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Institute for Frontier Life and Medical Sciences, Kyoto University

2020-2021

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Institute for Frontier Life and Medical Sciences, Kyoto University
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A Message from the Director

This institute is based on the Institute for Frontier Medical Sciences, which was renamed in 1998 after passing through the Chest Disease Research Institute from the Tuberculosis Research Institute established in 1941 and the Institute for Virus Research established in 1956. Institute for Frontier Medical Science generated the establishment of human embryonic stem cells (ES cells), discovery of induced pluripotent stem cells (iPS cells), discovery of regulatory T cells (2019 Honorary Professor Shimon Sakaguchi, the Order of Culture from the Emperor of Japan) and bases in regenerative medicine, contributing to the establishment of an innovative foundation. Its clinical application is imminent. On the other hand, the Institute for Virus Research led the dawn of molecular biology in Japan and produced many molecular biologists, and also discovered the causative virus (HTLV) of adult T-cell leukemia (ATL) in viral infectious diseases. (2009 Honorary Professor Yurio Hinuma, the Order of Culture from the Emperor of Japan). The virus research has been succeeded by RNA virus research such as AIDS virus, Borna virus (CNS virus), and Influenza virus. Research on the new coronavirus, which had an outbreak in 2019, was started, and the importance of virus research was again recognized. In addition to these researches, it is a research center for medical and life sciences with an expert in Immunology, Embryology, Stem cell science, Protein science, Mathematical science, and Genomic medicine.

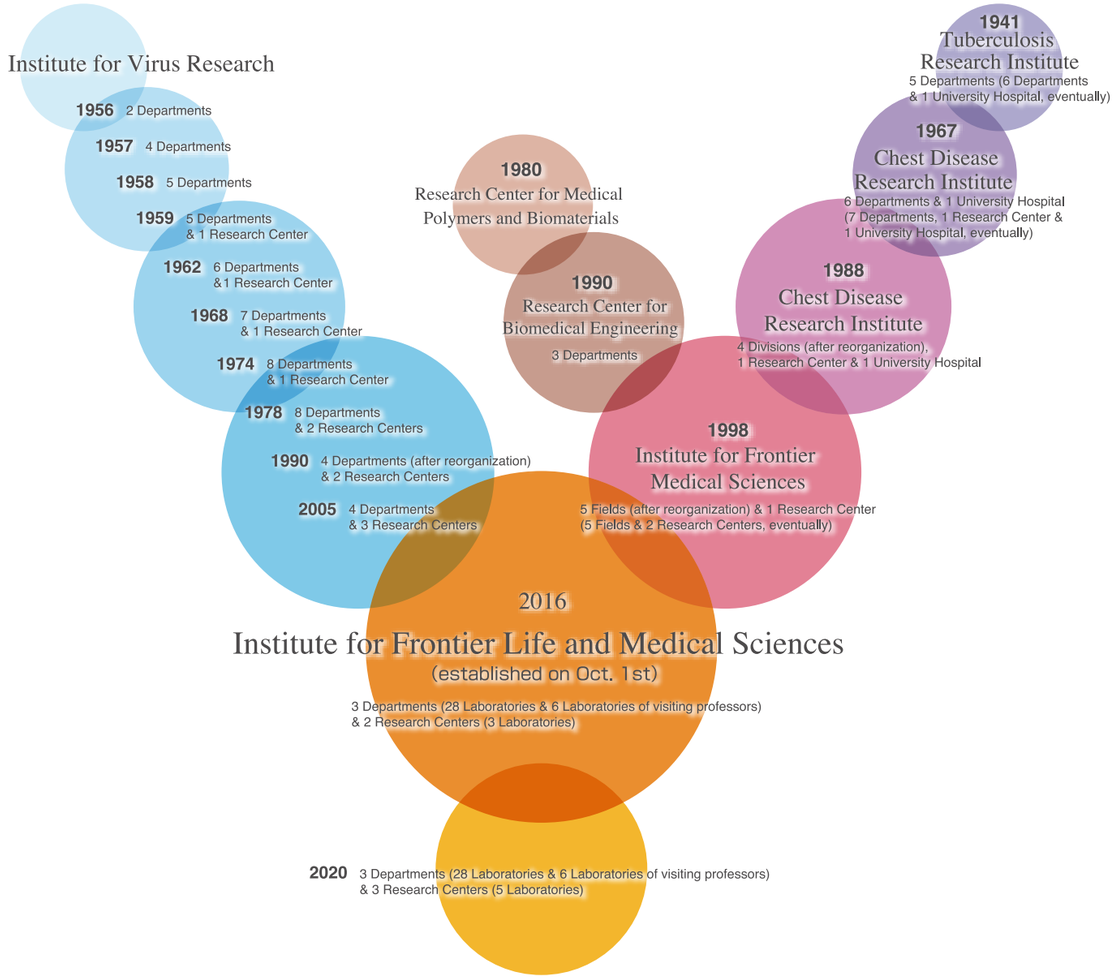
Our institute has been appointed as Joint Usage/Research Center for Transdisciplinary Collaboration on Tissue Engineering and Regenerative Medicine and as Joint Usage/Research Center for Fusion of Advanced Technologies and Innovative Approaches to Viral Infections and Life Science. In addition, we have many achievements to further develop the basic functions and to flourish as a biomedical research hub.

