International University of Health and Welfare (IUHW)
Graduate School of Medicine

Introduction to the Department of Basic Medical Sciences

Molecular Biology Tesshi Yamada, MD, PhD

Specialty: Molecular biology, Pathological Oncology, Thoracic surgery, Therapeutics development

Research Project:
Development of therapeutics targeting cancer stem cells
Prediction and prevention of the recurrence of early-stage non-small cell lung cancer

Selected Publication:

1. Masuda, *et al*. TNIK Inhibition Abrogates Colorectal Cancer Stemness. ***Nature Communications.*** 2016; 26;7:12586.
2. Masuda, *et al*. Therapeutic targets in the Wnt signaling pathway: feasibility of targeting TNIK in colorectal cancer. ***Pharmacology & Therapeutics***. 2015; 156:1-9.
3. Noro, *et al*. Distinct outcome of stage I lung adenocarcinoma with ACTN4 cell motility gene amplification. ***Ann Oncol.*** 2013; 24:2594-600.
4. Honda, *et al*. Actinin-4 increases cell motility and promotes lymph node metastasis of colorectal cancer. ***Gastroenterology.*** 2005; 128:51-62.
5. Honda, *et al*. Possible detection of pancreatic cancer by plasma protein profiling. ***Cancer Res.*** 2005; 65:10613-22.

Message to Applicants: I founded the Cancer Proteomics Project at the National Cancer Center (Tokyo, Japan) in 2001 and has been serving as a leader of clinical/translational proteomics in Japan. We are now recruiting PhD students who want to participate in the International Cancer Proteogenome Consortium.

Physiology Keiko Ikeda, MD, PhD

Specialty: Physiology, Neuroscience, Cell Biology

Research Project:
Role of the Sodium pump alpha subunit genes in the central nervous system
Role of Six gene family during sensory organ development
Cytoarchitecture and function of respiratory rhythm generator complex

Selected Publication:

1. Sugimoto, Ikeda, Kawakami. *Atp1a3* deficient heterozygous mice show lower rank in the hierarchy and altered social behavior. ***Genes Brain Behav***. 2017; Oct 23.doi: 10.1111/gbb.12435. PMID: 29057568.
2. Unekawa, Ikeda, *et al*. Enhanced susceptibility and responsibility to cortical spreading depression in Na+, K+-ATPase alpha2 subunit-deficient mice as a model of familial hemiplegic migraine 2. ***Cephalalgia*** 2017 Jul 1;1666:27-37.
3. Ikeda, *et al*. Knockout of sodium pump α3 subunit gene (Atp1a3-/-) results in perinatal seizure and defective respiratory rhythm generation. ***Brain Res.*** 2017; 1;1666:27-37.
4. Ikeda, *et al*. The respiratory control mechanisms in the brainstem and spinal cord: integrative views of the neuroanatomy and neurophysiology. ***J Physiol Sci.*** 2017 Jan;67(1):45-62
5. Ikeda, *et al*. A Phox2b BAC transgenic rat line useful for understanding respiratory rhythm generator neural circuitry. ***PLoS One.*** 2015 Jul 6;10(7):e0132475.

6. Ikeda, *et al*. Enhanced inhibitory neurotransmission in the cerebellar cortex in the Atp1a3-deficient heterozygous dystonia-susceptible mice. ***J Physiol.*** 2013 Jul 1;591(13):3433-49.

Message to Applicants:
Let's "do science" together.

Biochemistry Motoo Kitagawa, MD, PhD

Specialty: Biochemistry, Molecular Biology

Research Project:
Mechanisms of cellular signal transduction (especially Notch signaling)

