Institute for Genome Research of The University of Tokushima aims to elucidate the principles of unified biological systems and the mechanisms of diseases.

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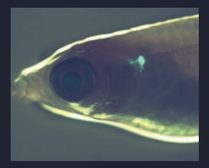

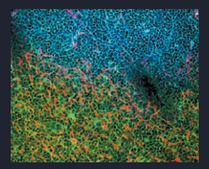

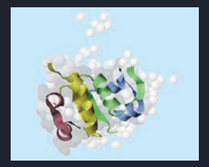

Institute for Genome Research
The University of Tokushima

Research 2008-2009

Human genome sequence was determined. It is now essential to clarify biological functions of the genome, especially focusing on genome functions associated with human diseases. Institute for Genome Research (IGR) of The University of Tokushima, originally founded in 1998, has been renewed on April1, 2008. The IGR aims to elucidate the principles of unified biological systems and the mechanisms of diseases. The IGR is fully aware of the importance of collaborations with various academic, governmental, and industrial institutions. The IGR is also firmly committed to the education at graduate and undergraduate schools at The University of Tokushima.

Section of Genomics

Division of Immune Regulation

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2000-2004	JSPS fellow
2004	Assistant Professor, Department of Medical Chemistry, Graduate School of Medicine, Kyoto University
2004-2008	COE Associate Professor, 21st Center of Excellence Formation, Graduate School of Medicine, Kyoto University
2008-	Professor, Division of Immune Regulation, Institute for Genome Research, University of Tokushima

Assistant Professor : Il-mi Okazaki Ph.D.

Genetic dissection and reconstitution of autoimmune diseases

Most of the autoimmune diseases are polygenic disease and many genetic polymorphisms are involved in the development and the progression of the disease. Thanks to the recent advancement in the genetic engineering, many genes have been identified and their functions in the immune system have been vigorously analyzed. However, it is largely unknown which genes are really involved and how multiple genes collaborate in the regulation of autoimmune diseases. We are trying to identify autoimmune susceptible genes comprehensively by genetically dissecting autoimmune susceptible mice and analyze their synergistic function to fully understand the molecular mechanisms of immunological tolerance.

Although genetic linkage analyses have been widely employed on both human patients and model animals, responsible genes have hardly been identified. The involvement of too many genes and the weak influence of individual gene are supposed to be the main cause of the difficulty. We are trying to overcome this difficulty by using PD-1 deficient mice that develop different type of autoimmune disease on different genetic background.

Mice deficient for PD-1 gene develop lupus-like glomerulonephritis on C57BL/6 background and autoimmune dilated cardiomyopathy on BALB/c background. When we introduced PD-1 deficiency on NOD mice, which spontaneously develop type I diabetes. NOD-PD-1$^{-/-}$ mice developed diabetes much earlier and completely (from 4 weeks of age, 100% by 8 weeks of age) compared to NOD-wild type mice (from 15 weeks of age, 40-70% by 30 weeks). Because the quick and the complete incidence of diabetes were supposed to assure more sensitive and accurate genetic linkage analyses, we performed genetic linkage analyses using intercross progenies of NOD-PD1$^{-/-}$ mice and C57BL/6-PD-1$^{-/-}$ mice. Among 26 known diabetes susceptible loci, only 2 loci showed significant association to the diabetic incidence. Moreover, dominant susceptible genes could not be analyzed with NOD-wild type mice because of the low incidence of diabetes in F2 intercross progenies. In virtue of PD-1 deficiency, we could also screen dominant diabetes susceptible loci throughout genome and identified two new loci and named these as *Iddp1* and *Iddp2*. These results suggest that diabetic incidence on NOD-PD-1$^{-/-}$ mice can be explained only by 5 genes including PD-1, which is a great advancement compared to the 26 genes. We are currently trying to generate C57BL/6-congenic mice, which develop diabetes spontaneously by introducing NOD-derived chromosomal fragments.

On the other hand, inhibition of immune responses by PD-1 may dampen beneficial tumor immunity or anti-infectious immunity. We have found that cancer cells and viral infected cells express ligands of PD-1 and induce paralysis of anti-tumor or anti-viral immune responses. Therefore, we are trying to develop methods to block PD-1-dependent immune suppression to treat cancer and infectious diseases.

