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Institute for Frontier Life and Medical Sciences, Kyoto University

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A Message from the Director

In October 2016, former Institute for Virus Research and Institute for Frontier Medical Sciences were merged, and Institute for Frontier Life and Medical Sciences was newly established.
Institute for Virus Research, being established in 1956, first identified adult T-cell leukemia virus/ human T-cell lymphotropic virus (ATLV/ HTLV) as the causative agent of adult T-cell leukemia (ATL), which was one of the representative achievements as a leading research institute in the field of viral infection as well as molecular biology in Japan.
Institute for Frontier Medical Sciences, being established in 1998, has developed innovative foundation for regenerative medicine by successfully establishing embryonic stem cells (ES cells) and discovering induced pluripotent stem cells (iPS cells) as well as regulatory T cells.
In 2008, Institute for Frontier Medical Sciences was designated as Joint Usage/Research Center for Transdisciplinary Collaboration on Tissue Engineering and Regenerative Medicine. And in 2009, Institute for Virus Research was designated as Joint Usage/Research Center for Fusion of Advanced Technologies and Innovative Approaches to Viral Infections and Life Science. Since then, these two institutes have individually functioned as a core of joint research among related scientists. On the occasion of the establishment of new institute, we are determined to further develop these important functions and to flourish as a research hub.
Since Japan has a rapidly aging society, establishment of measures against viral infection as well as regenerative medicine is undoubtedly the most urgent and priority task for the medical community in the nation. Though these two seem absolutely different, they are combined in the hidden dimension of “variously structured cell society” in the body. By exploring research in this dimension, our new institute is expected to contribute building a new research community for scientists and establishing a new foundation of medical technology.

Yuji Hiraki Ph.D.
Director of Institute for Frontier Life and Medical Sciences,
Kyoto University

History

Institute for Virus Research

1956 2 Departments

1957 4 Departments

1958 5 Departments

1959 5 Departments & 1 Research Center

1962 6 Departments & 1 Research Center

1968 7 Departments & 1 Research Center

1974 8 Departments & 1 Research Center

1978 8 Departments & 2 Research Centers

1990 4 Departments (after reorganization) & 2 Research Centers

2005 4 Departments & 3 Research Centers

1980 Research Center for Medical Polymers and Biomaterials

1990 Research Center for Biomedical Engineering
3 Departments

1941 Tuberculosis Research Institute
5 Departments (6 Departments & 1 University Hospital, eventually)

1967 Chest Disease Research Institute
6 Departments & 1 University Hospital
(7 Departments, 1 Research Center & 1 University Hospital, eventually)

1988 Chest Disease Research Institute
4 Divisions (after reorganization), 1 Research Center & 1 University Hospital

1998 Institute for Frontier Medical Sciences
5 Fields (after reorganization) & 1 Research Center
(5 Fields & 2 Research Centers, eventually)

2016
Institute for Frontier Life and Medical Sciences
(established on Oct. 1st)
3 Departments (28 Laboratories & 6 Laboratories of visiting professors)
& 2 Research Centers (3 Laboratories)

The original cover picture

The motif of the cover picture is from wall decorative paintings “Stoclefries”, one of the masterpieces of Gustav Klimt (1862-1918) in the late Austrian Empire.
Klimt’s work is described as giving the impression of the “chain of life and death” as well as the “permanency of life” because there is always scent of death in his gorgeously colored paintings. On this motif, we overlaid a “formula”, a common language of science, to express how a basic unit of life such as a nucleic acid molecule, a virus, a cell, an organ or a concrete life existence (consisted of the basic units of life) leads a dynamic life. This shows our direction to fulfill our mission to research into “variously structured cell society” of life in order to reveal the whole structure of strategy for life to exist.

Entwurf fur den Wandfries im Palais Stoclet in Brussel, Goldener Ritter - 1909

organization

- Committee for Programming and Management
- Director
  - Vice Director
  - Vice Director
- Faculty Council
- Steering Committee on "Joint Usage/ Research Center Program for Fusion of AdvancedTechnologies and Innovative Approaches to Viral Infections and Life Science"
- Steering Committee on "Joint Usage/Research Center Program for Transdisciplinary Collaboration on Tissue Engineering and Regenerative Medicine"

Research Departments

Department of Virus Research
- Lab. of Molecular Genetics
- Lab. of Virus Control
- Lab. of RNA Viruses
- Lab. of Ultrastructural Virology
- Lab. of Tumor Viruses
- Lab. of Cell Regulation
- Lab. of Immune Regulation
- Lab. of Infection and Prevention
- Lab. of Bioresponse Regulation ※
- Lab. of Viral Immunology ※

Department of Regeneration Science and Engineering
- Lab. of Molecular and Cellular Biology
- Lab. of Biomaterials
- Lab. of Tissue Stem Cell Biology
- Lab. of Immunology
- Lab. of Tissue Regeneration
- Lab. of Organ and Tissue Reconstruction
- Lab. of Developmental Epigenome
- Lab. of Embryonic Stem Cell Research
- Lab. of Integrative Biological Science
- Lab. of Experimental Immunology ※
- Lab. of Material Biophysics ※
- Lab. of Medical Engineering ※

Department of Biosystems Science
- Lab. of Cellular Differentiation
- Lab. of Nano Bioprocess
- Lab. of Biomechanics
- Lab. of Developmental Systems
- Lab. of Systems Virology
- Lab. of Growth Regulation System
- Lab. of Integrated Biological Information
- Lab. of RNA System
- Lab. of Biological Membrane System
- Lab. of Tissue Homeostasis
- Lab. of Tumor Biogenesis
- Lab. of Regulatory Information ※

Attached Facilities

Research Center for Infectious Diseases
- Lab. of Primate Model
- Lab. of Infectious Disease Model
- Lab. of Virus-Host Coevolution

Center for Animal Experiments

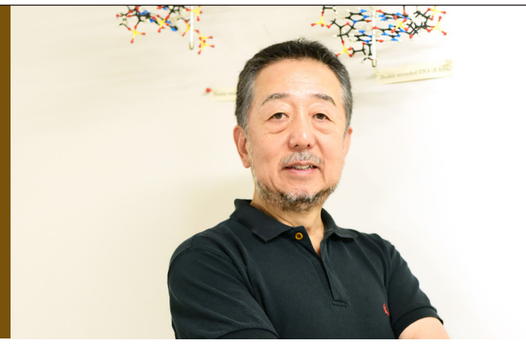
Division of Technical Support

Administration Office

※Visiting

Unveiling of Nameplate “Institute for Frontier Life and Medical Sciences Kyoto University” (October 3rd, 2016)

Establishment Ceremony of Institute for Frontier Life and Medical Sciences Kyoto University (December 21st, 2016)



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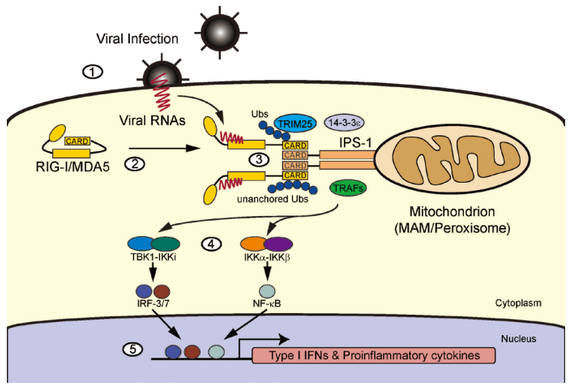
Laboratory of Molecular Genetics

Virus infections, such as influenza A epidemic and Chronic Hepatitis C virus infection are still important diseases and outbreaks of newly emerging viruses are serious problems for modern society. Higher animals, including humans, are genetically equipped with mechanisms, collectively known as innate immunity, to counteract viral infections. During the course of replication, many viruses generate double-stranded (ds)RNA, which is virtually absent in normal cells and likely serves as a “foreign molecule” in cells. RIG-I, MDA5 and LGP2, collectively termed as RIG-I-Like Receptors (RLRs) function as sensor for viral dsRNA to initiate production of interferon (IFN) and proinflammatory cytokines (Figure), which block viral replication and promote acquired immunity against viruses. Recently we discovered that persistent activation of MDA5 leads to lupus-like autoimmune disorder in mice. The purpose of our project is to clarify the molecular mechanism underlying the antiviral innate immunity and autoimmunity regulated by RLR, and to develop new diagnostic and therapeutic tools for these diseases. This laboratory belongs to Graduate School of Biostudies. Associate Professor Okabe studies on regulation of tissue-resident macrophage specialization and tissue homeostasis.



Sensing viral dsRNA and activation of RLR
When cells were infected with virus (1), viral dsRNA is sensed by RIG-I or MDA5 (2). CARD of RIG-I and MDA5 interacts with another CARD-containing protein expressed on mitochondria, termed Interferon Promoter Stimulator-1 (IPS-1) (3). AS a result of these molecular interactions, transcription factors, IRF-3, IRF-7 and NF-κB are activated (4). These transcription factors cooperatively activate several antiviral genes, including those of type I and type III interferon are activated (5).

Lab URL *http://www.virus.kyoto-u.ac.jp/Lab/akiyama/index.html*

Lab. of Virus Control

The major targets of our research are two human retroviruses, human T-cell leukemia virus type 1 (HTLV-1) and human immunodeficiency virus (HIV). We are studying the molecular mechanisms for pathogenesis of HTLV-1, and trying to develop the novel strategy for the treatment. Regarding HIV,our research purposes are understanding the dynamics of HIV infection and developing novel antiviral drugs.

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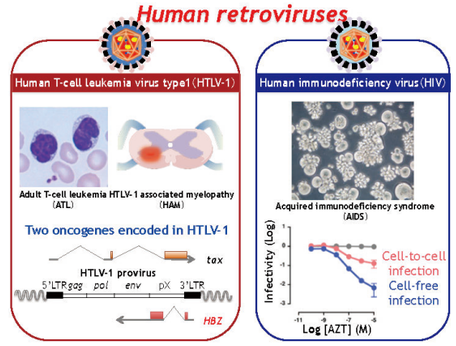

HTLV-1 is an etiological agent of a malignant disease, ATL, and several inflammatory diseases such as HAM. Two viral oncogenes, tax and HBZ, play important roles in the pathogenesis. HIV causes AIDS. HIV infects target cells through cell-to-cell and cell-free fashions, which have different sensitivity to anti-viral drugs.

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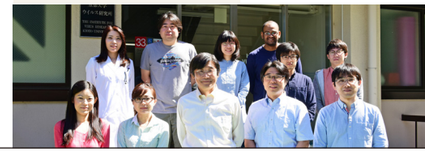
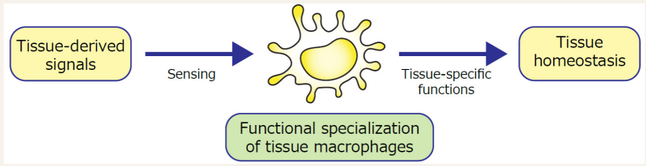


Lab URL *http://www.virus.kyoto-u.ac.jp/Lab/VirusControl/index.html*

Topics

Lab. of Molecular Genetics

Macrophages, present in virtually every mammalian tissue, are highly specialized in terms of their functions as a consequence of adaptation to different tissue environments. Functional specialization of tissue-resident macrophages has crucial roles in the maintenance of tissue homeostasis. Accordingly, abnormality of tissue macrophage functions often links to various diseases and pathogenesis. Our study focuses on development and functional specialization of tissue-resident macrophages, as well as the association of macrophage malfunction with various disease states.



Tissue signals induce functional sprcialization of tissue-resident macrophages, that are crucial for the maintenance of tissue homeostasis.

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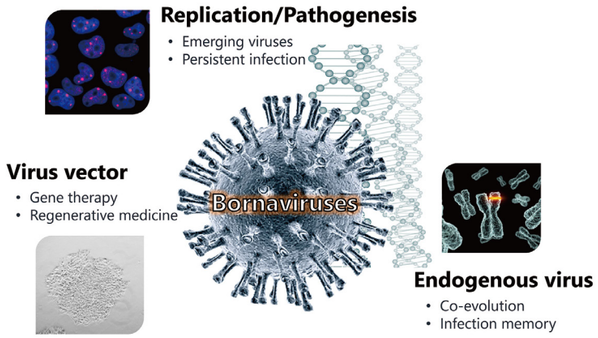
Lab. of RNA Viruses

All viruses rely on the cellular machinery to complete their replication cycles. Therefore, the study of viruses can provide fundamental knowledge and understanding not only of viral pathogenesis and host responses but also of cellular function. The researches carried out in this laboratory are focused on negative strand RNA viruses replicating in the cell nucleus, especially bornaviruses. All our projects aim to understand the fundamental mechanisms of the replication, pathogenesis and evolution of bornaviruses. In current researches, we are investigating the replication and persistent mechanism of the bornaviruses in the cell nucleus. The understanding the biological and evolutional significances of the endogenous bornavirus-like elements (EBLs) found in the genomes of many mammalian species is one of the main focuses of our laboratory. Furthermore, we are analyzing emerging bornaviruses, which include avian bornaviruses as well as a squirrel bornavirus that may be highly pathogenic to humans. We also aim to develop a novel RNA virus vector using bornavirus, which can stably express foreign genes, including functional small RNAs, and be applied for gene therapy of stem cells, such as iPS cells.



In Laboratory of RNA viruses, we are working on several projects regarding replication/pathogenesis of bornaviruses, endogenous bornavirus and development of novel RNA virus vectors using bornavirus.

Lab URL *https://t.rnavirus.virus.kyoto-u.ac.jp/*

Lab. of Ultrastructural Virology

Our laboratory has been studying negative-strand RNA viruses such as influenza virus and Ebola virus, which are pathogenic for humans and animals. Especially, we have focused on: 1. The packaging mechanisms of influenza virus eight-segmented genome, 2. Mechanisms of influenza virus genome transcription and replication, 3. Mechanisms of Ebola virus helical nucleocapsid formation, 4. Generation of neutralizing monoclonal antibodies inhibiting influenza virus and Lassa virus replication, 5. Development of antiviral drugs by drug repositioning, and 6. The structure of influenza virus mRNAs. So our interests cover not only fundamental, but also practical research. In addition, our laboratory is skilled at imaging analyses by using microscopes. In addition to conventional virological, molecular biological, and cellular biological techniques, we employ microscopic analyses such as transmission electron microscopy, cryoelectron microscopy, and high-speed atomic force microscopy to understand virus replication mechanisms from an ultrastructural point of view. We would like to contribute to the progress of virus research as well as the control of infectious virus diseases through our research.

