcus aureus.* **Microb Environ** 25, 75-82. 2010. *Review*

20. Immunology

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Major Scientific Interests
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, Fca/mR, MAIR-I, MAIR-II, and Allergin-1, all of which were identified in our laboratory, in immune responses
2) The pathophysiological roles of the immunoreceptors in tumors, autoimmune diseases, allergy and infectious disease

Study Programs for Short Stay Students (one week ~ one trimester)
1) Generation of monoclonal antibodies and their application for expression analyses by flow cytometry and immunohistochemistry
2) Cell separation by sorting on flow cytometry or magnetic beads and analyses of cytokine production or proliferation upon antigen stimulation

Recent Publications
1) Nakahashi-Oda C, Tahara-Hanaoka S, Shoji M, Okoshi Y, Nakano-Yokomizo T, Ohkohchi N, Yasui T, Kikutani H, Honda S, Shibuya K, Nagata S, Shibuya A. Apoptotic cells suppress mast cell inflammatory responses via the CD300a immunoreceptor. ***J. Exp. Med.*** 209, 1493-1503, 2012
2) Nakano-Yokomizo T, Tahara-Hanaoka S, Nakahashi-Oda C, Nabekura T, Tchao N K, Kadosaki M, Totsuka N, Kurita N, Nakamagoe K, Tamaoka A, Takai T, Yasui T, Kikutani H, Honda S, Shibuya K, Lanier L L and **Shibuya A**. The immunoreceptor adapter protein DAP12 suppresses B lymphocyte-driven adaptive immune responses. ***J. Exp. Med.*** 208, 1661-1671, 2011.
3) Hitomi K, Tahara-Hanaoka S, Someya S, Fujiki A, Tada H, Sugiyama T, Shibayama S, Shibuya K and **Shibuya A**. An immunoglobulin-like receptor, Allergin-1, inhibits immunoglobulin E-mediated immediate hypersensitivity reactions. ***Nat Immunol.*** 11: 601-607, 2010
4) Honda S, Miyamoto A, Cho Y, Usui K, Kurita N, Takeshita K, Takahashi S, Kinoshita T, Fujita T, Tahara-Hanaoka S, Shibuya K, **Shibuya A**. Enhanced humoral immune responses against T-independent antigens in Fcα/μR-deficient mice. **Proc Natl Acad Sci USA.** 106:11230-11235, 2009

21. Neurobiology

Principal Investigator **Takashi Shiga**
E-mail address tshiga@md.tsukuba.ac.jp
URL http://www.md.tsukuba.ac.jp/basic-med/anatomy/shiga-group/anatomy3rd.html
Other Faculty Members
Associate Professor Tomoyuki Masuda: tmasu@md.tsukuba.ac.jp

Major Scientific Interests
We are examining the mechanisms underlying the formation of neural network by multidisciplinary approaches from molecules to behavior, using mouse, rat and chick embryos.

Projects for Regular Students in Doctoral or Master's Programs
1) Monoamines in the dendrite formation and synaptogenesis
2) Environmental factors affecting development of brain and behavior
3) Axon guidance mechanisms of sensory neurons with special reference to Runx transcription factors and axon guidance molecules

Study Programs for Short Stay Students (one week ~ one trimester)
1) Anaysis of mouse behavior (spatial memory, anxiety and depression)
2) Quantitative RT-PCR of mRNA in brain regions (5-HT receptors etc)