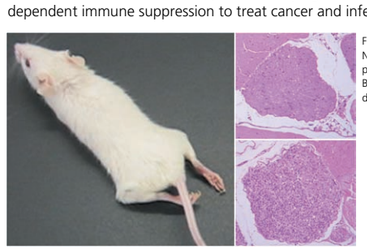

Fig.1
NOD.H2b.PD-1$^{-/-}$ mice develop peripheral polyneuropathy similar to human Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy.

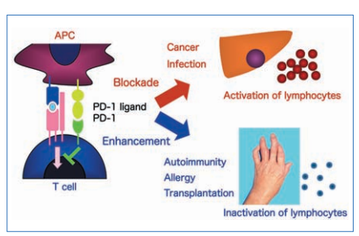

Fig.2
Blockade of PD-1 signaling leads to the eradication of tumor cells and clearance of pathogens. While enhancement of PD-1 signaling can be applied to autoimmunity, allergy, and transplant rejection.

Kido M, Watanabe N, Okazaki T, Akamatsu T, Tanaka J, Saga K, Nishio A, Honjo T, Chiba T.
Fatal autoimmune hepatitis induced by concurrent loss of naturally arising regulatory T cells and PD-1 mediated signaling.
Gastroenterology. 135:1333-1343 (2008)

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Okazaki T, Honjo T.
Rejuvenating exhausted T cells during chronic viral infection.
Cell. 122:459-461 (2006)

Okazaki T, Tanaka Y, Nishio R, Mitsuiye T, Mizoguchi A, Wang J, Ishida M, Hiai H, Matsumori A, Minato N, Honjo T.
Autoantibodies against cardiac troponin I are responsible for the dilated cardiomyopathy in PD-1 deficient mice.
Nature Med. 9:1477-1483 (2003)

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Toyomasa Katagiri Ph.D.

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1991-1992	Research Associate, Otsuka Pharmaceutical Co., Ltd.
1992-1995	Research Associate, Department of Biochemistry, Cancer Institute, Japanese Foundation for Cancer Research.
1995-1998	Research Associate, Department of Human Genome Analysis, the Cancer Chemotherapy Center, Japanese Foundation for Cancer Research.
1998	PhD, Medical School, Osaka University.
1998-2001	Postdoctoral Fellow, Department of Medical and Molecular Genetics, Division of Genetics and Development, Guy's Kings and St Thomas' School of Medicine, King's College London.
2001-2004	Assistant Professor, Human Genome Center, Institute of Medical Science, The University of Tokyo.
2004-2008	Associate Professor, Human Genome Center, Institute of Medical Science, The University of Tokyo.
2008-present	Professor, Division of Genome Medicine, Institute for Genome Research, The University of Tokushima.

Assistant Professor : Taisuke Matsuo M.Sc.

Characterization and identification of novel molecular-targets for cancer therapy though human genome analysis

The determination of human genome sequence has been completed on April 2003 as a result of human genome project. Thus, it is now crucial to clarify the function of genes in the genome. Particularly functional analysis of genes associated with human diseases, especially human cancer is a matter of great importance for development of novel diagnostic and therapeutic tools.

Our division was launched in May 2008. The major goal of our division is to identify genes which are involved in carcinogenesis, and to develop novel diagnostic and therapeutic strategies. We have been attempting to identify genes involved in carcinogenesis by means of technologies developed through genome-wide cDNA microarray and SNP-analyses (Fig.1). We have been working on the following major projects;

1) Characterization and identification of molecular-targets for novel diagnostic and therapeutic drugs for cancer therapy,

2) Investigation of mechanisms underlying triple-negative breast cancer (estrogen receptor-negative, progesterone-negative and Her2-negative)