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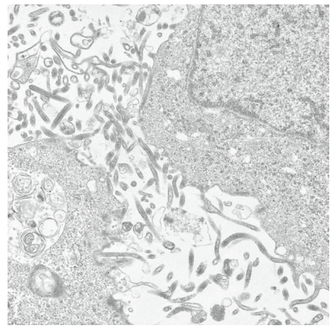


Figure 1 Transmission electron microscopic image of filamentous Ebola virus particles budding from infected cells.

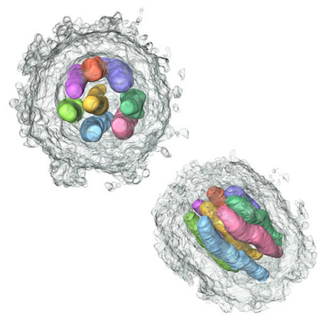
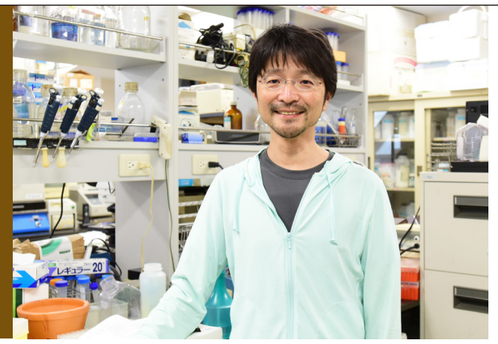


Figure 2 Three dimensional model of an influenza virus particle reconstructed by electron tomography. Eight RNPs arranged in a characteristic "1+7" pattern are present within the virion.

Lab URL *http://www.ims.u-tokyo.ac.jp/noda-lab/*



Lab. of Tumor Viruses

Papillomavirus infection and its tumorigenic potential: The infection of papillomavirus induces benign tumors, such as warts and condylomas, and occationally they are converted into cancers. We are investigating the molecular mechanisms of the virus replication and the virus-related tumor progression. Analysis of Wnt intracellular signaling pathway: Wnt signaling regulates a variety of adult and developmental processes and mutations in several components of the Wnt pathway are oncogenic. I am analyzing this pathway in vitro and in vivo.

Lab URL *http://www.virus.kyoto-u.ac.jp/Lab/sakai2012/Home2.html*

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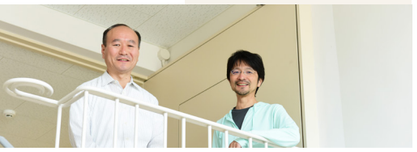

Horn-shaped warts induced by Shope papillomavirus infection

The main purpose our research group is to clarify the molecular mechanisms of carcinogenesis caused by the infection of human hepatitis viruses. Molecular and cellular biological analyses of the viral lifecycle and the cellular events related with viral infection have been investigated. We have found several candidates of the drugs against HCV and HBV through those studies.

Lab URL *http://www.virus.kyoto-u.ac.jp/Lab/HCV/index.html*

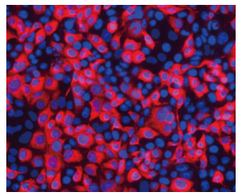

Figure 1 Cultured liver cancer cells infected with HCV. HCV infected cells are indicated by immunofluorescence using anti-HCV proteins antibody (red).

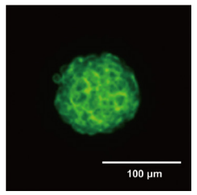

Figure 2 Immortalized human hepatocytes producing the HBV receptor molecule cultured in three-dimensional condition. The HBV receptor molecule is visualized with fused green fluorescent protein.

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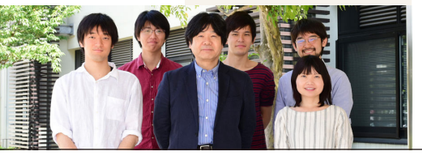

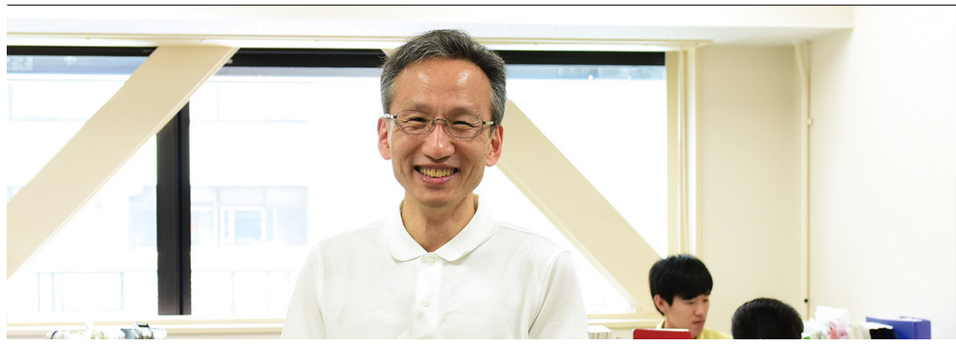

Lab. of Cell Regulation

The universe of antigens recognized by the immune system has recently been expanded to include not only protein antigens but also lipid and lipopeptide antigens. By orchestrating immunological, cell biological, biochemical and structural approaches and by developing valuable animal systems, our laboratory aims to establish the molecular and cellular basis underlying “lipid immunity” and disclose its relevance to cancer, microbial infections, and autoimmunity. These studies have important medical implications, including development of a new type of lipid-based vaccines. We have recently identified monkey molecules, LP1, capable of binding lipopeptide antigens and presenting them to lipopeptide-specific T lymphocytes. This study has guided us to the identification of human LP1, and previously unappreciated human immune pathways are now beginning to be unraveled in our laboratory.

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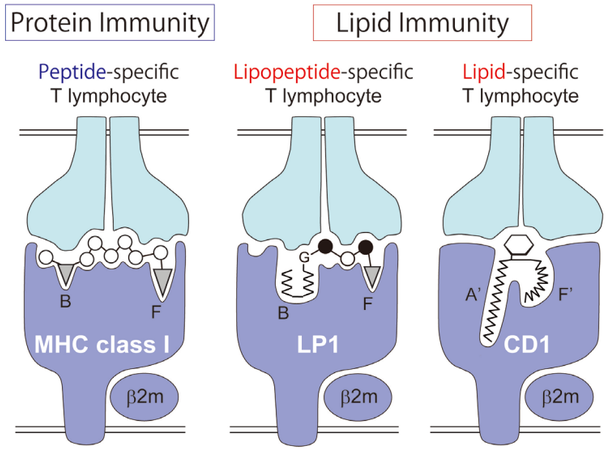
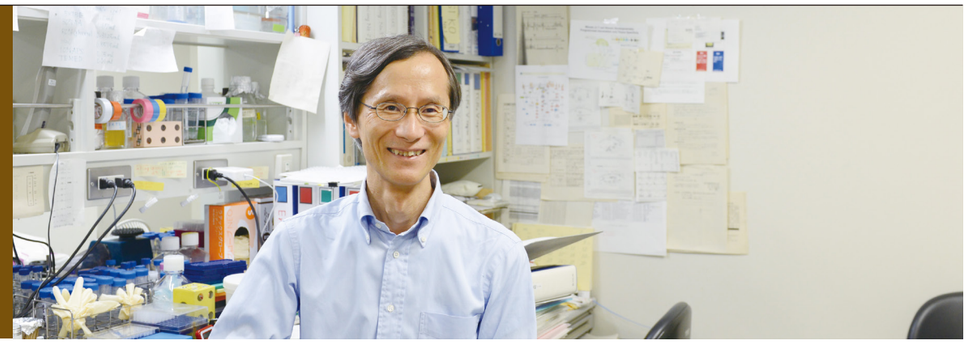


Whereas MHC molecules bind peptide antigens and present them to T lymphocytes, LP1 and CD1 molecules bind lipopeptide and lipid antigens, respectively, and present them to specific T lymphocytes. Our frontier research focusses on these new immune pathways that we call "lipid immunity".

Lab URL *http://www.virus.kyoto-u.ac.jp/Lab/SugitaLab.html*



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Lab. of Immune Regulation

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The immune system has acquired sophisticated control mechanisms as a result of evolution at the front line of the battles between hosts and pathogenic microorganisms. We are pursuing research on development of the immune system and regulation of immune response, focusing on the cytokine, interleukin-7 (IL-7), important for development, maintenance, and function of lymphocytes. We are now carrying on the following projects: (1) control of DNA recombination of antigen receptor genes by IL-7; (2) differentiation and maturation signals of the IL-7 receptor; (3) regulation of IL-7 receptor expression during lymphocyte differentiation and immune response; (4) circadian control of dynamics and function of lymphoid cells by steroid hormones; and (5) visualization and local function of cytokine-producing cells, in relation with metabolic syndrome and obesity. Laboratory of Immune Regulation is affiliated with the Graduate School of Medicine and receives many graduate students on various backgrounds.

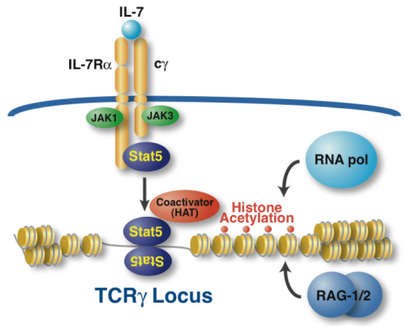


Figure 1 Control of DNA recombination of antigen receptor genes by IL-7
IL-7 induces DNA recombination of the T cell receptor γ locus by Stat5 and histone acetylation.

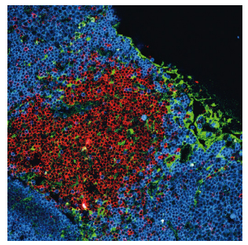
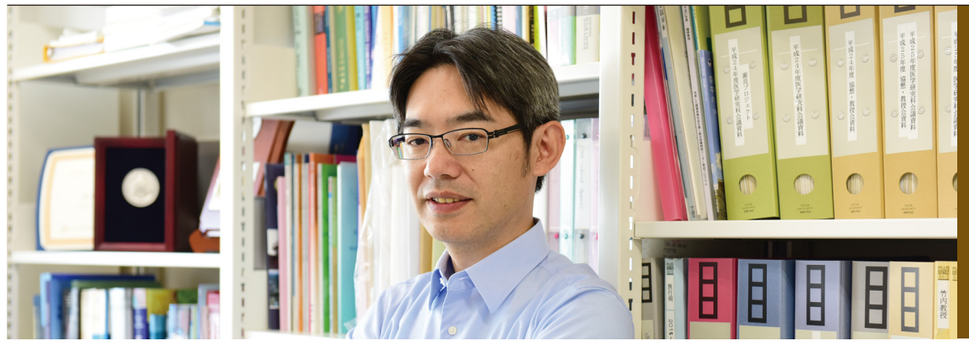


Figure 2 Visualization of IL-7-producing cells in Peyer's patch
Immunohistochemistry of the Peyer's patch from IL-7-GFP knock-in mouse. IL-7/GFP (green), T cells (red), B cells (blue). IL-7-producing cells are scattered with green color.

Lab URL ***http://www.virus.kyoto-u.ac.jp/Lab/ikutalab/ikuta.html***



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Lab. of Infection and Prevention

Inflammation is a host response against diverse stresses including infection with viruses and bacteria. Furthermore, inflammation is revealed to be involved in various diseases such as autoimmunity, cancer and metabolic syndrome. Innate immune cells such as macrophages and dendritic cells are important for initial inflammatory responses against infection via production of cytokines, and activation and inhibition of innate immune responses are elaborately balanced in the body. We are aiming to uncover the molecular mechanisms of inflammation and its regulation in the innate immune system by using genetically modified animals. We identified an RNase Regnase-1, which degrades mRNAs encoding inflammatory proteins such as cytokines. Regnase-1 is critical for the maintenance of immune homeostasis. In addition, we are focusing on positive regulators of immune responses such as Akirin. We aim to uncover regulatory mechanisms of immunity and manipulate the immune reactions. This laboratory belongs to Graduate School of Medicine.

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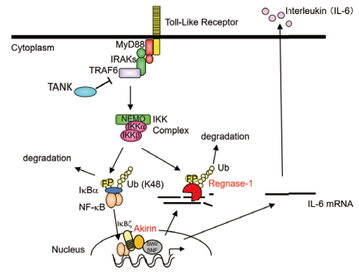

Figure 1 Innate immune signaling and its regulation
The Toll-like receptor signaling pathways triggered by pathogen infection are regulated by various intracellular molecules such as Regnase-1 and Akirin2. These molecules control levels of cytokines and inflammation appropriate.

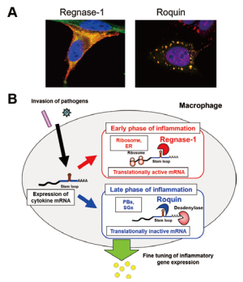

Figure 2 Spatiotemporal regulation of cytokine mRNA decay by Regnase-1 and Roquin
(A) Regnase-1 and Roquin localize in the endoplasmic reticulum and the stress granule, respectively. (B) Regnase-1 and Roquin, which recognize common stem-loop mRNAs, control inflammation by degrading cytokine mRNAs in a translation-dependent and -indepenent manners.

Lab URL ***http://www.virus.kyoto-u.ac.jp/Lab/Takeuchi_HP/index.html***

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Lab. of Bioresponse Regulation (Visiting)

Influenza has been recognized in history for hundreds of years. Yet, while medicine has advanced, influenza continues to cause epidemics and take lives every year. In 2009, pandemic (H1N1) 2009 influenza arose and spread quickly around the world. Meanwhile, highly pathogenic H5N1 avian influenza viruses continue to circulate and infect humans. We study the mechanisms responsible for the high pathogenicity and transmissibility of influenza viruses, focusing on viral and host factors. In addition, current inactivated influenza vaccines have limited efficacy because they do not induce mucosal immunity and cytotoxic T-cell responses; we, therefore, also study approaches for novel vaccine development that would overcome these limitations. To better understand pathogenesis and host responses, and to improve the efficacy assessment of anti-viral drugs and novel vaccines, we study influenza virus infection in a macaque model in the BSL-3 non-human primate facility at this institute.