Recent Publications
1) Yoshikawa M, Murakami Y, Senzaki K, Masuda T, Ozaki S, Ito Y, **Shiga T**. Co-expression of Runx1 and Runx3 in mechanoreceptive dorsal root ganglion neurons. **Dev. Neurobiol.** 73, 469-479, 2013.
2) Li F, Ohtani A, Senzaki K, **Shiga T**. Receptor-dependent regulation of dendrite formation of noradrenaline and dopamine in non-GABAergic cerebral cortical neurons. **Dev. Neurobiol.** 73, 370-383, 2013.
3) Kobayashi A, Senzaki K, Ozaki S, Yoshikawa M, **Shiga T**. Runx1 promotes neuronal differentiation in dorsal root ganglion. **Mol. Cell Neurosci.** 49, 223-31, 2012.
4) Yoshida H, Kanamaru C, Ohtani A, Li F,Senzaki K, **Shiga T**. Subtype specific roles of serotonin receptors in the spine formation of cortical neurons in vitro. **Neurosci. Res.** 71, 311-314, 2011.
5) Senzaki K, Ozaki S, Yoshikawa M, Ito Y, **Shiga T**. Runx3 is required for the specification of TrkC-positive mechanoreceptive trigeminal ganglion neurons. **Mol. Cell. Neurosci.** 43, 296-307, 2010.
6) Hayashi, T., Ohtani, A., Onuki, F., Natsume, M., Li, F., Satou, T., Yoshikawa, M., Senzaki, K., **Shiga, T**. Roles of serotonin 5-HT3 receptor in the formation of dendrites and axons in the rat cerebral cortex: An in vitro study. **Neurosci. Res.** 66, 22-28, 2010.

22. Endocrinology and Metabolism

Principal Investigator Hitoshi Shimano
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URL http://www.u-tsukuba-endocrinology.jp/
Other Faculty Members
Assistant Professor: Naoya Yahagi (nyahagi-tky@umin.ac.jp)
Assistant Professor: Takahsi Matsuzaka (t-matsuz@md.tsukuba.ac.jp)
Research Associate: Kiyoaki Ishii (kishii@md.tsukuba.ac.jp)

Major Scientific Interests

We are working to understand the molecular mechanisms of energy metabolism using the newest technologies, such as molecular and cellular biology, gene-engineered animals, genome informatics. We also extend our investigations to understand the molecular basis of metabolic disease, and try to develop new therapeutic approaches for preventing obesity, diabetes, and cardiovascular disease.

Projects for Regular Students in Doctoral or Master's Programs

1) Research on energy metabolism and transcription factors.
2) Research on lipid metabolism for various metabolic diseases.
3) Research on pathogenic mechanisms and treatment of diabetes.
4) Research on pathogenic mechanisms and treatment of atherosclerosis.

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

1) Transfection and Luciferase assay for analyzing the function of transcription factors.
2) Experimental procedures for mouse metabolic disease model.

Recent Publications

1) Izumida Y, Yahagi N, Takeuchi Y, Nishi M, Shikama A, Takarada A, Masuda Y, Kubota M, Matsuzaka T, Nakagawa Y, Iizuka Y, Itaka K, Kataoka K, Shioda S, Niijima A, Yamada T, Katagiri H, Nagai R, Yamada N, Kadowaki T, **Shimano H**. Glycogen shortage during fasting triggers liver-brain-adipose neurocircuitry to facilitate fat utilization. **Nat Commun.** 4:2316, 2013.
2) Sunaga H, Matsui H, Ueno M, Maeno T, Iso T, Syamsunarno MR, Anjo S, Matsuzaka T, **Shimano H**, Yokoyama T, Kurabayashi M. Deranged fatty acid composition causes pulmonary fibrosis in Elovl6-deficient mice. **Nat Commun.** 4:2563, 2013.
3) Horie T, Nishino T, Baba O, Kuwabara Y, Nakao T, Nishiga M, Usami S, Izuhara M, Sowa N, Yahagi N, **Shimano H**, Matsumura S, Inoue K, Marusawa H, Nakamura T, Hasegawa K, Kume N, Yokode M, Kita T, Kimura T, Ono K. MicroRNA-33 regulates sterol regulatory element-binding protein 1 expression in mice. **Nat Commun.** 4:2883, 2013.
4) Matsuzaka T, Atsumi A, Matsumori R, Nie T, Shinozaki H, Suzuki-Kemuriyama N, Kuba M, Nakagawa Y, Ishii K, Shimada M, Kobayashi K, Yatoh S, Takahashi A, Takekoshi K, Sone H, Yahagi N, Suzuki H, Murata S, Nakamuta M, Yamada N, **Shimano H**. Elovl6 promotes nonalcoholic steatohepatitis. **Hepatology**. 56(6):2199-208, 2012