In the modern world, rapid globalization has progressed, and scientific research fields have progressed day by day, making it both fascinating and attentive. We at the University Research Institute play the role of fostering human resources who will carry out scientific research and the promotion of the acquisition of human intelligence. We are striving every day to fulfill our mission as a research organization that conducts medical and life science research that contributes to humanity, not limited to regenerative medicine and virology. We would appreciate your support.

May, 2020

Yoshio Koyanagi MD., Ph.D.
Director of Institute for Frontier Life and Medical Sciences

History



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

Data

Faculty and Staff (As of May 1st, 2020)

Professor	18 (4)	Program-Specific Assoc.Prof.	3
Assoc.Prof.	15 (1)	Program-Specific Senior Lecturer	1
Senior Lecturer	3	Program-Specific Assist. Prof.	7
Assist.Prof.	28	SUBTOTAL	11
SUBTOTAL	**64** (5)	**TOTAL**	**75** (5)

*Numbers in parenthesis indicate visiting professors

Program-Specific Researcher	12	Re-employed staff	1
Technical Staff	9	Researcher (Part-Time)	34
Administrative Staff	4	Other	72
TOTAL	**132**		

Graduate Students (As of May 1st, 2020)

Graduate School of Medicine	19	Graduate School of Human and Environmental Studies	2
Graduate School of Science	9	Graduate School of Biostudies	59
Graduate School of Engineering	29	Graduate School of Pharmaceutical Sciences	9
TOTAL	**127**		

Research Fellows and Research Students (As of May 1st, 2020)

Special research student	1	JSPS*	2
Research student	4	Contracted Researcher	8
Research Fellow	1	Private Sector Researcher	11
TOTAL	**27**		

*The Japan Society for the Promotion of Science

Financial data in academic year 2019 [Unit: JPY]

International exchange (As of May 1st, 2020)

Academic exchange memoranda	**[China]** China Medical University China Rehabilitation Research Center **[Taiwan]** College of Oral Medicine, Taipei Medical University **[Germany]** Bonn Institutes of Immunosciences and Infection, Medical Faculty, University of Bonn

Joint Usage / Research Center Initiatives

The following two joint usage/research centers have been designated by the Ministry of Education, Culture, Sports, Science and Technology within our institute, offering our resources and research techniques to research communities in Japan and overseas through joint research initiatives.

Joint Usage/Research Center for Fusion of Advanced Technologies and Innovative Approaches to Viral Infections and Life Science

P3 level infection experiments using mice and monkeys are indispensable to understanding human infectious diseases and developing new therapeutic strategies for applications in clinical settings. These experiments require animal-raising facilities as well as supervision, support and education by academic and technical staff with sufficient expertise. The institute is equipped with a large-scale facility for P3 infection experiments involving mice and monkeys. As well as virus research at the gene and cellular levels using state-of-the-art research techniques, we use this facility to conduct in vivo infection experiments. Our accumulated research techniques are distributed widely to research communities through joint usage/research.
Major research outcomes in FY2019 included elucidation of the mechanisms of transcription and replication of Ebola and influenza viruses, identification of host factors involved in HIV replication, development of novel RNA virus vectors and IL-7Rα signal balance associated with T-cell development and homeostasis. These joint research efforts were published in high-impact international scientific journals.

Number of approved joint research projects (FY2020)

1. Viral Infection Experiments on Non-human Primates at BSL-3 Facility	4
2. Viral Infection Experiments on Mice at BSL-3 Facility	2
3. Gene and Cell-level Virus and Biological Science Research	18
Total	**24**

Joint Usage/Research Center for Transdisciplinary Collaboration on Tissue Engineering and Regenerative Medicine

Based on our expertise and technology in regenerative medicine, we promote a wide range of cutting-edge joint research projects and assist the education and training of researchers actively engaged in regenerative medicine.
Our main research includes fundamental research to understand biological mechanisms, regulations and materials and develop related technologies and applied research to develop treatments and create regenerative tissues or organs for clinical applications.
In FY2019, we conducted 19 projects including two international joint research projects and actively collaborated with researchers including many junior scientists and postgraduate students. We also promoted joint usage of our animal laboratories, with the total number of users reaching 2,310. We actively organize lectures for the general public and high school students, supply various research resources including human ES cells, and promote joint usage of our animal laboratories.

Number of approved joint research projects (FY2020)

1. Interdisciplinary research	7
2. Exploratory research	13
Total	**20**

organization

※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)

Department of Virus Research

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.