Selected Publication:
1. Masuda, *et al*. Enhanced surface presentation and activation of Notch1 by transmembrane 2 domain containing 3, a mammalian homologue of Drosophila neurogenic gene product Almondex. Submitted.
2. Toritsuka, *et al*. Regulation of striatal dopamine responsiveness by Notch/RBP-J signaling. ***Transl. Psychiatry*** 7, e1049,2017. [PubMed]
3. Kitagawa M. Notch signaling in the nucleus: roles of Mastermind-like transcriptional coactivators. ***J. Biochem.*** 159, 287-294, 2016. [PubMed]
4. Muroyama, *et al*. Olfactory sensory neurons control dendritic complexity of mitral cells via Notch signaling. ***PLOS Genet.*** 12, e1006514, 2016. [PubMed]
5. Watanabe, *et al*. MAML1 enhances the transcriptional activity of Runx2 and plays a role in bone development. ***PLOS Genet.*** 9, e1003132, 2013. [PubMed]
6. Oyama, *et al*. Mastermind-like 1 (MamL1) and mastermind-like 3 (MamL3) are essential for Notch signaling in vivo. ***Development*** 138, 5235-5246, 2011. [PubMed]
7. Köchert, *et al*. High-level expression of Mastermind-like 2 contributes to aberrant activation of the NOTCH signaling pathway in human lymphomas. ***Oncogene*** 30, 1831-1840, 2011. [PubMed]
8. Sasaki, *et al*. The repression of Notch signaling occurs via the destabilization of mastermind-like 1 by Mesp2 and is essential for somitogenesis. ***Development*** 138, 55-64, 2011. [PubMed]
9. Ishitani, *et al*. Nemo-like kinase suppresses Notch signalling by interfering with formation of the Notch active transcriptional complex. ***Nature Cell Biol.*** 12, 278-285, 2010. [PubMed]
10. Fukami, *et al*. Mastermind-like domain containing 1 (MAMLD1 or CXorf6) transactivates the *Hes3* promoter, augments testosterone production, and contains the SF1 target sequence. ***J. Biol. Chem.*** 283, 5525-5532, 2008. [PubMed]
11. Oyama, *et al*. Mastermind-1 is required for Notch signal-dependent steps in lymphocyte development in vivo. ***Proc. Natl. Acad. Sci. U.S.A.*** 104, 9764-9769, 2007. [PubMed]
12. Ishikawa, *et al*. Notch deficiency implicated in the pathogenesis of congenital disorder of glycosylation IIc. ***Proc. Natl. Acad. Sci. U.S.A.*** 102, 18532-18537, 2005. [PubMed]
13. Sasamura, *et al*. *Neurotic*, a novel maternal neurogenic gene, encodes an *O*-fucosyltransferase that is essential for Notch–Delta interactions. ***Development*** 130, 4785-4795, 2003. [PubMed]
14. Lin, *et al*. Identification of new human mastermind proteins defines a family that consists of positive regulators for Notch signaling. ***J. Biol. Chem.*** 277, 50612-50620, 2002.[PubMed]
15. Kitagawa, *et al*. A human protein with sequence similarity to Drosophila Mastermind coordinates the nuclear form of Notch and a CSL protein to build a transcriptional activator complex on target promoters. ***Mol. Cell. Biol.*** 21, 4337-4346, 2001. [PubMed]

Message to Applicants: I wish to organize a laboratory that carries out both *in vitro* structural/functional analyses of proteins and their biological analyses with genetically modified mice. I also wish to promote collaborations with both domestic and foreign researchers having different expertise. Notch signaling plays pivotal roles for both normal differentiation/developmental processes and various pathological processes including tumor development. I am looking for students, who wish to join the research.

Pharmacology Hiroyuki Kobori, MD, PhD, FJSIM, FAHA, FASN, FJSH, FJSN, FACP

Specialty: Pharmacology, Physiology, Nephrology, and Hypertension

Research Project: Dr. Kobori's lab focuses on the pathophysiological study of the kidney mainly on the renal renin-angiotensin system (especially intrarenal and urinary angiotensinogen, which is the only known substrate of the system).

Selected Publication:

1. Kobori, *et al.* Expression of angiotensinogen mRNA and protein in angiotensin II-dependent hypertension. ***J Am Soc Nephrol.*** 2001; 12:431-439.
2. Kobori, *et al.* Urinary excretion of angiotensinogen reflects intrarenal angiotensinogen production. ***Kidney Int.*** 2002; 61:579-585.
3. Kobori, et al. The intrarenal renin-angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. ***Pharmacol Rev.*** 2007; 59:251-287.
4. Kobori, *et al.* Urinary Angiotensinogen as a Novel Biomarker of the Intrarenal Renin-Angiotensin System Status in Hypertensive Patients. ***Hypertension.*** 2009; 53:344-350.
5. Rafiq, Kobori, *et al.* Renal sympathetic denervation suppresses de novo podocyte injury and albuminuria in rats with aortic regurgitation. ***Circulation.*** 2012; 125:1402-1413.