23. Anatomy and Embryology/ Laboratory Animal Resource Center

Principal Investigator Satoru Takahashi
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Major Scientific Interests
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
Molecular mechanism of the development of organs. We are researching the molecular mechanisms of the development of organs by analyzing the function of the large Maf family of transcription factors. In both human and mouse, four large Maf transcription factors, MafA, MafB, c-Maf and Nrl, have been identified. We genetically manipulate mice about these genes and analyze their in vivo function.

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) 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.
2) 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, Ishii. Histone variants enriched in oocytes enhance reprogramming to induced pluripotent stem cells. ***Cell Stem Cell***. 14, 217-227,2014.
3) Katsumata T, Oishi H, Sekiguchi Y, Nagasaki H, Daassi D, Ema M, Kudo T, Takahashi S. In vivo monitoring of pancreatic b-cell mass and intrahepatic insulin gene activity in Ins1-luc BAC transgenic mice by bioluminescence imaging. ***Plos One***. 8, e60411, 2013.
4) 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.
5) Hishida T, Nozaki Y, Nakachi Y, Mizuno Y, Okazaki Y, Ema M, Takahashi S, Nishimoto M, Okuda A. Indefinite self-renewal of ES cells through Myc/Max transcriptional complexes-independent mechanisms. ***Cell Stem Cell***. 9, 37-49, 2011.
6) 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.

24. Health Services Research

Principal Investigator **Nanako Tamiya**
E-mail ntamiya@md.tsukuba.ac.jp

Major Scientific Interests

Health services research (HSR) is a scientific research filed from a multidisciplinary prospective that examines quality of care, accessibility to health care services, the cost of care, and results of the care. We assess and analyze the quality of various medical services (including nursing care, health and welfare) through the method of health services research. Our goal is to improve the service quality via the outcome of the interdisciplinary research based on the verified data to help realize the medical care that harmonizes with patients' living.

Projects for Regular Students in Doctoral or Master's Programs

1) Longitudinal evaluation studies of long-term care insurance and assistance benefit supply system
2) Quality assessment of in-home or institutional care for older people and the disabled

Study Program for short Stay Students

1) Evaluation and international comparison of the medical welfare system
2) Understanding and implementation of the methodology of health services research and basic statistical analyses of our data set related to long-term care.

Selected publications

- Tamiya N, Noguchi A, Reich MR, et al. Population ageing and wellbeing: lessons from Japan's long-term care insurance policy. Lancet 2011, 378(9797):1183-1192.
- Olivares-Tirado P, Tamiya N: Trends and Factors in Japan's Long-Term Care Insurance System: Japan's 10-year Experience (Springer Briefs in Aging), Springer,2013
- F.Sandoval, Tamiya N, et al. Relationship between structural characteristics and outcome quality indicators at health care facilities for the elderly requiring long-term care in Japan from a nationwide survey. Geriatr Gerontol Int. 2013:doi: 10.1111/ggi.12098.
- Kashiwagi M, Tamiya N, Sato M and Yano E. Factors Associated with the Use of Home-visit Nursing Services Covered by the Long-Term Care Insurance in Rural Japan: BMC Geriatrics. 2013 Jan 2;13:1.
- Ito T, Tamiya N, Takahashi H, et al. Factors that prolong the "post-mortem interval until finding"(PMI-f) among community-dwelling elderly individuals in Japan: Analysis of registration data. BMJ Open. 2012;27;2(5). pii: e001280.
- Olivares-Tirado P, Tamiya N, Kashiwagi M. Effect of in-home and community-based services on the functional status of elderly in the long-term care insurance system in Japan. BMC Health Servi Res.2012, 12:239.