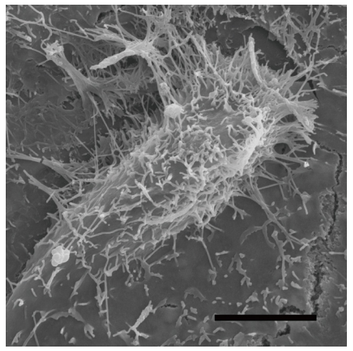


Figure 1 Pandemic (H1N1) 2009 virus-infected cell. Viral particles are budding from the cell surface.

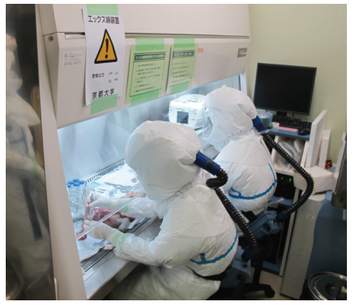
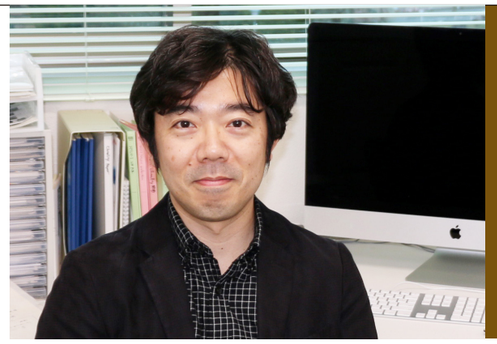


Figure 2 Analysis of influenza viruses in a macaque model at the BSL-3 non-human primate facility at this institute.

Lab. of Bioresponse Regulation (Visiting)

There are two human retroviruses associated with human diseases, HIV-1 and HTLV-1. Retroviruses insert their viral genome into the host genomic DNA and achieve persistent infection by exploiting the host transcriptional machinery. The infection induces deregulation of the host cell homeostasis, resulting in viral pathogenesis in the host. We are investigating these two retroviruses, in order to elucidate the mechanism of persistent infection and their pathogenesis.



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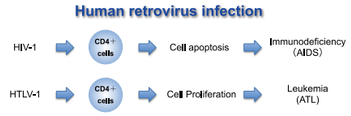

Figure 1 Pathogenesis of HIV-1 and HTLV-1
HIV-1 induces apoptosis of the infected cells and cause AIDS, whereas HTLV-1 induces proliferation of the infected cells and cause leukemia of infected cells.

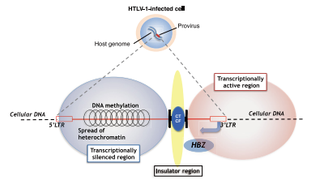

Figure 2 Epigenetic regulation of HTLV-1 provirus
A host epigenetic regulatory molecule, CTCF, directly binds to the integrated HTLV-1 genome. The virus utilizes the host molecule to achieve persistent infection in the host.

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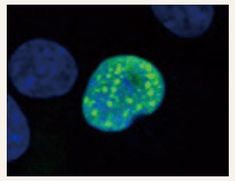
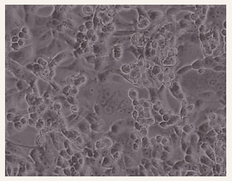
Topics

Hakubi Center for Advanced Research

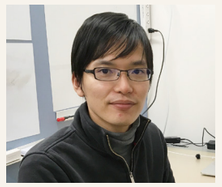
I am a member of the Hakubi project in Kyoto University, and my research topic in the Hakubi project is “Paleovirology of RNA viruses”.
I am studying the replication mechanisms and evolution of RNA viruses as well as co-evolution between the viruses and their hosts. Because viruses do not leave their body fossils, the evolution and diversification history of RNA viruses are largely unknown. However, we and others recently discovered sequences derived from ancient RNA viruses in the genomes of many eukaryotes, namely molecular fossils of RNA viruses. By a combination of evolutionary analyses of the viral fossils and basic virological studies, I am aiming to understand the deep evolutionary history of RNA viruses.
Because I am a veterinarian, in addition to the above topics, I am also doing researches on viral infectious diseases and the diversity of viruses in animals.



Nyamanini virus-infected cells



Porcine epidemic diarrhea virus-infected cells



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Lab. of Viral Immunology (Visiting)

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Human T-lymphotropic virus type 1 (HTLV-1) is widespread in the tropics and subtropics. Ninety percent of people infected with this virus are unaware of the infection and remain healthy, but 5% develop a leukaemia or lymphoma, known as ATL, and up to a further 5% develop a chronic inflammatory disease of the nervous system known as HAM/TSP, which results in paralysis of the legs. HTLV-1 is the main cause of adult leukaemia in southern Japan.

We aim to answer the questions:

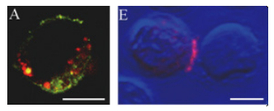
- why do some HTLV-1-infected people develop these serious diseases, while the majority remain healthy? and
- how does HTLV-1 persist lifelong in the individual, despite a strong immune response?

In the Imperial College laboratory we study the immunology and virology of HTLV-1 infection, using a wide range of molecular, cellular and mathematical techniques. We have longstanding and valuable collaborations with colleagues in the UK and overseas, especially in Japan.

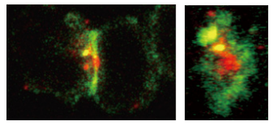
Continuing our collaboration with colleagues in Japan, we recently reported (Satou et al 2016: Proc. Nat. Acad. Sci. USA 113, 3054) that HTLV-1 alters the higher order structure of host chromatin. This highly unexpected observation raises new hypotheses about the pathogenesis of the leukaemia associated with HTLV-1 infection. In addition, we found (Kirk et al 2016: Nature Microbiology, doi: 10.1038/NMICROBIOL.2016.212) that HTLV-1 and other exogenous retroviruses integrate into a shared, non-palindromic DNA sequence motif, unlike what has been believed for the last 25 years.

Discovery of the virological synapse (VS): triggered, directional transfer of HTLV-1 from cell to cell

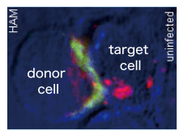
Gag protein complexes (red) polarize to the cell-cell contact area



- which contains organized adhesion domains (green)

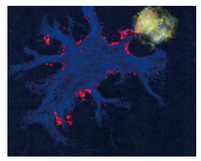


Gag is then transferred with the HTLV-1 genome to the target cell

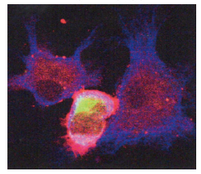


Igakura et al 2003: Science **299**, 1713-6

30 minutes



120 minutes



Dendritic cells (blue) can also be efficiently infected by contact with an HTLV-1-infected cell (green)

Lab. of Molecular and Cellular Biology

In our Lab., three indpendent groups are working on the following projects:

In Hosokawa G, we are fucusing on the quality control mechanism of proteins and on the molecules such as chaperones and lectins that are involved in this system. Protein misfolding occures in cells that are exposed to various stresses, or that have mutations in the protein-encoding genes. We are also analyzing on the protein degradation mechanis named ERAD (endoplasmic reticulum-associated degradation), and on the intracellular transport of proteins.

In Hirayoshi G, we are analysing on the transition stage from the formation of pre-initiation complex to elongation using RNA aptamer.

In Fujimoto G, we are investigating on the illegitimate V(D)J recombination within T cell receptor β chain gene during normal T cell development in relation to tumorigenicity.

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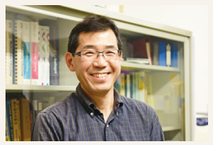

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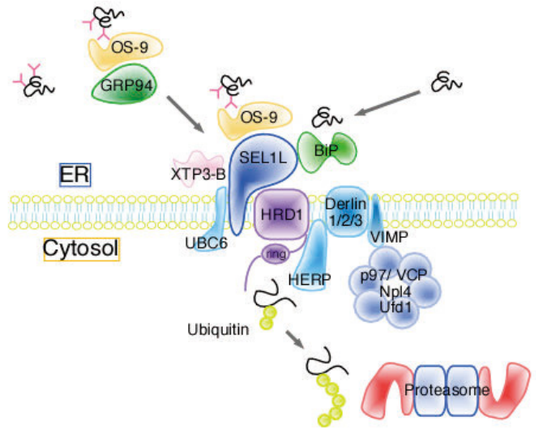
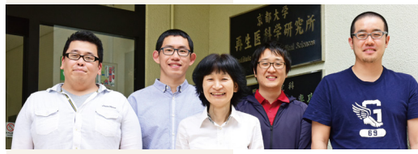
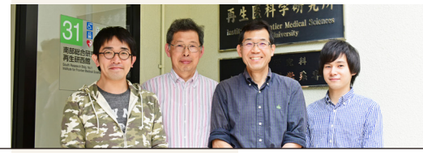
Ubiquitin ligase complex in the ER



Ubiquitin-ligase complex in the endoplasmic reticulum (ER) membrane
Proteins that have misfold in the ER are degraded by the cytoplamic proteasome, a mechanism named ERAD. The ubiquitin-ligase complex in the ER membrane regulates ERAD. Chaperone proteins and lectins associate with this complex from the lumenal side.





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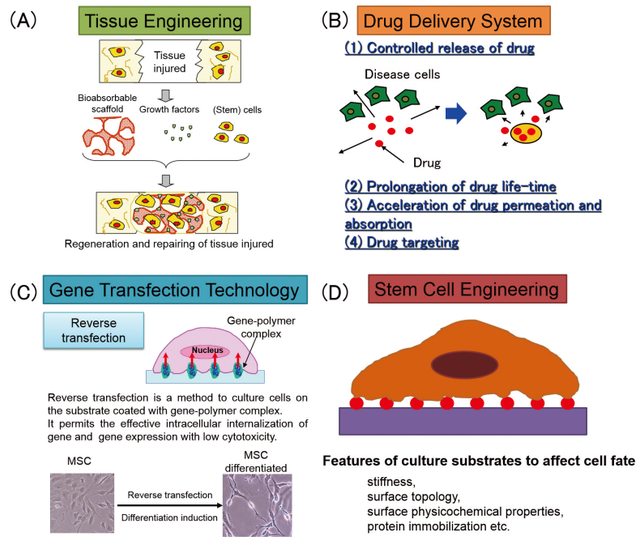
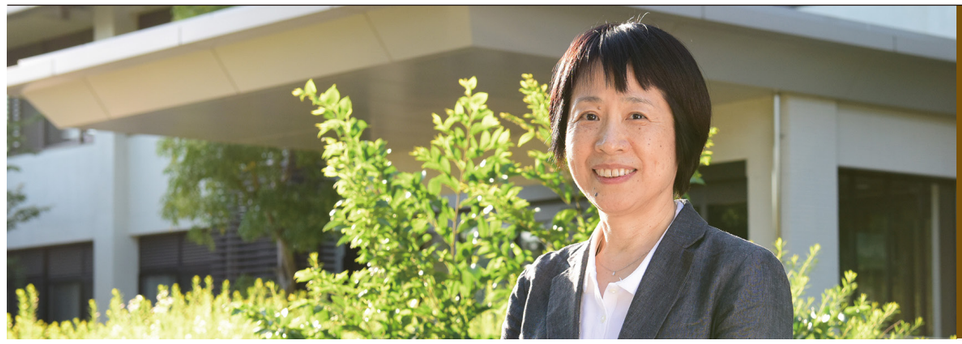
Lab. of Biomaterials

The main objective of our department is to proceed the research and development of methods, procedures, and technologies applicable to basic research of biology and medicine, and medicines (therapy, diagnosis, and prophylaxis) from the viewpoint of material sciences. The biomedical materials (biomaterials) to use in the body and to contact biological substances are being designed and created from biodegradable and non-biodegradable materials. Our goal is not only to carry out researches of tissue regenerative therapy (tissue engineering, cell transplantation, cell research, and drug discovery), drug delivery system (DDS), biomedical engineering, and stem cell technology, but also put the research results to clinical and practical uses.



Technologies developed in this laboratory. (A)Tissue engineering is the research and development of biomaterial technologies to realize the regenerative therapy by making use of cell-based natural healing potential. Biomaterials can enhance the cell-based potential to achieve the regeneration and repairing of tissues. (B)Drug delivery system is technologies and methodologies to maximize the action of drugs (substances with a certain biological activity and function) by the combination with biomaterials. Drugs include therapeutic, diagnostic, and preventing drugs or cosmetics. (C)Reverse transfection enables genes to safely internalize into weak cells of mesenchymal stem cells (MSC) and achieve the prolonged gene expression. (D)Behavior of stem cells is modified by the stiffness, surface topology, and physicochemical properties of materials (hydrophilicity and charge etc.) and the extent of protein immobilized to materials. The objective of stem cells engineering is to create materials which mimic the cell environment in the body for cell research and drug discovery.

Lab URL *http://www.frontier.kyoto-u.ac.jp/te02/index_en.html*



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Lab. of Tissue Stem Cell Biology

We are interested in molecular and cellular mechanisms of organ development and regeneration, especially from an aspect of cell-cell interactions required for cellular growth and differentiation. Our research is mainly focusing on (1) molecular mechanisms of skeletal myogenesis and muscle regeneration, (2) regulatory roles of ADAM (A Disintegrin And Metalloprotease) family proteins in cell-cell interactions and the ectodomain shedding, and (3) skeletal muscle atrophy.

There are many questions to be solved.

(i) How are MuSCs established during development and growth after birth?

(ii) What activates MuSCs and make them to differentiate to muscle fibers?

(iii) What makes MuSCs cell cycle arrested?

Screening of miRNAs of which expression increased in MuSCs during juvenile to adult phase transition enabled us to identify miRNAs that convert juvenile proliferating MuSCs into those in quiescent states through targeting cell cycle genes. Quiescence-induced juvenile MuSCs with those miRNAs exhibited biochemical properties of quiescent adult MuSCs, and efficiently transplanted into regenerating muscles of Dystrophin-deficient mice, suggesting roles of those miRNAs in the maintenance of quiescence and stemness of MuSCs and their potential utility in stem cell therapies of muscle diseases (Sato T., et al., Nature Commun., 2014).