1. Characterization and identification of novel molecular-targets for the diagnosis and treatment of human cancers

To identify novel molecular-targets for the diagnosis and treatment of cancer, we have been analyzing the gene expression profiles in breast cancers, renal cell carcinomas and bladder cancers as well as normal human tissues by means of cDNA microarray in collaboration with Prof. Yusuke Nakamura's laboratory in Institute of Medical Science, the University of Tokyo. Through these microarray data, we have identified several candidate genes that are overexpressed in cancer cells and not expressed in normal human organs, especially vital organs, as novel molecular targets for therapeutic drugs (compounds, antibody drugs or RNAi drugs), and/or diagnosis of human cancers. Particularly, through analysis of breast cancer expression profile, we focused on, PBK/TOPK (PDZ-binding kinase/T-LAK cell-originated protein kinase), as a drugable target molecule. The expression of this gene was highly and frequently upregulated in breast cancer specimens, but not or undetectable in normal vital organs. Knocking down of PBK/TOPK expression by siRNA resulted in significant suppression of breast cancer cell growth (Fig. 2). Furthermore, we demonstrated that PBK/TOPK could phosphorylate histone H3 as a substrate, at Ser10 *in vitro* and *in vivo*, and mediated its growth-promoting effect through histone H3 modification. Currently, we are studying the functional analysis of several target molecules involved in carcinogenesis including PBK/TOPK for cancer therapy in clinical use.

2. Investigation of mechanisms underlying triple-negative breast cancer (ER-negative, PgR-negative and Her2-negative)

Triple-negative breast cancers (TNBC) are defined by a lack of estrogen, progesterone, and Her2 receptors. TNBC has distinct clinical and pathologic features, and is a clinical problem because of its relatively poor prognosis, aggressive behavior and lack of targeted therapies, leaving chemotherapy as the mainstay of treatment. We are aiming at understanding molecular mechanism of TNBC carcinogenesis, and identifying therapeutic-targets for effective treatment of TNBC.

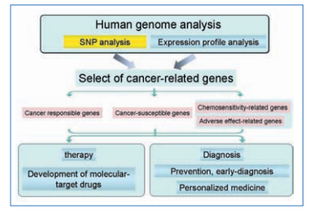

Fig.1. Development of strategies for better diagnosis, effective treatment and prevention oh human cancer on the basis of human genome analysis.

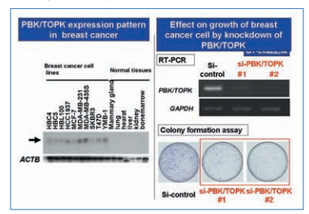

Fig.2 (left panles) PBK/TOPK expression pattern in breast cancer and normal human tissues. (right panels) Growth inhibitory effects of PBK/TOPK-siRNAs in breast cancer cell.

Fukukawa C, Nagayama S, Tsunoda T, Toguchida J, Nakamura Y, Katagiri T.
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Oncogene. 28:1110-1120 (2009)

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Oncogenic role of MPHOSPH1, a cancer-testis antigen specific to human bladder cancer.
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Cancer Res. 66:9186-9195 (2006)

Togashi A, Katagiri T, Ashida S, Fujioka T, Maruyama O, Wakumoto Y, Sakamoto Y, Fujime M, Kawachi Y, Shuin T, Nakamura Y.
Hypoxia-inducible protein 2 (HIG2), a novel diagnostic marker for renal cell carcinoma (RCC) and potential target for molecular therapy.
Cancer Res. 65:4817-4826 (2005)

Miki Y, Katagiri T, Kasumi F, Yoshimoto T, Nakamura Y
Mutation analysis in the *BRCA2* gene in primary breast cancers.
Nature Genet. 13:245-247 (1996)

Section of Proteomics

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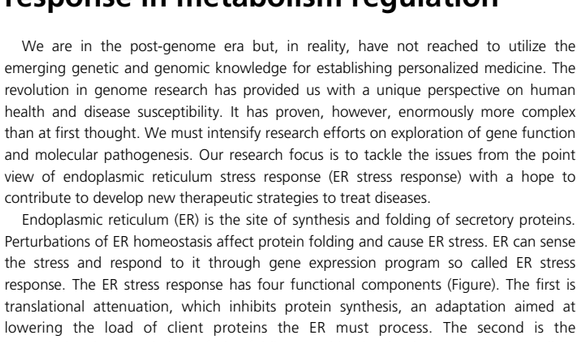
Role of endoplasmic reticulum stress response in metabolism regulation

We are in the post-genome era but, in reality, have not reached to utilize the emerging genetic and genomic knowledge for establishing personalized medicine. The revolution in genome research has provided us with a unique perspective on human health and disease susceptibility. It has proven, however, enormously more complex than at first thought. We must intensify research efforts on exploration of gene function and molecular pathogenesis. Our research focus is to tackle the issues from the point view of endoplasmic reticulum stress response (ER stress response) with a hope to contribute to develop new therapeutic strategies to treat diseases.