25. Radiation Biology

Principal Investigator **Koji Tsuboi**
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Other Faculty Members
Assistant Professor Takashi Moritake: moritake@pmrc.tsukuba.ac.jp

Major Scientific Interests
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 Program for Short Stay Student (2 weeks – 6 months)
1) Cell culture techniques and basic in vitro radio sensitivity assays
2) Methods to evaluate DNA damage in cells and tissues
3) Studies on physical parameters to evaluate biological effects

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

26. Laboratory Animal Science

Principal Investigator **Ken-ichi Yagami**
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Other Faculty Members
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Research Associate Seiya Mizuno: konezumi@md.tsukuba.ac.jp

Major Scientific Interests

Laboratory animals are essential and important bio-resources for the advancement of medical sciences. Gene-modified animals are used very often to study *in vivo* function of genes and proteins in development, homeostasis and disease. In particular, we focus on 1) establishment of germline-competent embryonic stem cells from various inbred strains of mice and rats for developing gene-modified animals and 2) generation of bacterial artificial chromosome (BAC) based Cre driver mice and novel photoconversion Cre reporter mice and rats for assembling high specific conditional Knockout systems. In addition, we investigate 3) the mechanisms of embryo implantation and early embryo development on novel mutant and Knockout mouse strains.

Projects for Regular Students in Doctoral or Master's Programs

1) Development of embryonic stem cells in mice and rats.
2) Development of advanced Cre-LoxP system in mice.
3) Investigate peri-implantation development in mutant mice.

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

1) Manipulation of mouse preimplantation embryos.

Recent Publications

1) Mizuno S, Iijima S, Okano T, Kajiwara N, Kunita S, Sugiyama F, Yagami K. Retrotransposon-mediated Fgf5(go-Utr) mutant mice with long pelage hair. Exp Anim. 2011;60(2):161-7.
2) Iijima S, Tanimoto Y, Mizuno S, Daitoku Y, Kunita S, Sugiyama F, Yagami K. Effect of different culture conditions on establishment of embryonic stem cells from BALB/cAJ and NZB/BINJ mice. Cell Reprogram. 2010 Dec;12(6):679-88.
3) Mizuno S, Mizobuchi A, Iseki H, Iijima S, Matsuda Y, Kunita S, Sugiyama F, Yagami K. A novel locus on proximal chromosome 18 associated with agenesis of the corpus callosum in mice. Mamm Genome. 2010 Dec;21(11-12):525-33.
4) Tanimoto Y, Iijima S, Hasegawa Y, Suzuki Y, Daitoku Y, Mizuno S, Ishige T, Kudo T, Takahashi S, Kunita S, Sugiyama F, Yagami K. Embryonic stem cells derived from C57BL/6J and C57BL/6N mice. Comp Med. 2008 Aug;58(4):347-52.
5) Shigematsu Y, Yoshida N, Miwa Y, Mizobuti A, Suzuki Y, Tanimoto Y, Takahashi S, Kunita S, Sugiyama F, Yagami K. Novel embryonic stem cells expressing tdKaede protein photoconvertible from green to red fluorescence.(Int J Mol Med. 2007 Oct;20(4):439-44)
6) Shimizu Y, Motohashi N, Iseki H, Kunita S, Sugiyama F, Yagami K. A novel subpopulation lacking Oct4 expression in the testicular side population. Int J Mol Med. 2006 Jan;17(1):21-8.
7) Shimizukawa R, Sakata A, Hirose M, Takahashi A, Iseki H, Liu Y, Kunita S, Sugiyama F, Yagami K. Establishment of a new embryonic stem cell line derived from C57BL/6 mouse expressing EGFP ubiquitously. Genesis. 2005 May;42(1):47-52.