On the other hand, skeletal muscle regeneration requires inflammatory reactions prior to regenerative myogenesis, by which injured muscle fibers are eliminated to make new myotubes. We are currently investigating roles of inflammatory cells in muscle regeneration more precisely. We have also succeeded (Nishimura D., Mechan. Dev., 2015) in visualization of ectodomain shedding of Neuregulin I, a transmembrane growth factor involved in myelination of neurons and neuron-dependent development of skeletal muscle (Kamezaki A., et al., Sci. Rep., 2016).

We are also interested in the skeletal muscle atrophy caused by aging or cachexia and by the stay in the Space. We launched our zebrafish into the Space in order to clarify whether the Space environment causes muscle atrophy also in fish (Fig.2). If you are interested in this research, please visit http://iss.jaxa.jp/kiboexp/theme/second/zebrafishmuscle/.

Fig.1 Muscle stem cells regenerate injured muscle

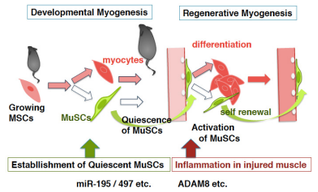

Figure 1 Adult skeletal muscle stem cells (MuSCs), the major cellular source for skeletal muscle regeneration, are kept cell cycle arrested in muscle tissues except when they break the quiescence upon myofiber injury or under pathogenic condition such as Duchenne Muscular Dystrophy.

Figure 2 JAXA Project "Zebrafish Muscle"

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Project for the development
of fundamental technology
for organ regeneration

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The major aim of our laboratory is to elucidate the molecular mechanisms that regulate cell fate decisions in the process of lineage restriction from multipotent hematopoietic stem cells to unipotent progenitors. Among various events occurring during hematopoiesis, we are mainly focusing on the process towards the production of T cells. We have recently clarified the mechanisms for the maintenance of T cell lineage (Figure 1).

As another project, we have been developing an approach aiming to apply our culture method in clinical settings. Whereas cytotoxic T lymphocytes (CTLs) represent the most promising therapeutic avenue in cancer immunotherapy, adaptive transfer of antigen-specific CTLs has faced difficulty in efficient expansion of CTLs from patients in ex vivo culture. To solve this issue, we have proposed a strategy to use iPSC technology for cloning and expansion of tumor antigen specific CTLs; iPSCs produced from T cells (T-iPSCs) should inherit rearranged TCR genes, and thus all regenerated T cells from T-iPSCs should express the same TCR. Based on this idea, we have succeeded in regenerating MART1-specific CTLs from a melanoma patient (Vizcardo et al, Cell Stem Cell, 2013). Recently we have developed a culture method by which CTLs expressing CD8 αβ heterodimer with high antigen specific cytotoxic activity can be generated (Figure 2). This new method provides a convincing rationale for application of this strategy in clinical settings.

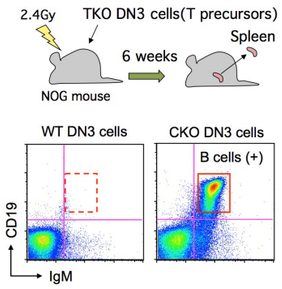

Figure1
Conversion of T cells to B cells by inactivation of polycomb-mediated epigenetic suppression
In T cell-specific Ring1A/B deficient mice, T cell development was severely blocked at an immature stage. We found that these developmentally arrested T cell precursors gave rise to functional B cells upon transfer to immunodeficient mice (Ikawa et al, Genes & Development, 2016).

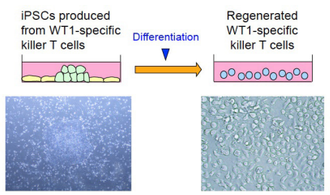

Figure2
Regeneration of antigen specific T cells using the iPSC technology
iPS cells were firstly produced from WT1-spcific CTLs, and then CTLs were regenerated from these iPSCs. Our novel culture system has made it possible to regenerated high quality CTLs with antigen specific cytotoxicity comparable to original CTLs (Maeda et al, Cancer Research, 2016). Applying this method to regenerate WT1 tumor antigen-specific CTLs, we showed that they prolonged survival of mice bearing WT1-expressing leukemic cells.

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Lab. of Tissue Regeneration

The objectives of our department are to disclose the pathology of disorders in mesenchymal tissues at the molecular level and to develop new therapeutic modalities by understanding physiological growth and differentiation of mesenchymal cells. Following projects are currently undertaken.

1. Research on the regeneration of mesenchymal tissues.
We have analyzed on the growth and differentiation property of mesenchymal stem cells (MSC) that exist among bone marrow stromal cells and performed a clinical trial of cell therapy for the condition know as osteonecrosis.

2. Research on the transformation of mesenchymal cells
Sarcomas are malignant tumors derived from mesenchymal tissues. We have analyzed the genomic and epigenomic mechanisms of the development of sarcomas using MSC and pluripotent stem cells (PSC).

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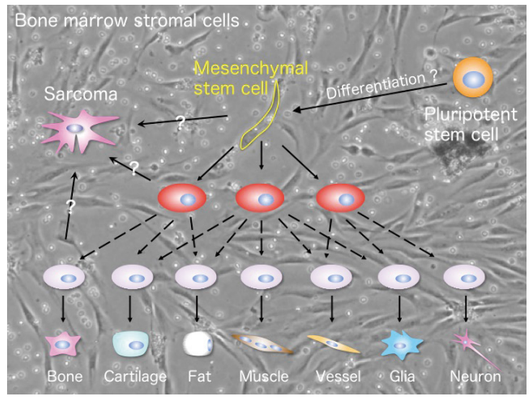
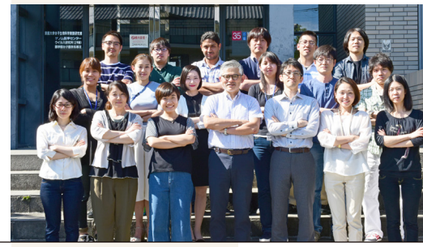
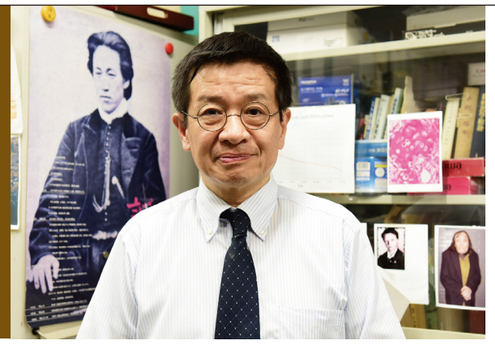


Our laboratory is investigating the mechanis of differentiation and proliferation of mesenchymal stem cells to achieve regeneration of mesenchymal tisseus, and also the mechanism of sarcoma development from mesenchymal tisseus.



Lab URL *http://www.infront.kyoto-u.ac.jp/research/lab15/?lang=en*



Lab. of Organ and Tissue Reconstruction

The target organs currently being considered for this development project are the heart, heart valves, esophagus, stomach, intestine, gallbladder, trachea, lung, liver, kidney, peripheral nerves, spinal cord, cornea, tendons, ligaments, cartilage, bone, fatty tissue, periodontal tissue, and permanent teeth. We plan to employ the two majour methods as described below.

ECM Method

To obtain the purified extracellular matrix, cell components

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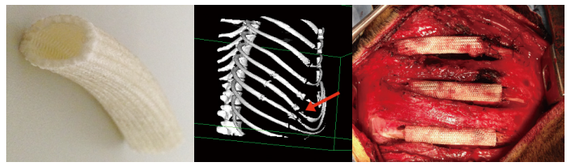

Costal coaptation pins made of poly-L-lactide (PLA) are often utilized for the fixation of surgically divided ribs, for instance, in case of closure of posterolateral thoracotomy. However, its clinical results regarding rib fixation have not been so satisfactory. The objective of this study is to develop a new rib coaptation socket system.
PLA fiber woven rib sockets were developed for costal fixation and studied, using canine rib fracture models. Mechanical analysis of the sockets, and radiological and histological examination of costal fixation were planned to be performed to evaluate the effectiveness of the newly developed socket system for rib stabilization.
In our experimental study, completing 1 month follow-up after socket implantation, PLA-fiber woven rib coaptation socket system was shown to be durable enough for stabilization of divided ribs with biocompatibility. This finding is quite promising for this system to be applied for divided rib stabilization in a clinical setting.

Our major mission is to develop regenerative medicine for endocrin (primarily diabetes) and metabolic (liver etc.) diseases. In addtion, we are studying devices for 3D cell culture, methods of high content analyses, tissue (primarily islets) preservation, cell fusion for cancer therapy and so on. In the studies of regenerative medicine, our macro-encapsulation device that protects cell/tissue against immune attack and allows full retrieval without cell leakage awaits wide application for various diseases.

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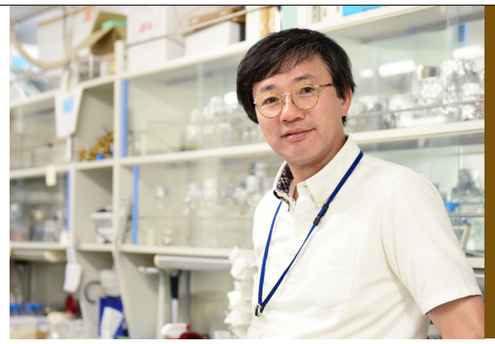
Lab. of Developmental Epigenome

Regenerative medicine and aging are closely linked subjects. Stem cell functions in repair and replacement of old tissues with young tissues. Induced pluripotent stem (iPS) cell generated through transformation of somatic cell by forced expression of reprogramming factors is expected to contribute to regenerative medicine. Anti-aging factors, which function in maintaining to keep body young, could be related to stem cell. Reprogramming and anti-aging sharing rejuvenation as a goal are regulated by the molecular mechanism of epigenome.



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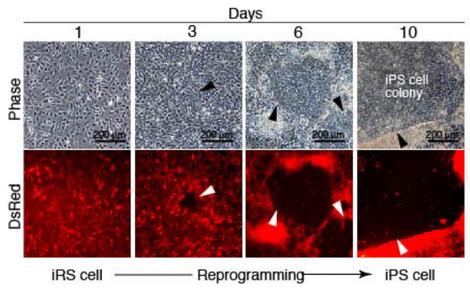

Reprogramming of iRS (intermediately reprogrammed stem) cell to iPS cell

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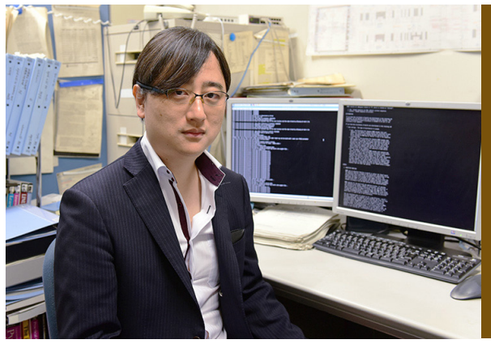
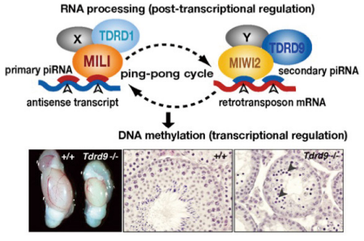
During development of multicellular organisms, genetic stability is differentially regulated depending on developmental stages, cellular lineages and physiological conditions etc. We are currently investigating (1) how pluripotent stem cells and germline cells maintain their genome and epigenome integrity, and (2) how the genome and epigenome stability is coordinated with developmental programs of the germline-stem cell cycle. We also aim to identify genes and pathways with which the genetic stability of stem cell resources can be improved.





Tdrd1 and Tdrd9 protect the germline genome and epigenome from retrotransposon activity through the piRNA pathway

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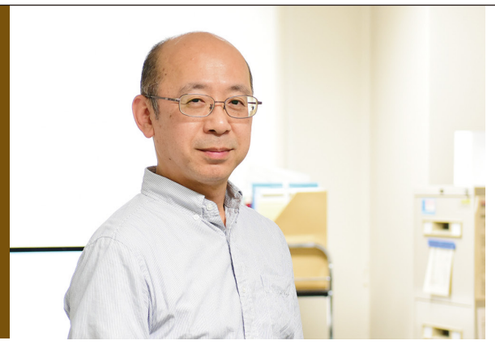

Lab. of Embryonic Stem Cell Research

Human ES cell lines are considered to have great potential in medical research and application such as cell transplantation therapy and drug discovery. We established human ES cell lines at a high efficiency and analyzed their characters in detail. We derived 5 ES cell lines, named KhES-1, KhES-2, KhES-3, KhES-4 and KhES-5, and distributed to over 50 research projects in Japan. We are also performing researches on molecular mechanisms of self-renewal and differentiation of human ES cells, and developing techniques for genetic manipulation of hES cells.

We have constructed a Cell Processing Facility (CPF) to develop core technologies to produce and supply clinical grade.

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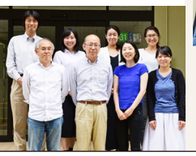


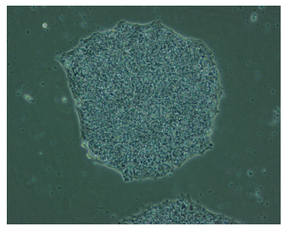


Figure 1 Human Embryonic Stem Cell

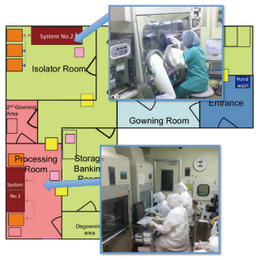


Figure 2 Clinical-grade hESC Processing Facility

Lab URL ***http://www.frontier.kyoto-u.ac.jp/es01/top.htm***

Topics

Lab. of Immunology

Our laboratory has been studying molecular mechanisms of T cell development. Based on such basic research, we are trying to apply our cell culture methods in cancer immuno-therapy. Adoptive T cell therapy is one of the most promissing strategies in cancer immunotherapy, but it is difficult to expand tumor antigen-specific T cells without exhaustion. To solve this problem, we are now developing a new method by which tumor antigen-specific T cells can be unlimitedly regenerated utilizing the iPS cell technology.