Endoplasmic reticulum (ER) is the site of synthesis and folding of secretory proteins. Perturbations of ER homeostasis affect protein folding and cause ER stress. ER can sense the stress and respond to it through gene expression program so called ER stress response. The ER stress response has four functional components (Figure). The first is translational attenuation, which inhibits protein synthesis, an adaptation aimed at lowering the load of client proteins the ER must process. The second is the transcriptional upregulation of the folding machineries in the ER to process client proteins. The third is enhancing degradation of misfolded protein in the ER, which is called ER-associated degradation (ERAD). The fourth is apoptosis, which occurs when the ER function is severely impaired. ER stress response is important for normal cellular homeostasis and development and suggested to involve in the pathogenesis of many diseases. We have shown that pancreatic beta-cells (which produce the hormone insulin) are highly susceptible to ER stress and mal-adaptation to ER stress causes diabetes.

Diabetes is emerging as one of the most serious health problems in the world. Diabetes develops when a critical number of pancreatic beta-cells become damaged or die. We speculate that ER stress is occurred in pancreatic beta-cells by overworking and overproducing insulin in pre-diabetic obesity. The high levels of ER stress for long time will lead pancreatic beta-cells into exhaustion or death. We hypothesize ER stress may be main contributor to the development of diabetes. The long-term goal of our research is to understand the role of ER stress response in metabolism regulation and to integrate these into an understanding of the pathogenesis of diabetes and other ER stress-related diseases. We expect that our work may eventually provide new targets for prevention and treatment of diabetes, as well as other ER stress-related disease. We are welcoming everyone who is interested in joining us in our endeavor to unravel the great mystery of nature.



The functional components of the ER stress response. Accumulation of unfolded proteins in the ER activates four cellular responses.

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2001 Clinical Fellow, Department of Metabolic Medicine, Kumamoto University
2002 Research Fellow, Department of Molecular Genetics, Kumamoto University
2003 Research Fellow, Skirball Institute of Biomolecular Medicine, New York University School of Medicine
2004 Professor, Institution for Genome Research, The University of Tokushima

Assistant Professor : Keisuke Yamamoto Ph.D.

Oyadomari S, Harding HP, Zhang Y, Oyadomari M, Ron D.
Dephosphorylation of translation initiation factor 2alpha enhances glucose tolerance and attenuates hepatosteatosis in mice.
Cell Metabolism. 7: 520-532 (2008)

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Cotranslocational degradation protects the stressed endoplasmic reticulum from protein overload.
Cell. 2006 126: 727-739 (2006)

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Roles of CHOP/GADD153 in endoplasmic reticulum stress.
Cell Death Differ. 11: 381-389 (2004)

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Targeted disruption of the Chop gene delays endoplasmic reticulum stress-mediated diabetes.
J Clin Invest. 109: 525-532 (2002)

Oyadomari S, Takeda K, Takiguchi M, Gotoh T, Matsumoto M, Wada I, Akira S, Araki E, Mori M.
Nitric oxide-induced apoptosis in pancreatic beta cells is mediated by the endoplasmic reticulum stress pathway.
Proc Natl Acad Sci U S A. 98: 10845-10850 (2001)

Division of Protein Expression

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2002-present Professor, Institute for Genome Research and Faculty of Pharmaceutical Sciences, University of Tokushima
2002-present Invited Researcher, National Institute of Advanced Industrial Science and Technology (AIST)

Assistant Professor : Takenori Yamamoto Ph.D.

Control of cellular fate and energy metabolism

Our major research interests are regulatory mechanisms of the energy metabolism and programmed cell death. Especially, we are studying two research projects of i) structure and function of mitochondria and ii) energy metabolism specifically occurring in adipose tissues.

As for the first research topics, we are interested in the status of mitochondrial inner membrane. Under the ordinary physiological conditions, permeability of inner mitochondrial membrane is kept very low, to enable effective energy conversion. However, under certain conditions, permeability of inner mitochondrial membrane is known to be remarkably elevated. The physiological meanings of this increase in the permeability of inner mitochondrial membrane have been uncertain, however, recent studies indicated that it is associated with the release of mitochondrial cytochrome c, and regulation of programmed cell death. Thus, we are studying the relationship between the status of inner mitochondrial membrane and release of mitochondrial cytochrome c. Our recent studies revealed that cytochrome c could be released from mitochondria accompanied with or without changes in the permeability of mitochondrial inner membrane. These distinct mechanisms causing release of cytochrome c were also successfully explained by proteomics analysis.