27. Functional Neuroanatomy

Principal Investigator **Hiromasa Funato**
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Major Scientific Interests

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

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

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

Recent Publications

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

28. REM Sleep and Dreams

Principal Investigator **Yu Hayashi**
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Major Scientific Interests

Sleep in mammals is composed of two distinct states, REM (rapid eye movement) sleep and non-REM sleep. REM sleep is the major source of dreams, whereas non-REM sleep is characterized by a synchronous brain activity called slow waves. Little is known, however, about the evolutionary origin or individual roles of these two sleep states. We address these questions through identification and manipulation of the neurons that function as the REM/non-REM sleep switch using mice. In addition, we search for the molecular entity of "sleepiness" using *C. elegans* as a model.

Projects for Regular Students in Doctoral or Master's Programs

- Brain remodeling during sleep
- Roles of brain activation during dreaming or REM sleep in neural plasticity
- Evo-devo approach to identify the evolutionary origin of REM and non-REM sleep
- Search for novel sleep-regulating molecules using *C. elegans*

Study Program for Short Stay Students

- Design knock-in or knock-out mice
- Search for novel brain areas that control sleep or consciousness
- Screen for novel *C. elegans* mutants with sleep defects

Recent Publications

1) Yu Hayashi†, Takaaki Hirotsu, Ryo Iwata, Eriko Kage-Nakadai, Hirofumi Kunitomo, Takeshi Ishihara, Yuichi Iino, Takeo Kubo (†Corresponding author)
"A trophic role for Wnt-Ror kinase signaling during developmental pruning in *Caenorhabditis elegans*." ***Nature Neuroscience*** 12, 981-987（2009）

2) *Eriko Kage, *Yu Hayashi, Hideaki Takeuchi, Takaaki Hirotsu, Hirofumi Kunitomo, Takao Inoue, Hiroyuki Arai, Yuichi Iino, Takeo Kubo (*Equal contribution)
"MBR-1, a novel helix-turn-helix transcription factor, is required for pruning excessive neurites in *Caenorhabditis elegans*." ***Current Biology*** 15, 1554-1559（2005）

29. Systems Sleep Biology

Principal Investigator **Michael Lazarus** (Dr. rer. nat.)
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URL http://wpi-iiis.tsukuba.ac.jp/research/
Other Lab Members
Researcher Yo Oishi, Ph.D.
Researcher Yoko Takata, Ph.D.

Major Scientific Interests

1) Role of adenosine and dopamine in sleep-wake regulation
2) Feedback mechanisms between sleep-wake regulation and behavior
3) Effects of polyphenols on the sleep-wake cycle

Projects for Regular Students in Doctoral or Master's Programs

1) Neuronal mechanisms of dopamine in sleep-wake regulation
2) Characterization of neuronal firing/activity in the nucleus accumbens during sleep-wake states
3) Identification of the neural source of extracellular adenosine

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

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

Recent Publications

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

30. Systems Biochemistry and Molecular Genetics

Principal Investigator **Qinghua Liu, Ph.D.**
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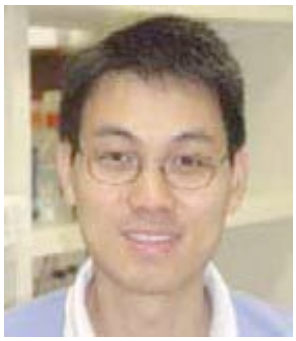
URL http://profiles.utsouthwestern.edu/profile/50723/qinghua-liu.html



Major Scientific Interests

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

Projects for Regular Students in Doctoral or Master's Programs

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

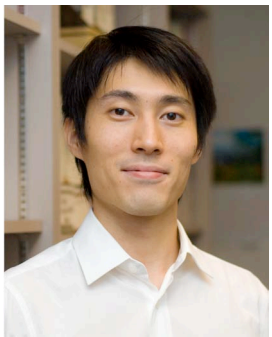
Training Programs for Short Stay Students (one week ~ one trimester)