Publication List:

http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40171722/?sort=date&direction=descending

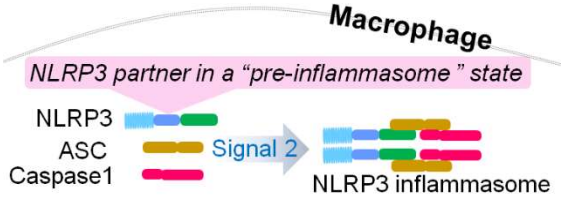
Message to Applicants:

It is very hard to continue a Physician Scientist, but the worth doing. I would like to support graduate students to be interested in becoming Physician Scientists.

Imunology Rimpei Morita, MD, PhD

Specialty: Immunology

Research Project: **1. Exploring of new factors that regulate NLRP3 inflammasome activation**



Inflammasome are molecular complexes that control production of pro-inflammatory cytokines IL-1β & IL-18 from macrophages. However, regulatory mechanisms of forming the NLRP3 inflammasome remain unknown. We are trying to elucidate the regulatory mechanisms by focusing on how NLRP3 exists in a "pre-inflammasome" state, especially NLRP3-binding partners (left figure). In addition, based on our achievements, we will develop new anti-inflammation reagents in the future.

2. Elucidating of mechanism in which follicular helper T cells differentiate

Biography:
1989 - 1995 M.D. Faculty of Medicine, Nara Medical University.
1999 - 2003 Ph.D. Department of Medicine, Graduate School of Medicine, Kyoto University .
2005 - 2008 Post-doc, Baylor Institute for Immunology Research. (Dallas, TX) (PI; Jacques Banchereau)
2008 - 2009 Post-doc, Department of Immunobiology, Yale University. (New Haven, CT) (PI; Richard Flavell)
2009 - 2016 Assistant & Associate Professor, Department of Immunology and Microbiology, Keio University School of Medicine.
2017 - Professor, Department of Immunology, IUHW School of Medicine.

Selected Publication:

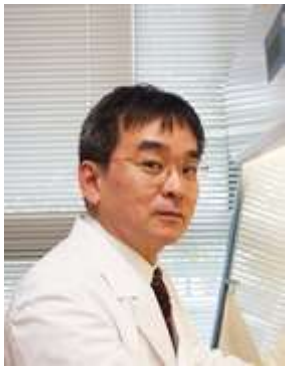
1. Shichita, *et al*. MAFB prevents excess inflammation after ischemic stroke by accelerating clearance of damage signals through MSR1. ***Nat Med.*** 2017; 23:723-732.

2. Kondo, *et al*. Notch-mediated conversion of activated T cells into stem cell memory-like T cells for adoptive immunotherapy. ***Nat Commun*.** 2017; 8:15338.
3. Sekiya, *et al*. Suppression of Th2 and Tfh immune reactions by Nr4a receptors in mature T reg cells. ***J Exp Med*.** 2015; 212:1623-40.
4. Kashiwagi, *et al*. Smad2 and Smad3 inversely regulate TGF-β autoinduction in *Clostridium butyricum*-activated dendritic cells. ***Immunity*.** 2015; 43:65-79.
5. Ito, *et al*. Bruton's tyrosine kinase is essential for NLRP3 inflammasome activation and contributes to ischaemic brain injury. ***Nat Commun*.** 2015; 6:7360.
6. Kim, *et al*. AMCase is a crucial regulator of type 2 immune responses to inhaled house dust mites. ***PNAS*.** 2015; 112:E2891-9.
7. Morita, *et al*. ETS transcription factor ETV2 directly converts human fibroblasts into functional endothelial cells. ***PNAS*.** 2015; 112:160-5.
8. Shichita, *et al*. Peroxiredoxin family proteins are key initiators of post-ischemic inflammation in the brain. ***Nat Med*.** 2012; 18:911-7.
9. Morita, *et al*. Human blood $CXCR5^{+}CD4^{+}$ T cells are counterparts of T follicular cells and contain specific subsets that differentially support antibody secretion. ***Immunity*.** 2011; 34:108-21.
10. Schmitt, *et al*. Human dendritic cells induce the differentiation of interleukin-21-producing T follicular helper-like cells through interleukin-12. ***Immunity*.** 2009; 31:158-69.
11. Dullaers, *et al*. A T cell-dependent mechanism for the induction of human mucosal homing immunoglobulin A-secreting plasmablasts. ***Immunity*.** 2009; 30:120-9.
12. Klechevsky*, Morita*, *et al*. Functional specializations of human epidermal Langerhans cells and $CD14^{+}$ dermal dendritic cells. ***Immunity*.** 2008; 29:497-510. (*; equal contribution)