As for the latter research topics, we have been studied the molecular basis of the thermogenic function occurring in brown adipose tissue. Of two kinds of adipose tissues present in mammals (brown and white adipose tissues, abbreviated as BAT and WAT, respectively), only BAT exerts thermogenic function. Thus, to visualize the molecular basis enabling thermogenesis in BAT, we compared gene expression profiles between BAT and WAT. As a result, genes preferentially expressed in BAT were found to be similar to those expressed in skeletal muscle rather than those in WAT. Thus, we concluded that metabolisms occurring in BAT and suitable for thermogenesis are similar to those occurring in skeletal muscle. We also started to identify and characterize the genes preferentially expressed in WAT.

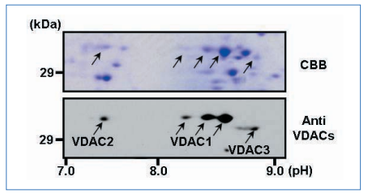

Fig. 1
Proteomics studies on the three voltage dependent anion channel (VDAC) isoforms expressed in mitochondria

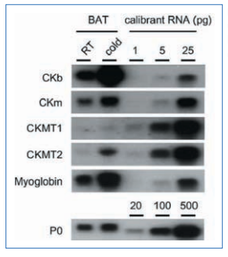

Fig. 2
Changes in the gene expression in brown adipose tissue induced by cold exposure of experimental animals

Yamada A, Yamamoto T, Yamazaki N, Yamashita K, Kataoka M, Nagata T, Terada H, Shinohara Y.
Differential permeabilization effects of Ca2+ and valinomycin on the inner and outer mitochondrial membranes as revealed by proteomics analysis of proteins released from mitochondria
Mol Cell Proteomics. in press (2009)

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Bioenerg Biomemb. 40:619-623 (2008)

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Synchronized changes in the transcript levels of the genes towards activated thermogenesis in brown adipose tissue induced by cold exposure of experimental animals
Biochim Biophys Acta. 1777:104-112 (2008)

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VDAC1, having a shorter N-terminus than VDAC2 but showing the same migration as it in an SDS-polyacrylamide gel, is the predominant form expressed in mitochondria of various tissues
J Proteome Res. 5:3336-3344 (2006)

Section of Systems Biology

Division of Genetic Information

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Genome analysis by correlating genetic variants with phenotypes

1) Elucidation of etiologic genes responsible for congenital metabolic disorders:

We discovered etiologic genes for monongenic disorders by linkage analysis of the affected pedigrees and positional cloning. We identified the etiologic mutations in the *UMOD* (uromodulin) gene in Familial Juvenile Hyperuricemic Nephropathy. We discovered splicing site mutations in the *CSPG5* (chondroitin sulfate proteoglycan) gene in Wagner syndrome. We discovered *GDD1* (*TMEM16E*) as the etiologic gene for Gnatho-Diaphyseal Dysplasia. By using antibody for GDD1, we examined the intracellular localization and the presence of glycosylation of GDD1. By the in situ hybridization, we examined the expression pattern of *GDD1* in the early developmental stages. The analysis of knockout mouse is under way.

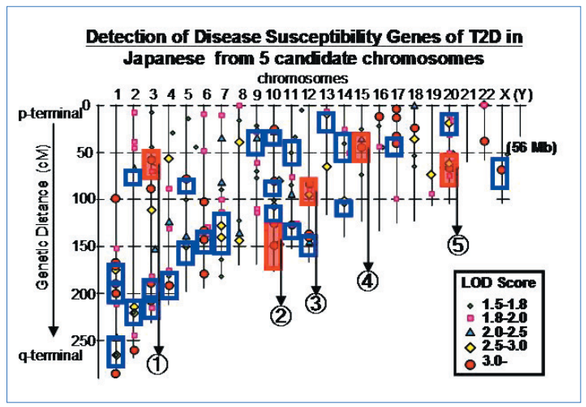
2) Identification of susceptibility genes for type 2 diabetes and rheumatoid arthritis:

We collected genomic DNA and established immortalized lymphoblast cell lines from more than 1,000 subjects each with type 2 diabetes or rheumatoid arthritis, and from 1,600 healthy control subjects. We examined minor allele frequency of about 90,000 SNPs in Japanese (http://www.genome.tokushima-u.ac.jp/dgi/ENGDGI/ASNPs_E/index_English.html). By 5 chromosome-wide association studies on 1,500~2,000 subjects with T2D based on the replicated candidate chromosomal regions by affected sib pair analysis, we found *ENDOGL1*, *SOCS2* as the candidate susceptibility gene for T2D. By the chromosome-wide analysis on rheumatoid arthritis, we have extracted *EXOC4* (*SEC8L1*) and *PRKCH* gene as the candidate gene for rheumatoid arthritis in Japanese. We are now analyzing the genetic basis of children with short stature by the mutation analysis and CNV (copy number variation) analysis.

3) QTL analysis of F2 intercrosses between mice developing diabetes and those which do not become diabetic:

By using the F2 generation between db mice with the deficiency of leptin receptor and C3H or DBA2 mice, we identified 20 or 27 QTLs. We made congenic mice between db and DBA2 for 4 QTL loci and one locus at chromosome 5 was shown to reproduce the phenotypes including body weight, intestinal fat amount, and others in F2 intercross. We identified the responsible gene for this phenotype and we are now examining the function of this gene by transgenic and knockout mice technology with the collaboration with Otsuka Pharmaceutical Company.

Based on the analysis on the genome function in humans and mice, we are trying to understand the disease mechanism relating with patho-physiology and metabolic regulation.



Extracted candidate genes:①*ENDOGL1* gene, ②A novel gene, ③*SOCS2* gene, ④*UBR1* gene, ⑤*MYL9* gene. Different Marks show the different magnitude of linkage in the literature.

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1973-1975	Internal Medicine Resident, Tokyo University Hospital
1976-1977	Research Fellow, Duke University Medical Center
1977	Clinical Fellow, Duke University Medical Center
1977-1980	Research Fellow, Duke University Medical Center
1980	Research Associate, Duke University Medical Center
1980-1990	Assistant Professor, Division of Endocrinology and Metabolism, Institute for Clinical Medicine, Tsukuba University
1995-1996	Visiting Professor, Division of Endocrinology, Metabolism, and Genetics, Duke University Medical Center
1990-2000	Visiting Professor, Otsuka Department of Clinical and Molecular Nutrition, The University of Tokushima.
1998-2008	Professor and Director, Division of Genetic Information, Institute for Genome Research, The University of Tokushima
2008-now	Professor, Division of Genetic Information, Institute for Genome Research, The University of Tokushima

Associate Professor : Hiroshi Inoue M.D., Ph.D.

Yasuda K, Miyake K, Horikawa Y, Hara K, Osawa H, Furuta H, Hirota Y, Mori H, Jonsson A, Sato Y, Yamagata K, Hinokio Y, Wang HY, Tanahashi T, Nakamura N, Oka Y, Iwasaki N, Iwamoto Y, Yamada Y, Seino Y, Maegawa H, Kashiwagi A, Takeda J, Maeda E, Shin HD, Cho YM, Park KS, Lee HK, Ng MC, Ma RC, So WY, Chan JC, Lyssenko V, Tuomi T, Nilsson P, Groop L, Kamatani N, Sekine A, Nakamura Y, Yamamoto K, Yoshida T, Tokunaga K, Itakura M, Makino H, Nanjo K, Kadowaki T, Kasuga M.
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Mol Genet Metab. 9:200-209 (2008)

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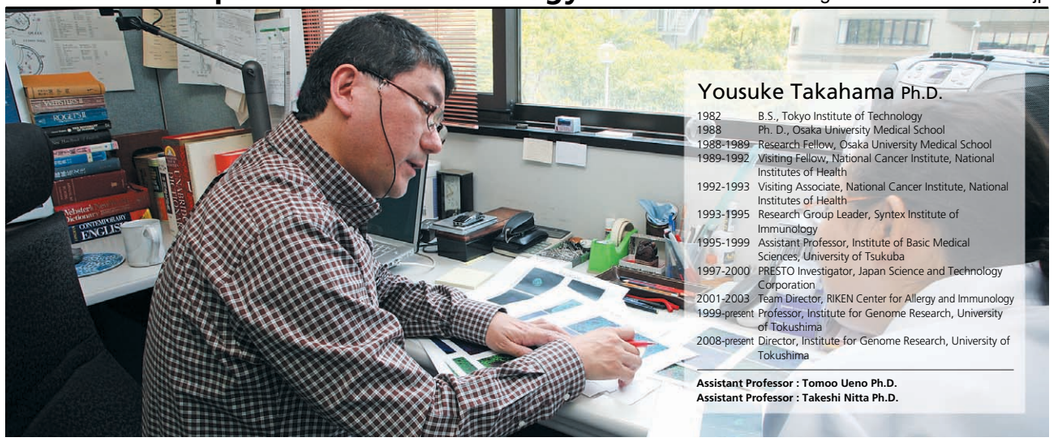

Yousuke Takahama Ph.D.