Researcher
Takuya Maeda

Industry-academia-government collboration promotioin section, Lab. of Embryonic Stem Cell Research

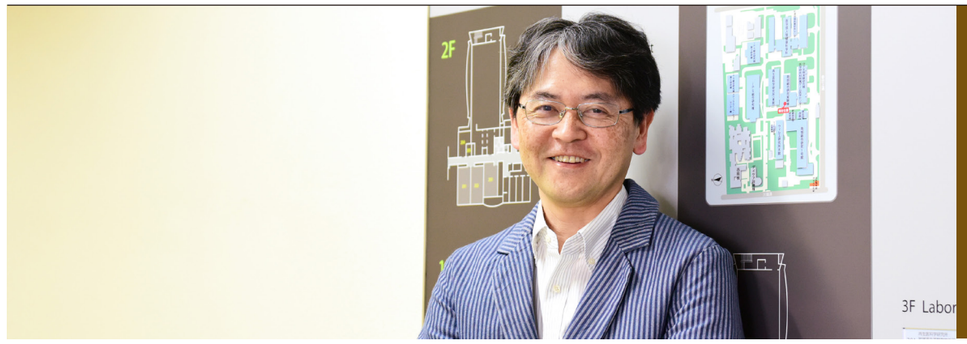
-My Mission of International Open Innovation
Think Globally, also Act Globally!-

My role is to support AMED project (Project Focused on Developing Key Evaluation Technology: Evaluation for Industrialization in the Field of Regenerative Medicine, Cardiomyocyte and Nerve,2014-2018) related matters which include negotiation with METI, AMED, and SCA and assistance for not only Subproject leader (Professor and founding Director Norio Nakatsuji, iCeMS Kyoto University) but also for participants of academia a nd industries to achieve the best goal of the Project.

METI: Ministry of Economy, Trade and Industry, AMED: Japan Agency for Medical Research and Development, SCA: Stem Cell Research Evaluation Technology Association.

Aim of Project & Participating Universities and Industries

Program-Specific
Prof. **Takashi Asada, PhD**



Lab. of Integrative Biological Science

Mammalian sperm undergo multiple maturation steps after leaving testis to be competent for fertilization. Serial important changes occur in the female reproductive tract on sperm, although the molecular mechanisms underlying these processes remain unclear. In our early study, we found that angiotensin-converting enzyme (ACE) releases GPI-anchored proteins (GPI-AP) from the cell membrane and plays a critical role in mammalian fertilization. We also found that sperm undergoing GPI-AP release associated with reorganization of lipid raft and acrosome reaction acquire fertilization potential. In terms of identifying factors triggering these processes in vivo, we found Lipocaline2 as a sperm maturation factor of female. Recently, we started new research projects elucidating character and function of new helper T cell, Th17 cell, to clarify the mechanism of inflammation.

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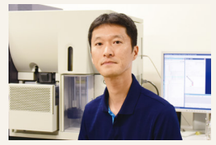

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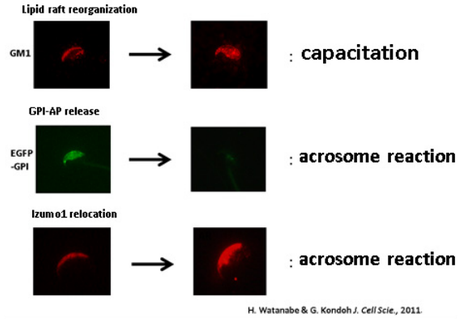

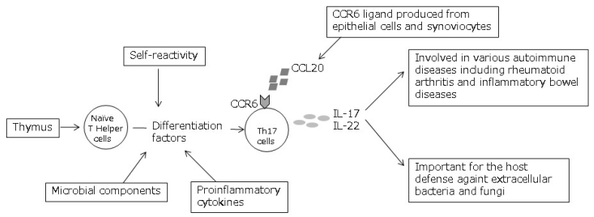

Lab URL ***http://an02-kaihen-anim.frontier.kyoto-u.ac.jp/contact.html***

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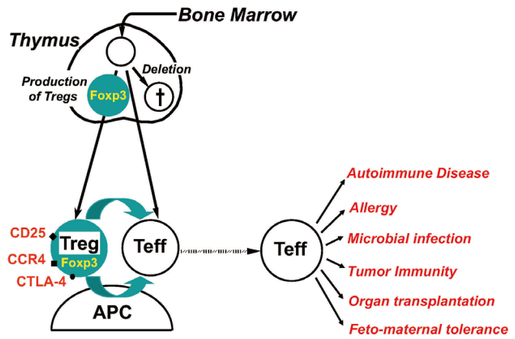
Lab.of Experimental Immunology (Visiting)

Our laboratory studies the mechanism of immunological tolerance. We discovered naturally occurring regulatory T (Treg) cells as a T-cell subpopulation that is specialized for immune suppression and engaged in the maintenance of immunological self-tolerance and homeostasis. We have been studying the molecular and cellular basis of Treg cells development and maintenance, in mice and humans by using immunological, epigenetic and bioinformatics approaches. Since Treg cells are involved in various physiological as well as pathological immune responses, we are developing various ways to manipulate Treg cells for clinical application, which is a novel immuno-therapy for autoimmune diseases, allergy, infection, organ transplantation and cancer.

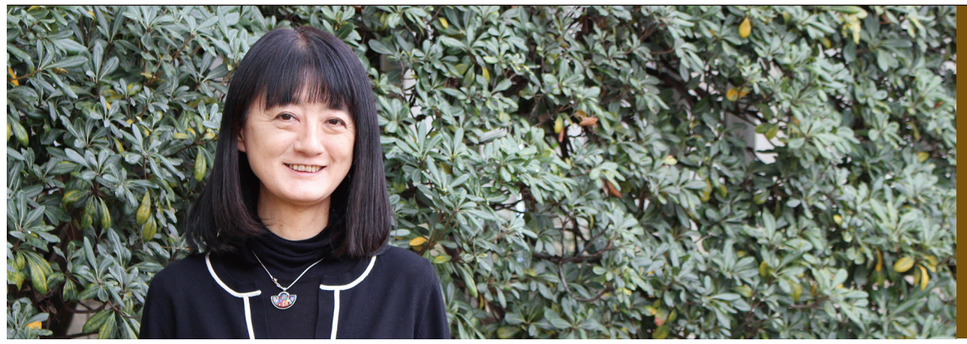
We are also studying the pathogenetic mechanism of rheumatoid arthritis by analyzing our newly developed model (SKG mouse). SKG mice have a mutation in ZAP70 gene, which plays a critical role in T cell recepter signaling. Because of this mutaion, SKG mice show altered thymic selection and allow a leakage of self-reactive T-cell from the thymus. We are investigating how such impaired signal transduction causes autoimmune diseases.

Control of immune responses by Foxp3⁺CD25⁺CD4⁺ Tregs



CD25⁺CD4⁺ regulatory T (Treg) cells are produced by the normal thymus as a functionally mature T-cell subpopulation. They specifically express the transcription factor FoxP3. Reduction of Treg cells or attenuation of their suppressive activity may enhance tumor immunity and microbial immunity. In contrast, increase of the number of Treg cells or augmentation of their suppressive activity can treat autoimmunity and induce transplantation tolerance.

Lab URL *http://exp.immunol.ifrec.osaka-u.ac.jp/*



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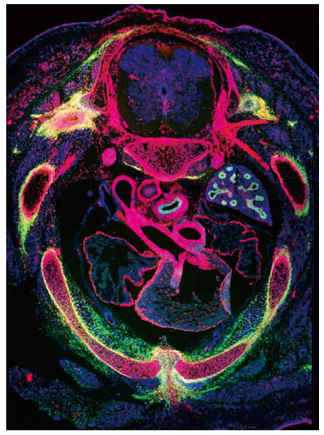
Lab.of Material Biophysics (Visiting)

We are aiming at the elucidation of the molecular and cellular mechanisms regulating the formation and regeneration of cartilage, bone, teeth, tendon, and ligament. Tendons connect muscles to the bone and function as the mechanical force transmitters, while ligaments bind bones together to stabilize joints. Each musculoskeletal primordium initially develops as an independent component, but tendons and ligaments subsequently integrate each component into a single functional locomotive unit. At the early stages of development, Scleraxis (Scx), a basic helix-loop-helix transcription factor, is induced and persistently expressed in the tendon/ligament primordia. Tenomodulin is then expressed in mature tendons and ligament at a high level. In the postnatal growth, hyaline cartilage in the chondrotendinous/chondroligamentous junction is gradually replaced by bone and fibrocartilage to generate the fibrocartilaginous enthesis in the osteotendinous/osteoligamentous junction. Through the lineage tracing studies using *Rosa-CAG-LSL-tdTomato* reporter mice crossed with *Cre-recombinase (Cre)* knock-in mice of SRY-box 9 (Sox9) or transgenic mice expressing Cre under the control of the promoter/enhancer of Scx, we found that Scx⁺/Sox9⁺ cells contribute to the establishment of the chondrotendinous/chondroligamentous junction. Currently, we also examine genetic disorders affecting cartilage, bone and teeth development in genetically modified mice generated by using genome editing tools such as CRISPR/Cas9 and TALEN.



Contribution of Sox9⁺ progenitors to axial tendon and ligament formation. A transverse section of a *Sox9$^{Cre/+}$;Rosa-CAG-LSL-tdTomato;ScxGFP* embryo at E14.5 is shown. Cells of the Sox9+ lineage were detected by tdTomato reporter expression (red) and Scx⁺ cells were detected with anti-GFP antibody (green). Scx⁺ cells of the Sox9⁺ lineage (yellow) are distributed in and around the junction between cartilage and tendon/ligament.

Lab URL *http://home.hiroshima-u.ac.jp/tnmd/e_html/e_index.html*

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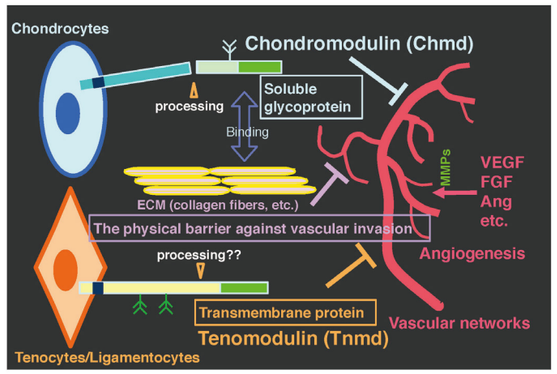
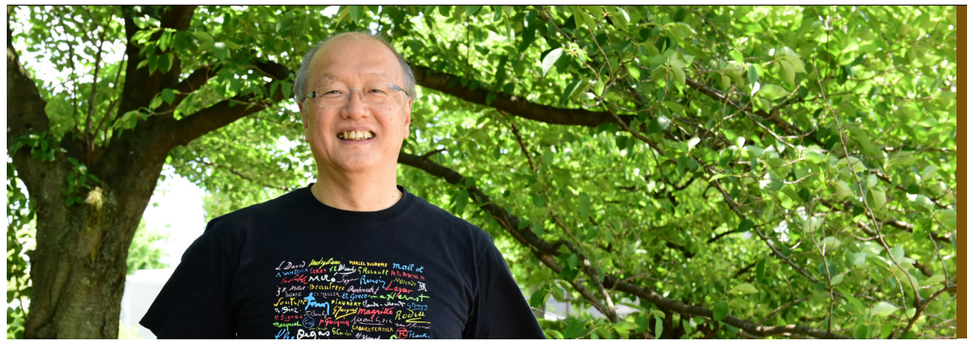
We are aiming at the elucidation of molecular interactions and signaling networks underlying bone and cartilage formation. Our current research efforts are focused on the following studies: (1) Regulatory mechanisms of endochondral bone formation initiated by vascular invasion into the cartilaginous bone precursor; (2) Action mechanisms of the cartilage-specific angiogenesis inhibitor Chondromodulin (Chmd) and the tendon/ligament-specific angiogenesis inhibitor Tenomodulin (Tnmd), and their therapeutic applications for angiogenic diseases; (3) Molecular mechanisms of tissue-specific transcription of chmd and tnmd genes; (4) Identification and functional analysis of Scx/Sox9 double-positive progenitors during establishment of junctional connections between cartilage and tendons/ligaments; (5) Molecular analysis of regenerative repair of articular cartilage and tendons/ligaments and its therapeutic application. In addition, we take approaches from material engineering in order to develop cell-based therapies: 1) semi-large scale production of islet-like cell aggregates from iPS cells; 2) Immunoprotection of transplanted islets; 3) Modification of cell surface with biomolecule-conjugated amphiphilic polymers; 4) Analysis of molecular events at the interface between artificial materials and biological systems.



Chondromodulin (Chmd) and Tenomodulin (Tnmd) as the tissue-specific components in the anti-angiogenic barriers within connective tissues
Among the mesenchymal tissues, most of which are rich in vascular networks, cartilage and tendon/ligament tissues are exceptional for their anti-angiogenic nature. We identified Chondromodulin (Chmd) and its related protein Tenomodulin (Tnmd) as angiogenesis inhibitors specific to these hypovascular tissues. These molecules are shown to participate in the ECM-associated anti-angiogenic barriers within connective tissues.



Lab. of Nano Bioprocess

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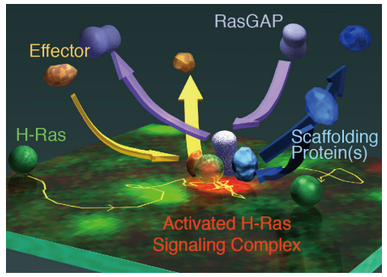
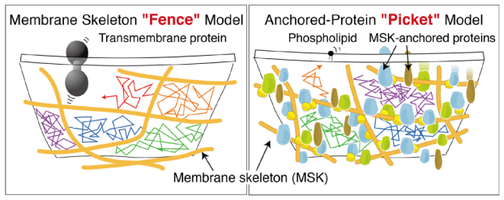
Our team is dedicated to methodology development for single-molecule observation and manipulation at nanometer precisions in living cells. The development is carried out simultaneously with the application for the studies of nano-bioprocesses occurring in living cells, in particular, signal transduction in the cell membrane and the formation and remodeling of the neuronal network. The smooth liaison between physics/engineering and biomedicine is a key for our methodology developments. On the basis of the knowledge of nano-bioprocesses learned in the cells (e.g., partitioning of the plasma membrane into submicron compartments and transient formation of signaling platforms in the cell membrane) and the single-molecule bionanotechnology developed here, we envisage the next-generation nanotechnology, regenerative medicine, and drug discovery protocols.