Publication List:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1BEquaYBBC5H/bibliography/53283373/public/?sort=date&direction=descending

Message to Applicants:
We are now creating a few sorts of genetically modified mice in which a newly identified NLRP3-binding partner is targeted. In addition, projects on follicular helper T cells are newly being launched. We are now recruiting graduate students who strongly proceed with these projects.

Anatomy Jun Kosaka, MD, PhD



Selected Publication:
1. Komatsu, *et al*. Vascularized peripheral nerve grafting promotes myelination of regrowing optic nerve. ***Neuroreport.*** 2013; 24:566-71
2. Sekiguchi-Tonosaki, Kosaka, *et al*.. Acetylcholine induces Ca2+ signaling in chicken retinal pigmented epithelial cells during dedifferentiation. American Journal of Physiology-Cell Physiology 296:C1195-C1206. ***Am J Physiol Cell Physiol.*** 2009; 296:C1195-206.
3. Kimura, Kosaka, *et al*. Quantification of in situ hybridization signals in rat testes. ***J Histochem Cytochem.*** 2004; 52:813-20.
4. Quan, Kosaka, *et al*. Survival of axotomized retinal ganglion cells in peripheral nerve-grafted ferrets. ***Invest Ophthalmol Vis Sci.*** 1999; 40:2360-6.
5. Kosaka, *et al*. Differential localization and expression of α and β isoenzymes of Protein Kinase C in the rat retina. ***J Neurosci Res.*** 1998; 54:655-63.

Pathology Takayuki Shiomi, MD, PhD

Specialty: Experimental pathology (Cellular communications and extracellular matrix metabolism), Diagnostic Pathology

(Pulmonary pathology)

Research Project: Our laboratory focuses on the analysis of cellular communications and ECM metabolism in pulmonary diseases and development of their manipulation as therapeutic targets.

Selected Publication:

1. D'Armiento, Shiomi, *et al*. Mesenchymal Tumorigenesis Driven by TSC2 Haploinsufficiency Requires HMGA2 and Is Independent of mTOR Pathway Activation. ***Cancer Res.*** 2016; 76: 844-854.
2. Carver, *et al*. Mmp1a and Mmp1b Are Not Functional Orthologs to Human MMP1 in Cigarette Smoke-induced Lung Disease. ***Exp Toxicol Pathol.*** 2015; 67:153-159.
3. Shiomi, *et al*. SFRP1 Maintains the Pluripotential State of Bronchial Alveolar Stem Cells and Regulates Proliferation Post Injury. ***FASEB J.*** 2014; 28:5242-5249.
4. Elkington, Shiomi, *et al*. MMP-1 drives immunopathology in human tuberculosis and transgenic mice. ***J Clin Invest.*** 2011; 121:1827–1833.
5. Shiomi, *et al*. Pericellular activation of proMMP-7 (promatrilysin-1) through interaction with CD151. ***Lab Invest.*** 2005; 85:1489-1506.