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

Recent Publications

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

31. Memory, Adult neurogenesis, and Sleep



Principal Investigator **Masanori Sakaguchi**
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http://researchmap.jp/masanorisakaguchi/?lang=english

Introduction of the PI and the Group

Thank you for having interest in my lab. After receiving my medical degree from the University of Tsukuba in 2001, I continued to pursue a research-oriented career in neuroscience, focusing on regenerative medicine utilizing adult neural stem cells and the function of adult neurogenesis in memory. My experience abroad and career thereafter provided me with a firm grasp of world-class techniques (optogenetics, neuronal tracing, behavioral neuroscience, etc.) but furthermore, with an open-mindedness in understanding both Western and Eastern cultures and sufficient communication abilities (e.g., fluent English and intermediate-level Chinese 'HSK Lvl4') all so vital in scientific research today.

Currently, at IIIS our group strives to investigate the relation between sleep, adult neurogenesis and memory. We hope to clarify the still unanswered questions regarding sleep and its significance towards memory and adult neurogenesis. Please also visit our lab homepage for the details. I welcome motivated and self-driven students and researchers anytime for lab visiting.

Projects for Regular Students in Doctoral or Master's Programs

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

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

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

Recent Publications (25 in total, 9 first-author publications: 3 international patents)

1) Sakaguchi M and Hayashi Y, Catching the engram: strategies to examine the memory trace, **Mol. Brain** 2012Oct, 5:32(359 viewed in the first 10days, 6th best viewed during the 1st month)
2) Hirota Y, Sawada M, Kida Y, Huang SH, Yamada O, Sakaguchi M, Ogura T, Okano H, Sawamoto K, Roles of planar cell polarity signaling in maturation of neuronal precursor cells in the postnatal mouse olfactory bulb, **Stem Cells**, 2012 Aug;30(8):1726-33.
3) Sakaguchi M, Okano H. Neural stem cells, adult neurogenesis and galectins: from bench to bedside, **Dev. Neurobiol.**, 2012 Jul;72(7):1059-67. doi: 10.1002/dneu.22023.
4) Stone S, Teixeira CM, Zaslavsky K, Wheeler AL, Canaball AM, Wang AH, Sakaguchi M, Lozano AM, Frankland PW, Functional Convergence of Developmentally- and Adult- Generated Granule Cells in Dentate Gyrus Circuits Supporting Hippocampus-Dependent Memory, **Hippocampus**. 2011 Dec;21(12):1348-62.
5) 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 Oct 19;31(42):15113-27., *The authors contributed equally

32. Molecular Pharmacology

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Major Scientific Interests

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

Projects for Regular Students in Doctoral or Master's Programs

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

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

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

Recent Publications

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

33. Olericulture and Floriculture

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Other Faculty Member:
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Assistant Professors Tohru Ariizumi, Ph.D., Daiki Mizuta, Ph.D., Satoko Nonaka, Ph.D., Kanna Izawa-Sato, Ph.D., Masahito Shikata, Ph.D., Hideo Yoshida Ph.D.

Major Scientific Interests

- Exploring genes regulating tomato fruit development
- Analysis of the mechanism for sugar and GABA metabolism in tomato
- Creation of genetic modified tomato accumulating functional materials benefit for human health
- Innovating crop transgenic technology and its application to bio-fuel production
- Improving cultivation method for increasing sugar accumulation in tomato fruit
- Identification of genes controlling pigment accumulation in ornamental plant

Projects for Regular Students in Doctoral or Master's Programs

1) Forward genetic screening of genes that influence fruit development in tomato
2) Reverse genetic screening of novel mutations that increase fruit shelf-life of tomato
3) Functional analysis of GABA metabolism genes in tomato

Study Programs for Short Stay Students (one week)