[Upper] In many signaling processes, we are finding cooperative formation of signaling complexes on the cytoplasmic surface of the plasma membrane (the upper surface in this figure). Interestingly, the lifetime of these complexes are short, often less than a second, which ensures turning off of the signaling based on thermal fluctuation. These results suggest that many signaling processes may work as a digital system.
[Lower] Paradigm shift of the structure of the cell membrane, based on our finding of the partitioning of the entire plasma membrane. Such partitioning is created by the membrane-skeleton (fence) and transmembrane proteins anchored to the skeleton (picket).

Lab URL ***http://www.nanobio.frontier.kyoto-u.ac.jp/***

Lab. of Biomechanics

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The Laboratory of Biomechanics aims at clarifying the self-organized regulation mechanism of a diversity of biological phenomena through an interdisciplinary approach, including mechanics, life science, and medical science. Our research topics cover developmental processes (cell differentiation, morphogenesis, and growth) and functional adaptation to environment by remodeling and regeneration of tissues and organs. The major focus of our research is to understand well-organized dynamics of living systems emerging from complex molecular and cellular interactions. Highlighting the roles of “adaptation to mechanical environment” and “hierarchy of structure and function” in the living organisms, we have dedicated to the integrated biomechanics and mechanobiology investigation based on mathematical modeling and simulation combined with experiments.

Figure 1 Biomechanics of bone functional adaptation

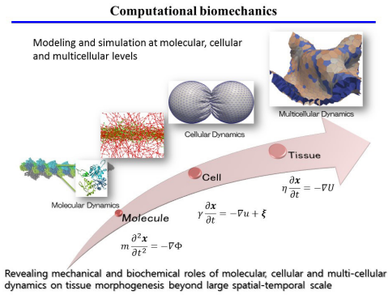
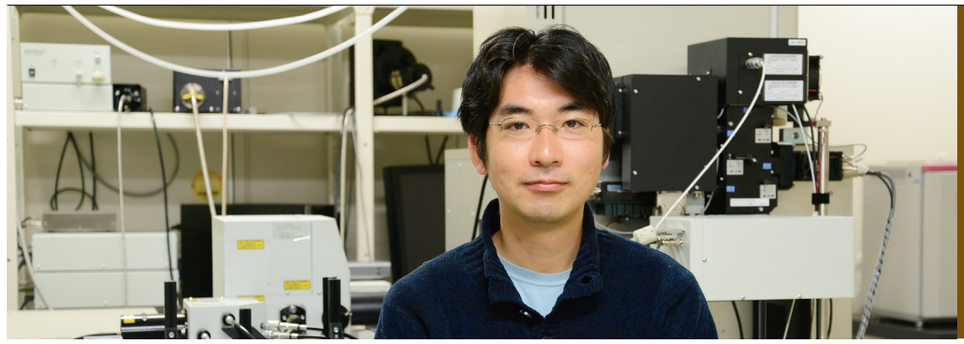


Figure 2 Multiscale computational biomechanics on tissue morphogenesis

Lab URL **http://www.frontier.kyoto-u.ac.jp/bf05/**



Lab. of Developmental Systems

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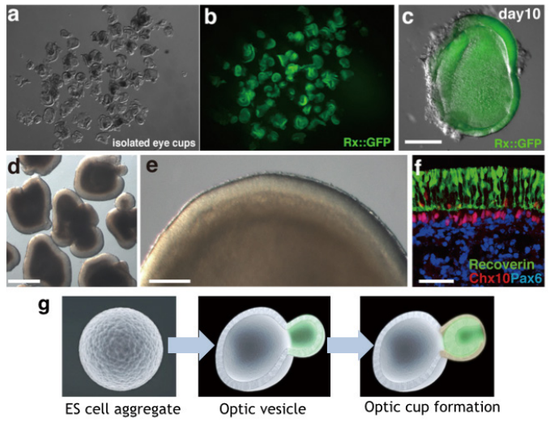
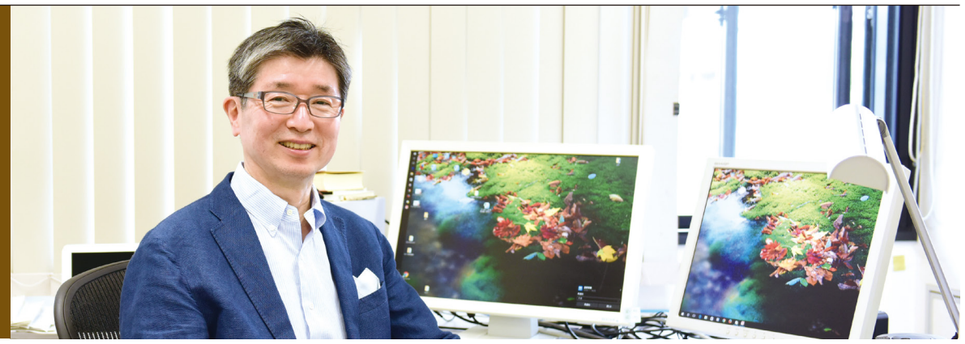
Organogenesis is a highly dynamic process in which multicellular behaviors are regulated by mechanisms in multiple scales from molecules and cells to tissues. In vitro generation of functional organ with complex structure is a major challenge of cell biology. Toward this goal, it is a reasonable strategy to recapitulate the ontogeny that is the most efficient and robust process for organogenesis acquired through evolution. Our laboratory aims to clarify molecular and cellular mechanisms underlying organogenesis, and to develop new technologies for in vitro recapitulation, that is, three-dimensional functional organ generation from stem cells. We have previously established efficient three-dimensional cultures for generation of mouse and human ES/iPS cell-derived brain and retinal tissue as well as other ectoderm-derived tissues. Based on our past achievements in 3D tissue formations from pluripotent stem cells, we have been attempting to extend our limit of understanding for self-organization phenomena in neural development and advance the culture technology for generation of more complex tissues from ES/iPS cells in a more robust manner. To do that, we mainly focus on following points.

1) Elucidation of self-organization phenomena in neural development and morphogenesis
2) Development of novel technologies for in vitro formation of functional organ
3) Molecular analysis of species-specific regulation for developmental timing and tissue size determination.



in vitro formation of optic cup and layered retina from ES cells
a-c, Isolated optic cup structure generated from mouse ES cells. d-f, ES cell-deirved optic cup differentiate into layered retinal structure. g, Scheme of in vitro optic cup formation in ES cell culture.

Lab URL **http://www.frontier.kyoto-u.ac.jp/bs01/**



Lab. of Systems Virology

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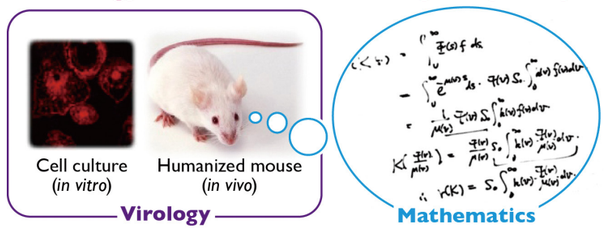
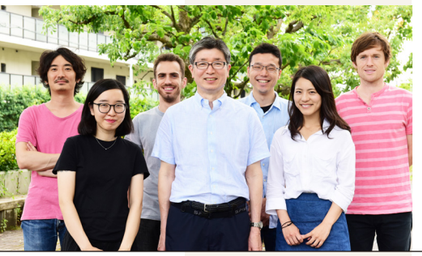
Virus infects cell and replicates. Viral genome transmits from infected cell to adjacent naive cells. This is a most significant characteristic of virus. The mechanism of this infection event is a primary theme of our laboratory. It has been found that various cellular factors positively and negatively associate with viral replication. However, we do not yet have the answer for how, which, and when cellular factors commit viral replication. The aim of our laboratory is to learn the mechanism how virus replicates in the cells. from the aspects of immunology and virology. The main subject of our research is HIV, which causes AIDS in human. The mechanism by which HIV infection results in AIDS remains unclear. We have been investigating how the immunodeficiency is triggered by HIV infection using in vitro (cell culture system) and in vivo (animal model) through the application of mathematics and bioinformatics. We developed a humanized mouse system in which the human immune system is reconstituted.

We address the mechanism of virus replication

Virology & Mathmatics interdisciplinary study



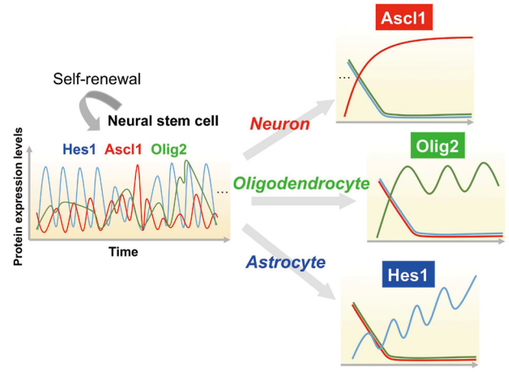
Virology and Mathmatics interdisciplinary study
Interdisciplinary research involves the combining of Virology from cell culture model and HIV-1-infection humanized mouse model generated by human hematopoietic stem cell-transplantation into NOG mice and Mathematical model application.

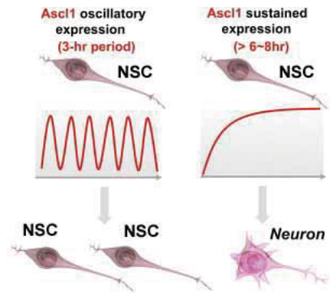


Lab URL *http://www.infront.kyoto-u.ac.jp/research/lab01/?lang=en*

Lab. of Growth Regulation System

Neural stem cells have multipotency to produce three cell types, neurons, oligodendrocytes, and astrocytes. Fate determination factors responsible for production of each cell type have been identified, but it was found that these factors also have an opposing function – enhancement of maintenance and proliferation of neural stem cells. By using a time-lapse imaging method, we found that the expression of three cell fate determination factors oscillates in neural stem cells, whereas one of them becomes dominant and exhibits sustained expression during cell fate determination (upper Fig.) Our optogenetic approach showed that oscillatory expression of the neuronal fate determination factor activates the proliferation of neural stem cells, whereas its sustained expression induces neuronal differentiation (lower Fig.) This optogenetic technology allows us to control neural stem cell proliferation and neuronal differentiation at will by simply changing the light illumination patterns. We now plan to apply this technology to neural regeneration.





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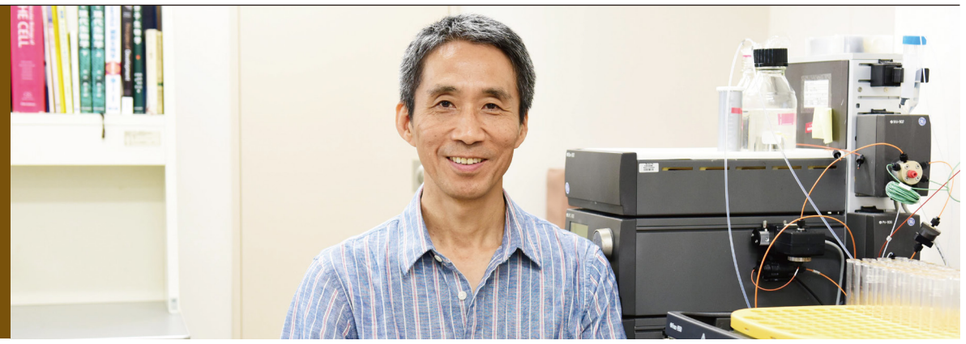

Lab. of RNA System

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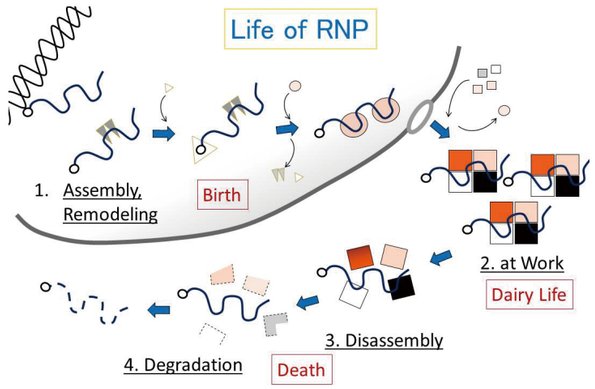
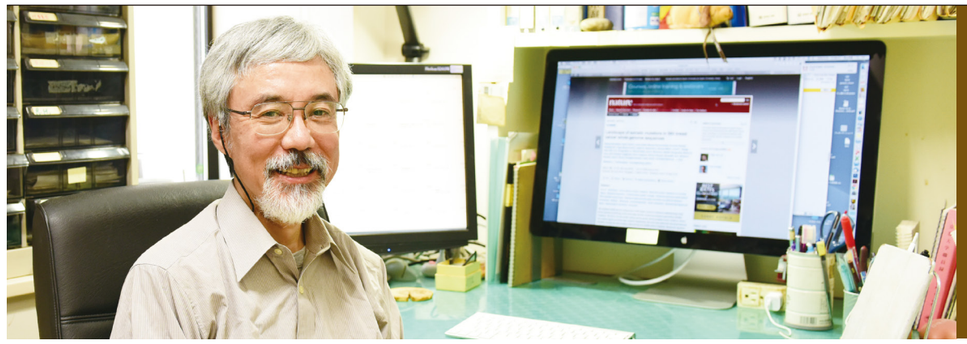
RNA in the cell is not naked but bound by various proteins. Specific RNA binding proteins gather onto the newly-made RNA and thus specific RNP (ribonucleoprotein) is born. RNA component usually undergoes maturation from its primary form through RNA processing. RNP frequently changes its protein composition. RNP is often transported to the place where it functions. If RNP becomes non-functional for various reasons, e.g. gene mutations, direct lesions, misassembly etc., it is disassembled and RNA component is degraded. Prof. Mutsuhito OHNO' s laboratory is studying various aspects (birth, dairy life and death) of such "Life of RNP". Major research subjects are (1) RNA processing and transport, (2) Regulation of RNA expression by HIV-1, (3) Quality control of the Ribosome, and (4) Sorting mechanisms between mRNAs and non-coding RNAs. This laboratory belongs to the Graduate School of Science, Kyoto University.