Publication List:

https://www.ncbi.nlm.nih.gov/sites/myncbi/takayuki.shiomi.1/bibliography/9051727/public/?sort=date&direction=descending

Message to Applicants: We are interested in cellular communications and ECM metabolism as the driving forces which cause morphological changes in diseases. We use various methodology from biochemistry/molecular biology study to analysis of animal models and human specimen, and even mathematical models to solve this complex puzzle. We envision to evolve morphology from the knowledge from experiences to the prediction of molecular behavior.

Pathology Yasuhiko Tomita, MD, PhD

Specialty: Human pathology

Research Project: I have revealed that molecules in ubiquitin-proteasome pathway have a relationship with cancer grade and metastasis. Now I am working on the involvement of these molecules in STAT3 and NFκB pathways.

Selected Publication:

1. Tomita, *et al*. Histologic grading in soft-tissue sarcomas. An analysis of 194 cases including AgNOR count and mast-cell count. ***Int J Cancer.*** 1993; 54:194-9.
2. Asai, Tomita, *et al*. VCP (p97) regulates NFkappaB signaling pathway, which is important for metastasis of osteosarcoma cell line. ***Jpn J Cancer Res.*** 2002; 93:296-304.
3. Yamamoto, Tomita, *et al*. Elevated expression of valosin-containing protein (p97) in hepatocellular carcinoma is correlated with increased incidence of tumor recurrence. ***J Clin Oncol.*** 2003; 21:447-52.
4. Qiu *et al*. Pre-B-cell leukemia transcription factor 1 regulates expression of valosin-containing protein, a gene involved in cancer growth. ***Am J Pathol.*** 2007; 170:152-9.
5. Wang, *et al*. GdX/UBL4A specifically stabilizes the TC45/STAT3 association and promotes dephosphorylation of STAT3 to repress tumorigenesis. ***Mol Cell.*** 2014; 53:752-65.

Message to Applicants:

Correlation of molecules in ubiquitin-proteasome pathway with tumor grade is now focused. Let's start to make new therapeutic strategies against cancer together.

Pathology Ryuji Fukuzawa, MD, PhD

Specialty: Paediatric and Developmental Pathology, Molecular Oncology

Research Project: My research focuses on the molecular pathology of tumours that recapitulate early embryogenesis and organogenesis (e.g., germ cell tumours, embryonal tumours) and their precursor lesions (developmental abnormalities occurring during the embryogenesis). To clarify molecular mechanisms of their tumorigenesis and developmental programmes, I am using not only molecular techniques (microarray, CGH, Exosome DNA sequencing etc.) but also pathologic and epidemiologic approaches as part of international collaborations. I am also analysing the histological changes of iPS cells transplanted into immunodeficient mice.

Selected Publication:

1. Fukuzawa, Anaka, *et al.* The developmental programme for genesis of the entire kidneyis recapitulated in Wilms tumour. ***PLoS One.*** 2017; 12:e0186333.
2. Sugai, Fukuzawa, *et al.* Pathological classification of human iPSC-derived neural stem/progenitor cells towards safety assessment of transplantation therapy for CNS diseases. ***Mol Brain.*** 2016 ;9:85.
3. Fukuzawa, Holman, *et al.* WTX mutations can occur both early and late in the pathogenesis of Wilms tumour. ***J Med Genet.*** 2010 ;47:791-4.
4. Fukuzawa, Anaka, *et al.* Canonical WNT signaling determines lineage specificity in Wilms tumour. ***Oncogene***. 2009 ;28:1063-75.
5. Jenkins, van Kogelenberg, *et al.* Germline mutations in WTX cause a sclerosing skeletal dysplasia but do not predispose to tumorigenesis. ***Nat Genet.*** 2009 ;41:95-100
6. Fukuzawa, Anaka, *et al.* Wilms tumour histology is determined by distinct types of precursor lesions and not epigenetic changes. ***J Pathol.*** 2008 ;215:377-87.
7. Fukuzawa, Breslow, *et al.* Epigenetic differences between Wilms' tumours in white and east-Asian children. ***Lancet.*** 2004;363:446-51.

Message to Applicants: Students and researchers who are interested in embryonic growth and development, cell differentiation, fetal and paediatric diseases are very much welcome.