1) DNA/RNA purification from plants
2) DNA amplification by PCR reaction, digestion by restriction enzymes, and electrophoresis
3) cDNA synthesis and RT-PCR reaction

Recent Publications

1) Someya T, Nonaka S, Nakamura K, Ezura H (2013) Increased 1-aminocyclopropane-1-carboxylate deaminase activity enhances *Agrobacterium tumefaciens*-mediated gene delivery into plant cells. ***Microbiology Open.*** 2(5): 873-880
2) Kimbara J, Yoshida M, Ito H, Kitagawa M, Takada W, Hayashi K, Shibutani Y, Kusano M, Okazaki Y, Nakabayashi R, Mori T, Saito K, Ariizumi T, Ezura H (2013) Inhibition of CUTIN DEFICIENT 2 causes defects in cuticle function and structure and metabolite changes in tomato fruit. ***Plant and Cell Physiology.*** 54(9): 1535-1548
3) Koike S, Matsukura C, Takayama M, Asamizu E, Ezura H (2013) Suppression of γ-amino butyric acid (GABA) transaminases induces prominent GABA accumulation, dwarfism and infertility in the tomato (Solanum lycopersicum L.). ***Plant and Cell Physiology***. 54(4): 793-807
4) Narusaka M, Kubo Y, Hatakeyama K, Imamura J, Ezura H, Nanasato Y, Tabei Y, Takano Y, Iwabuchi M, Shirasu K, Narusaka Y (2013) Interfamily transfer of dual NB-LRR genes confers resistance to multiple pathogens. ***PLoS ONE***. 8(2): e55954
5) Kimbara J, Yoshida M, Ito H, Hosoi K, Kusano M, Kobayashi M, Ariizumi T, Asamizu E, Ezura H, (2012) A novel class of sticky peel and light green mutations causes cuticle deficiency in leaves and fruits of tomato (*Solanum lycopersicum*). ***Planta***. 236: 1556-1570
6) Okabe Y, Asamizu E, Saito T, Matsukura C, Ariizumi T, Bres C, Rothan C, Mizoguchi T, Ezura H (2011) Tomato TILLING technology: Development of a reverse genetics tool for the efficient isolation of mutants from Micro-Tom mutant libraries. ***Plant and Cell Physiology***. 52(11): 1994-2005
7) Kusano M, Redestig H, Hirai T, Oikawa A, Matsuda F, Fukushima A, Arita M, Watanabe S, Yano M, Hiwasa-Tanase K, Ezura H, Saito K (2011) Covering the chemical diversity of genetically modified tomato using multi-platform metabolomics for an objective substantial equivalence assessment. ***PLoS ONE*** 6(2): e16989
8) Saito T, Ariizumi T, Okabe Y, Asamizu E, Hiwasa-Tanase K, Yamazaki Y, Fukuda N, Mizoguchi T, Aoki K, Ezura H (2011) TOMATOMA: A novel tomato mutant database distributing Micro-Tom mutant collections. ***Plant and Cell Physiology*** 52(2): 283-296
9) Hiwasa-Tanase K, Nyarubon M, Hirai T, Kato K, Ichikawa T, Ezura H (2011) High-level accumulation of recombinant miraculin protein in transgenic tomatoes expressing a synthetic miraculin gene with optimized codon usage terminated by the native miraculin terminator. ***Plant Cell Reports*** 30: 113-124
10) Yin YG, Tominaga T, Iijima Y, Aoki K, Shibata D, Ashihara H, Nishimura S, Ezura H and Matsukura C (2010) Metabolic alterations in organic acids and γ-amino butyric acid in developing tomato (*Solanum lycopersicum* L.) fruits. ***Plant and Cell Physiology***. 51(8): 1300-1314
11) Yin YG, Kobayashi Y, Sanuki A, Kondo S, Fukuda N, Ezura H, Sugaya S, Matsukura C (2010) Salinity induces carbohydrate accumulation and sugar- regulated starch biosynthetic genes in tomato (*Solanum lycopersicum* L. cv. 'Micro-Tom') fruits in ABA- and osmotic stress-independent manner. ***Journal of Experimental Botany.*** 61(2): 563-574
12) Nonaka S, Yuhashi K, Takada K, Sugawara M, Minamisawa K, Ezura H (2008) Ethylene production in plants during gene transformation suppresses *vir* gene expression in *Agrobacterium tumefaciens*. ***New Phytologist***. 178(3): 647-656