In the current world of life, the main genetic material is DNA, but the major functional molecules are both protein and RNA. Therefore, the current world of life can be called "RNP world". RNP, just like human, goes through a cycle of birth, life and death. Very important biological themes can be found in each step.

Lab URL *http://www.virus.kyoto-u.ac.jp/Lab/ohnolab.html*



Lab. of Biological Membrane System

The research projects carried out in this group are concerned with dynamic aspects of cell surface proteins in bacteria including *Escherichia coli* and *Vibrio alginolyticus*. Specifically, processes of protein folding, protein translocation across and integration into the membrane, membrane protein proteolysis and extracytoplasmic stress responses are studied by combined molecular genetic, biochemical biophysical and structural approaches. We are mainly focusing on the following two topics. (1) Function of protein translocation machinery: Protein export across the bacterial cytoplasmic membrane is promoted by cooperation of the evolutionary conserved SecYEG translocon associated with auxiliary facotrs (such as SecDF) and the SecA ATPase motor. We are investigating the structure and molecular function of these and related cellular factors. (2) Membrane protein degradation and extracytoplasmic stress response: Membrane proteins play central roles in the functions of biological membranes. We are investigating the functional mechanism and cellular roles of membrane proteases. We are also interested in the cellular system to sense and cope with abnormality of cell surface proteins.

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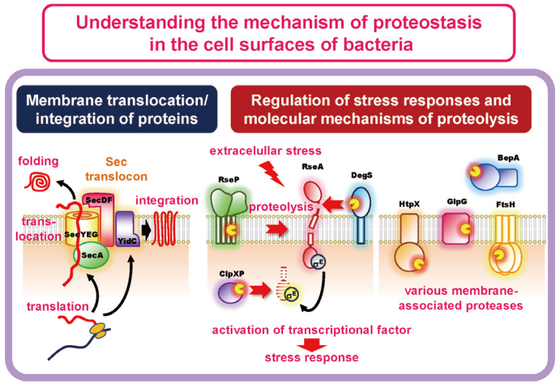
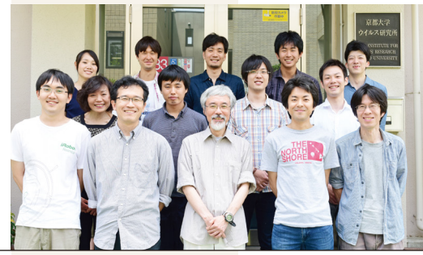


The research prejects carried out in the laboratory of Biological membrane system.



Lab URL *http://www.virus.kyoto-u.ac.jp/Lab/akiyama/index.html*

inFront

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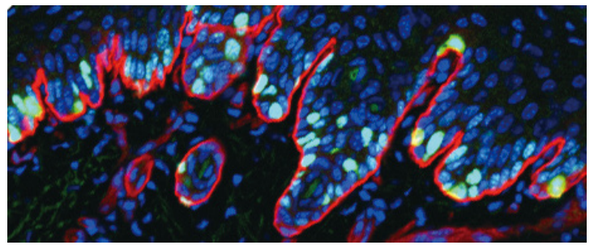
Lab. of Tissue Homeostasis

Stem cells in adult tissues exist in a quiescent state. When they are needed in tissue homeostasis or repair, they exit a quiescent state and undergo symmetric/asymmetric cell division to give rise to differentiation-committed progenitor cells. Our group seeks to explore the molecular mechanisms underlying oriented stem cell division, stem cell activation, and cell fate determination. We also want to know how stem cells adopt to physiological changes in the body. Current Projects; 1) Epidermal stem cell proliferation and differentiation in skin homeostasis. 2) Cell fate determination of lymphoid cells via symmetric/asymmetric cell division. 3) Tissue stem cell activation during pregnancy.



The palm skin tissue of an adult mouse. Red: basal lamina, Blue: Nucleus, Green: Proliferation marker.

Lab URL *http://www.virus.kyoto-u.ac.jp/Lab/Toyoshima-HP/toyoshima.html*

inFront

Lab URL *http://www.fas.lif.kyoto-u.ac.jp/Home_e.htm*

Lab. of Tumor Biogenesis

Apoptosis, or programmed cell death, plays an important role in many biological processes. Our main research project is to understand the molecular mechanisms and physiological roles of caspase-dependent and caspase-independent cell death.

1) Caspase-8 plays an essential role in Fas-mediated apoptosis. We are analyzing other kinds of biological activities of caspase-8, such as inhibition of programmed necrosis and regulation of retinoic acid (RA)-induced cell differentiation.

2) We are analyzing molecular mechanisms and physiological roles of the novel type of cell death induced by induced knockdown of essential genes for cell growth.

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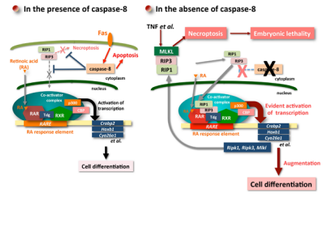
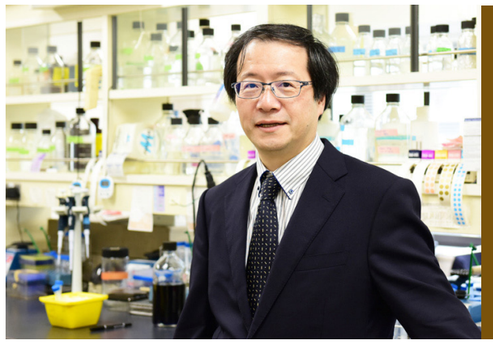


Caspase-8 regulates not only apoptosis and necroptosis but also cell differentiation induced by retionic acid (RA)

Thioredoxin interacting protein (Txnip/ TBP-2/ VDUP1) is a multifunctional regulator, especially in cancer suppression and metabolism. Txnip expression is downregulated in various tumor tissues and mutation of Txnip is seen in 7% of bladder cancer patients. Therefore, Txnip is a good candidate of anti-cancer drug development. We are investigating the molecular mechanisms of Txnip for developing anti-cancer and metabolic control therapy. We also study redox signaling and protection against oxidative stress, focusing on thioredoxin.



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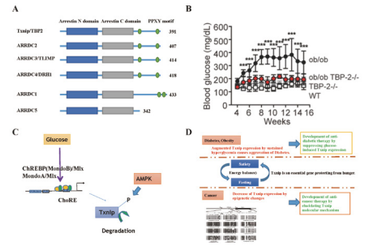
Lab URL *http://www.virus.kyoto-u.ac.jp/Lab/MasutaniHP/en/index.html*

Development of anti-cancer and metabolic control therapy by the study of Txnip
A. Txnip belongs to the alpha-arrestin family.
B. Disruption of Txnip in mice improves hyperglycemia by ameliorating insulin secretion, insulin resistance and pancreatic beta cell apoptosis.
C. Txnip expression is induced by glucose through transcriptional activation and suppression of AMPK-induced protein degradation.
D. Txnip is a critical gene for the protection from fasting, since the knockout mice are lethal in fasting. Txnip expression is down-regulated in cancer cells by epigenetic changes. We are taking specified approaches for metabolic control by suppressing glucose-induced Txnip induction and for cancer target therapy by elucidating cancer suppression mechanism of Txnip.



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Hiroshi Masutani
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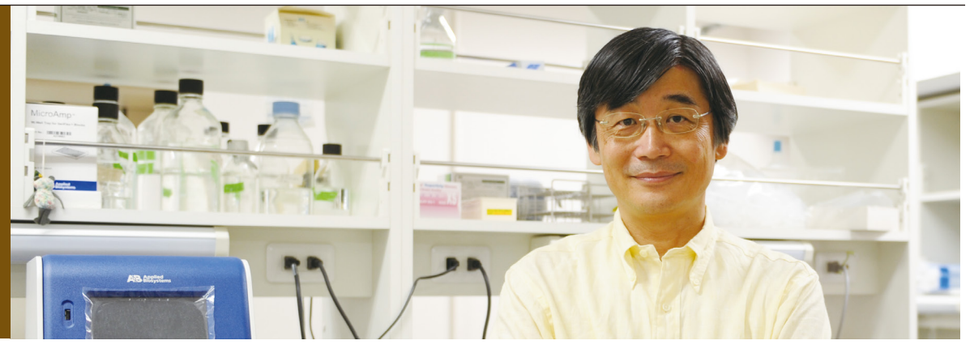

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Prof. Masao Matsuoka
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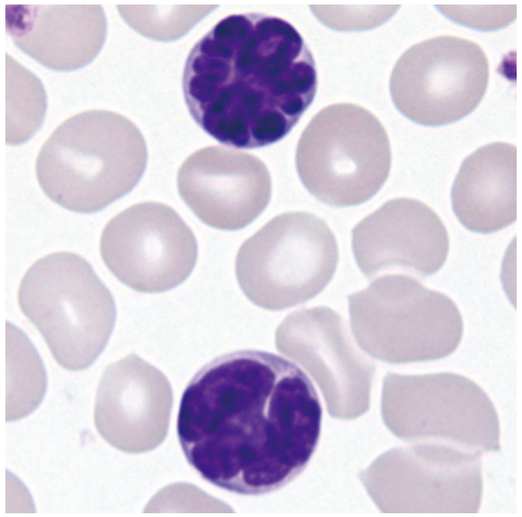
Lab. of Regulatory Information (Visiting)

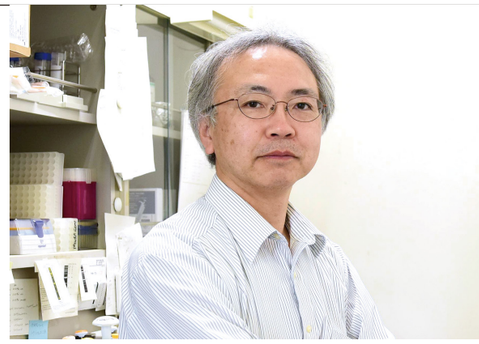
A human retrovirus, human T-cell leukemia virus type 1 (HTLV-1), is an etiological agent of adult T-cell leukemia (ATL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). There are 10 million HTLV-1 carriers throughout the world, and about 0.8 million in Japan. Kyushu area is an endemic area of HTLV-1, while a recent epidemiological survey showed that the number of HTLV-1 carriers in urban area was increased in the last 20 years. Therefore, HTLV-1 is still an important issue in this country. We are studying the molecular pathogenesis of HTLV-1 using clinical samples from the patients with ATL or HAM/TSP, and asymptomatic carriers.



ATL cells have a hyper lobulated nucleus, and are called "flower cells".

Lab. of Primate Model

Since the nonhuman primate is the closest experimental animal to human, it is expected to establish the most useful model for human infectious disease in many aspects. Some pathogenic viruses (HIV-1, for example) can only infect primates. We have a large scale facility for infection experiments using nonhuman primates at P3 level. We establish infection and disease development models using macaque monkeys, and carry out the basic research for clarifying the *in vivo* pathogenesis and developing prevention and cure of infectious diseases.



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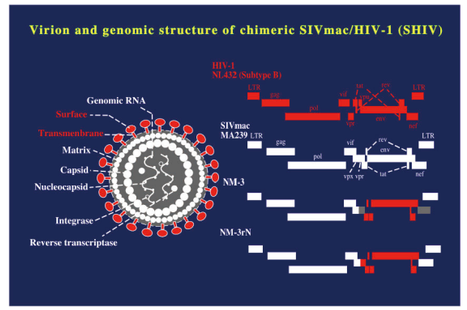

Virion and genomic structure of chimeric SIVmac/HIV-1 (SHIV).

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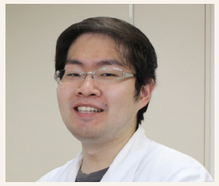
Lab URL ***http://www.virus.kyoto-u.ac.jp/Lab/primatemodelHP/index.html***

Topics

Lab. of Infection and Prevention

Our research focuses on the post-transcriptional regulation of innate immune system. Regnase-1 and Roquin are RNA binding proteins essential for degradation of inflammation-related mRNAs and maintenance of immune homeostasis. Recently, we have found that although Regnase-1 and Roquin regulate an overlapping set of mRNAs via a common stem-loop structure, they function in spatiotemporally distinct mechanisms. Our findings reveal that differential regulation of mRNAs by Regnase-1 and Roquin enables elaborate control of inflammation.



Assist. Prof.
Takashi Mino

Lab. of Systems Virology

Because human immunodeficiency virus (HIV) causes AIDS only in humans, it has been technically difficult to recapitulate the pathogenesis of HIV infection using animal models. To elucidate HIV pathogenesis, we have established a novel animal model called "humanized mouse", which possesses human immune cells de novo. By using this unique animal model, we investigate the dynamics of HIV infection in vivo.
Though the recent development of experimental techniques, now we are able to obtain various sorts of "bigdata" from biological experiments.
In order to address the "real" dynamics of virus infection, we conduct collaboration studies between experimental virology and a variety of scientific fields such as evolutionary biology, molecular phylogenetic, mathematics and omics, and call our approach "Systems virology".

Sr.Lect
Kei Sato

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Lab. of Infectious Disease Model

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Our laboratory is focusing on intractable viruses such as human immunodeficiency virus, hepatitis C virus and human T-cell leukemia virus. These viruses share common similarities; disease development after long-term persistent infection, presence of unique mechanism for the immune evasion, and narrow and selective host range. Especially, the last one leads us to be incapable of employing small laboratory animals as immunocompetent models for viral infection. In this point of view, we have challenged these issues and established novel non-human primate models for the intractable viruses. With the use of the model animals, we would like to unravel the molecular and immunological mechanisms by which the viral persistency and disease onset are induced, and further challenge applied research regarding the development of vaccines and new therapeutics.