1982	B.S., Tokyo Institute of Technology
1988	Ph. D., Osaka University Medical School
1988-1989	Research Fellow, Osaka University Medical School
1989-1992	Visiting Fellow, National Cancer Institute, National Institutes of Health
1992-1993	Visiting Associate, National Cancer Institute, National Institutes of Health
1993-1995	Research Group Leader, Syntex Institute of Immunology
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1997-2000	PRESTO Investigator, Japan Science and Technology Corporation
2001-2003	Team Director, RIKEN Center for Allergy and Immunology
1999-present	Professor, Institute for Genome Research, University of Tokushima
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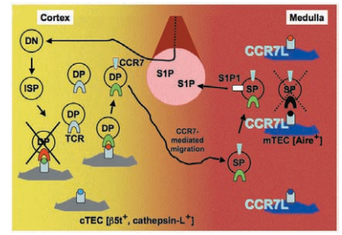
Towards understanding how immune system is established

Long-term goal of the laboratory is to unveil molecular mechanism that is essential for establishing immune system. One of the most prominent characteristics of the immune system is the discrimination of foreign substances from self-constituents, so that immune responses would attack various pathogens while maintaining tolerance to the self.

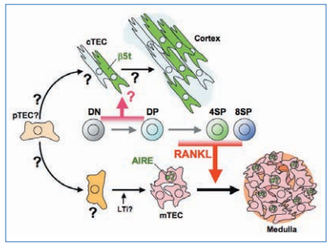
T lymphocytes are the cells that play an essential role in distinguishing non-self from self. T lymphocytes acquire this ability through shaping a repertoire of recognition specificity during the development in the thymus, by the process referred to as positive and negative selection. Much has been revealed during the past two decades how antigen-receptor signals in developing T lymphocytes control the cells' fate upon positive and negative selection. However, how T lymphocytes are generated and selected in the thymus environment is still poorly understood.

Thus, our current interest is to understand molecular programs (1) that build up functionally competent thymus, which is capable of supporting and selecting T lymphocytes, (2) that position developing T lymphocytes to localize within the thymus microenvironments for shaping T-lymphocyte repertoire, and (3) that control intrathymic selection to generate a healthy pool of mature T lymphocytes.

Unveiling molecular machinery that is essential for establishing functional thymus and T lymphocyte selection should aid controlling various immune diseases including autoimmunty and immunodeficiencies.



Lymphostromal interactions in T-cell development and repertoire formation in the thymus. Early development of lymphoid progenitor cells to the CD4 and CD8 double-positive (DP) thymocytes is supported in cortical microenvironment. In the thymic cortex, thymic cortical epithelial cells (cTEC) support TCR-mediated positive and negative selection of DP thymocytes. Positively selected thymocytes differentiate to CD4 or CD8 single-positive (SP) thymocytes and relocate to the medulla through CCR7-mediated chemotactic attraction by thymic medullary epithelial cells (mTEC). In the medulla, mTEC, along with DC, establish negative selection of self-reactive thymocytes. Mature SP thymocytes are exported from the thymus in response to circulating sphingosine-1-phosphate (S1P).



Development of cortical and medullary thymic microenvironments. The differentiation of TEC progenitor cells (pTEC) into functionally mature mTEC that express AIRE and CCR7L is regulated by RANKL-expressing lymphoid tissue inducer (LTi) cells during embryogenesis. In postnatal thymus, positive selection results in the generation of SP thymocytes that express RANKL and CD40L, which promote the proliferation of mTEC and thereby nurture the formation of thymic medulla. Molecular mechanisms that regulate the development of cTEC that express β5t-containing thymoproteasomes is unknown, but it is known that thymocyte development to the DP stage affects the expansion of cTEC to form the thymic cortex.

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