34. Applied Entomology and Zoology

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Assistant Professor, Natsuko Kinoshita: kinoshita.natsuko.gf@u.tsukuba.ac.jp

Major Scientific Interests

Experimental studies using insects, spiders and ticks for elucidation of behavioral and physiological mechanisms underlining host location behavior, physiology of reproduction and immunity, innate immune response to various infections, and molecular mechanisms inducing the release of plant volatiles from herbivore-infested plants.

Projects for Regular Students in Doctoral or Master's Programs

1) Flight response of parasitic wasps to the plant infested by host insect.
2) Endocrinological and gene regulatory mechanisms of tick and spider ecdysis, reproduction and immunity.
3) Molecular mechanisms in the regulation of insect immunity
4) Visualization and modeling of volatile compound mediated plant-plant and plant-insect interaction.

Study Programs for Short Stay Students

1) Head space volatile collection and olfactometer study using the volatile extract.
2) Measurement of insect immune activity against infection by molecular techniques.
3) Plant DNA extraction and amplification by PCR

Recent Publications:

1) Ichiki, R. T., G. T. T. Ho, E. Wajnberg, Y. Kainoh, J. Tabata, and S. Nakamura (2012) Different uses of plant semiochemicals in host location strategies of the two tachinid parasitoids. *Naturwissenschaften* 99:687-694.
2) Deshpande, S. A. and Y. Kainoh (2012) Herbivore egg deposition induces tea leaves arresting the egg-larval parasitoid *Ascogaster reticulata* Watanabe (Hymenoptera: Braconidae). *Entomol. Exp. Appl.* 144:172-180.
3) Ogihara, M. H. and D. Taylor (2013) Female Reproductive System: Anatomy, Physiology and Molecular Biology, Chapter 17. In D.E. Sonenshine and R.M. Roe (Editors). Biology of Ticks, Volume 1. Second Edition, Oxford University Press, New York, USA. pp. 449-483.
4) Horigane, M., T. Shinoda, H. Honda and D. Taylor (2010) Characterization of a vitellogenin gene reveals two phase regulation of vitellogenesis by engorgement and mating in the soft tick *Ornithodoros moubata* (Acari: Argasidae). *Insect Mol. Biol.* 19:501-515.
5) Furukawa, S., Tanaka, H., Sagisaka, A., Ishibashi, J. and Yamakawa, M. (2012) Both kB and C/EBP binding sites are indispensable for full expression of a nitric oxide synthase gene in the silkworm, *Bombyx mori*. *J. Seric. Sci. Jpn*. 81:13-20.
6) Furukawa, S., Tanaka, K., Ikeda, T., Fukatsu, T. and Sasaki, T. (2012) Quantitative analysis of the lytic cycle of WO phages infecting *Wolbachia*. *Appl. Entomol. Zool.* 47:449-456.
7) Kinoshita N., et al (2012) *IAA-Ala Resistant 3 (IAR3)*, a new evolutionarily conserved target of miR167, mediates *Arabidopsis* root architecture changes during high osmotic stress. *Plant Cell* **24**, 3590-602
8) Kinoshita N, et al (2010) Identification of growth insensitive to ABA3 (*gia3*), a recessive mutation affecting ABA Signaling for the control of early post-germination growth in *Arabidopsis thaliana*. *Plant Cell Physiol.* **51**, 239-251.