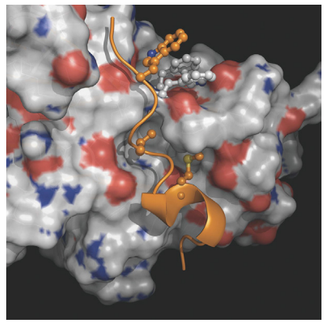


Figure 1 Interaction between HIV-1 Nef N-terminus and mu-1 subunit of adaptor protein-1

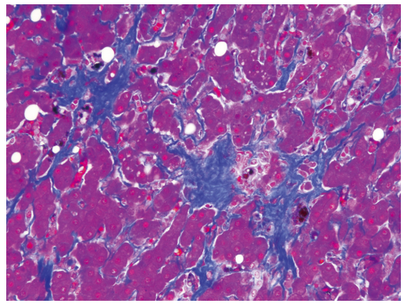
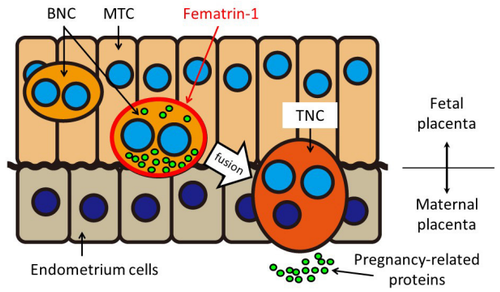


Figure 2 histopathological analysis of liver fibrosis in a tamarin persistently infected with GBV-B (Masson's trichrome staining)

Lab URL *https://akari-labo.jimdo.com/*

Lab. of Virus-Host Coevolution

Endogenous retroviruses (ERVs) occupy about 10% of mammalian genomes. New exogenous retroviruses arise from ERVs by recombination and induce diseases in the new hosts. On the other hand, cetrain ERVs are known to be involved in placental morphogenesis and reprogramming of somatic cells. In this laboratory, we aim to reveal the mechanisms of the emergence of new viral diseases and the process of coevolution between mammals and viruses.



Fematrin-1, a bovine endogenous retrovirus K1-derived protein, is involved in the formation of trinucleate cells (TNC) appreared in bovine placenta. BNC: binucleate cells; MTC: mononucleate trophoblast cells.

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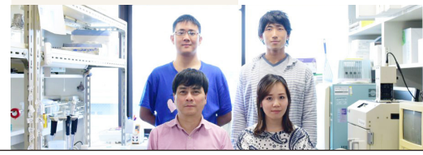
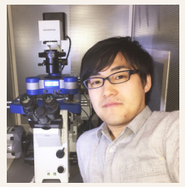


Lab URL *http://paleovirology.jimdo.com/*

Topics

Lab. of Biomechanics

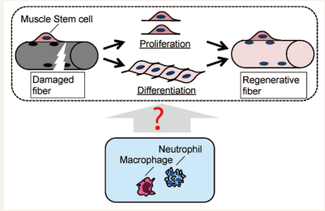
Cells in a multicellular tissue maintain the functional tissue architecture by sensing mechanical environment and generating a force feedback. In my research, I have focused on a mechano-sensor protein at cell-cell junction, i.e., α-catenin, to understand its mechanical behaviors at single-molecular level by atomic force microscopy (AFM)-based nanobiomechanical approach.



Ph.D student
Koichiro Maki

Lab. of Tissue Stem Cell Biology

Muscle tissue is highly regenerative, and injured muscle can be recovered as before. This is derived from the ability of the muscle stem cells. Under normal condition, stem cells are in a quiescent state. When muscle suffers injury, satellite cells are activated, proliferate, differentiate, and form regenerative muscle fibers. Then what signals induce such activation? The immune cells, such as neutrophils or macrophages, respond to tissue damage. I will elucidate contributions of immune cells to the induction of stem cell activation.



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Center for Animal Experiments

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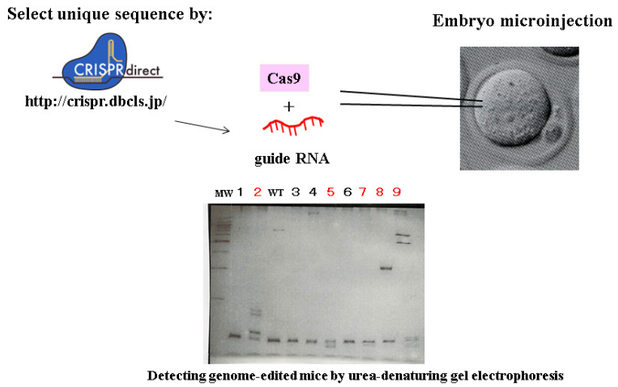
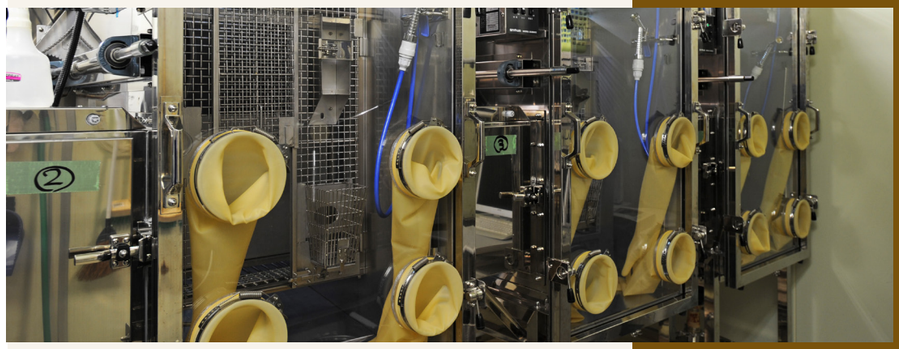
Experimental animals, such as mouse, rat and others, are housed in our Center under strict regulation of animal experimental committee and institutional guidelines for animal welfare. Moreover, we have been considered for long time: how to make gene-manipulated mice more rapidly and conveniently. Recently, genome engineering methods have been established using TALEN or CRISPR-Cas9 systems. We have searched for many methods and finally developed our own protocol making such mice more easily and reproducibly.



Detecting genome-edited mice by urea-denaturing gel electrophoresis

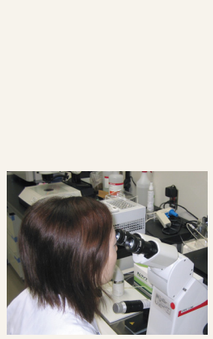
Our strategy for developing genome-edited mice using CRISPR-Cas9 system.

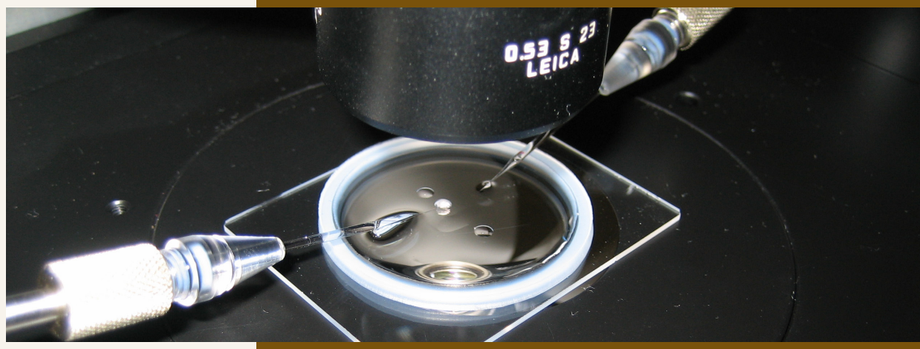
Lab URL *http://www.frontier.kyoto-u.ac.jp/an/newpage1.html*



Non-human Primate Experimental Facility

The center runs BSL-3 NHP facilities and has been accommodating various researches from all over Japan as a Joint Usage/Research Center for fusion of advanced technologies and innovative approaches to viral infections and life science. Facility veterinarians and other staffs support researchers by doing daily animal care and use and facility management. By March 2012, a new BSL-2 facility is constructed and one of BSL-3 facility is renovated. The center is expected to grow in use and popularity.

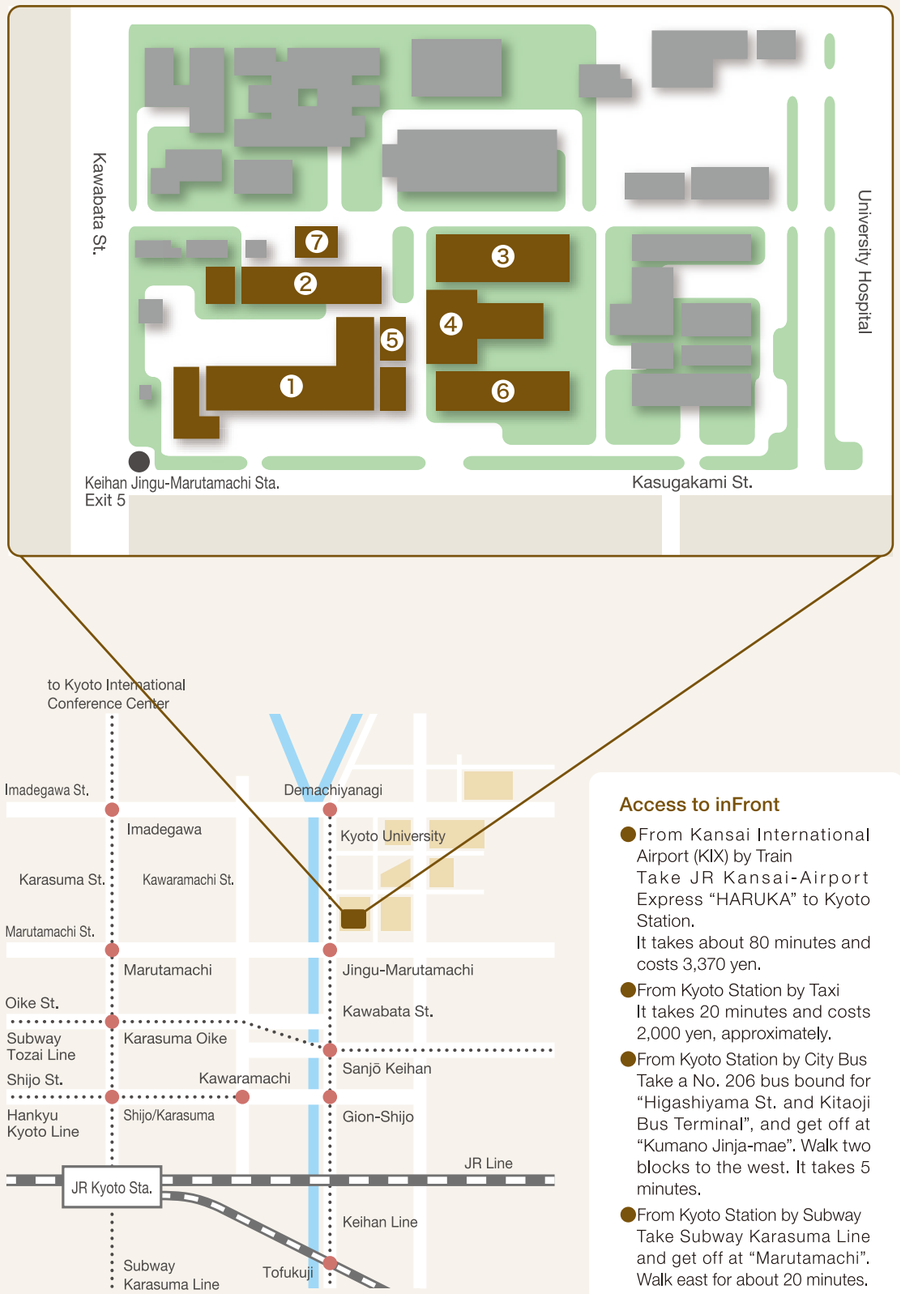




Reproductive Engineering Team

Reproductive engineering team is a support unit for generating transgenic mouse (Tg) and knockout mouse (KO). We also perform cryopreservation of mouse-fertilized eggs.

Map & Access



Access to inFront

- From Kansai International Airport (KIX) by Train
  Take JR Kansai-Airport Express “HARUKA” to Kyoto Station.
  It takes about 80 minutes and costs 3,370 yen.
- From Kyoto Station by Taxi
  It takes 20 minutes and costs 2,000 yen, approximately.
- From Kyoto Station by City Bus
  Take a No. 206 bus bound for “Higashiyama St. and Kitaoji Bus Terminal”, and get off at “Kumano Jinja-mae”. Walk two blocks to the west. It takes 5 minutes.
- From Kyoto Station by Subway
  Take Subway Karasuma Line and get off at “Marutamachi”. Walk east for about 20 minutes.

❶ South Research Bldg. No.1 Institute for Frontier Life and Medical Sciences Bldg. No.1

- Lab. of Tumor Viruses
- Lab. of Molecular and Cellular Biology
- Lab. of Tissue Stem Cell Biology
- Lab. of Immunology
- Lab. of Developmental Epigenome
- Lab. of Embryonic Stem Cell Research
- Lab. of Integrative Biological Science
- Lab. of Experimental Immunology
- Lab. of Developmental Systems
- Administration Office

❷ Institute for Frontier Life and Medical Sciences Bldg. No.2

- Lab. of Molecular Genetics
- Lab. of Virus Control
- Lab. of Tumor Viruses
- Lab. of Cell Regulation
- Lab. of Immune Regulation
- Lab. of Infection and Prevention
- Lab. of Growth Regulation System
- Lab. of RNA System
- Lab. of Biological Membrane System
- Lab. of Tissue Homeostasis
- Lab. of Tumor Biogenesis
- Lab. of Virus-Host Coevolution

❸ Institute for Frontier Life and Medical Sciences Bldg. No.3

- Lab. of Biomaterials
- Lab. of Tissue Regeneration
- Lab. of Organ and Tissue Reconstruction
- Lab. of Cellular Differentiation
- Lab. of Nano Bioprocess
- Lab. of Biomechanics

❹ Institute for Frontier Life and Medical Sciences Bldg. No.4

- Lab. of Immune Regulation
- Center for Animal Experiments

❺ Institute for Frontier Life and Medical Sciences Bldg. No.5

- Lab. of Developmental Epigenome
- Lab. of Embryonic Stem Cell Research
- Lab. of Integrative Biological Science
- Lab. of Cellular Differentiation
- Lab. of Developmental Systems

❻ Molecular Biology Research Bldg.

- Lab. of RNA Viruses
- Lab. of Ultrastructural Virology
- Lab. of Systems Virology
- Lab. of Primate Model
- Reproductive Engineering Team
- Non-human Primate Experimental Facility

❼ Institute for Frontier Life and Medical Sciences North Research Bldg.

- Lab. of Molecular Genetics
- Lab. of Growth Regulation System
- Lab. of Infectious Disease Model