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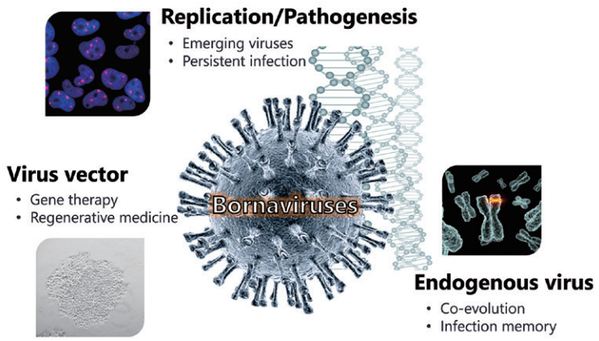
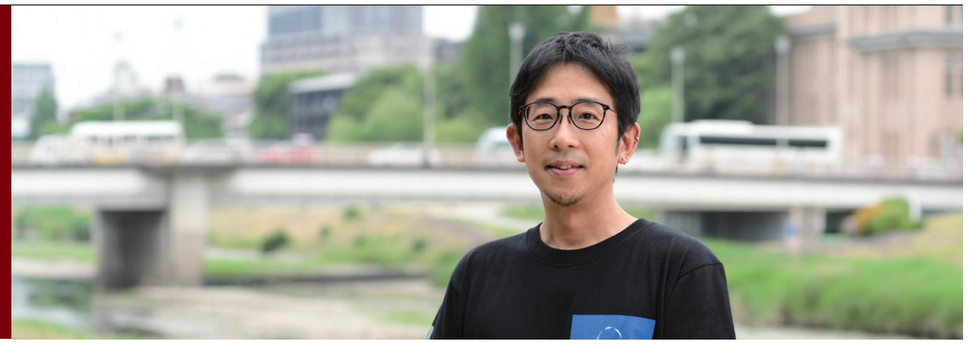


In Laboratory of RNA viruses, we are working on several projects regarding replication/ pathogenesis of bornaviruses, endogenous bornavirus and development of novel RNA virus vectors using bornavirus.

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



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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.

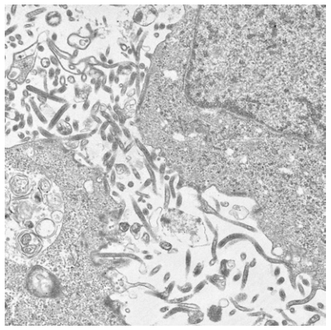


Figure 1 Transmission electron microscopic image of filamentous Ebola virus particles budding from infected cells.

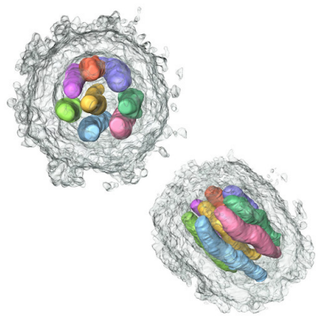
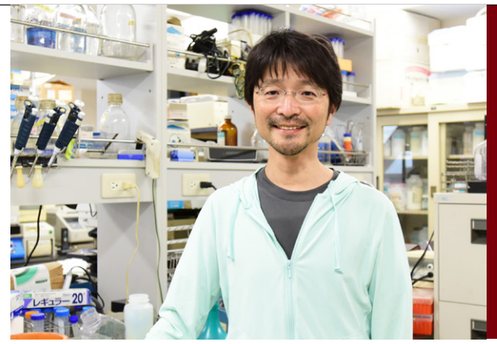


Figure 2 Three dimensional model of an influenza virus particle reconstructed by electron tomography. Eight RNPs arranged in a characteristic "1+7" pattern are present within the virion.

Lab URL *https://www.facebook.com/NodaLab/*

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.



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Lab URL *https://www.infront.kyoto-u.ac.jp/ex_ivr/Lab/sakai2012/Home2.html*

Horn-shaped warts induced by Shope papillomavirus infection

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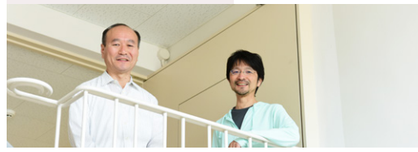

The main purpose our research group is to clarify the molecular mechanisms of carcinogenesis caused by the infection of human hepatitis viruses. Molecular and cellular biological analyses of the viral lifecycle and the cellular events related with viral infection have been investigated. We have found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

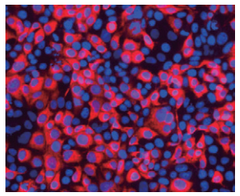

Figure 1 Cultured liver cancer cells infected with HCV. HCV infected cells are indicated by immunofluorescence using anti-HCV proteins antibody (red).

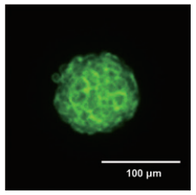

Figure 2 Immortalized human hepatocytes producing the HBV receptor molecule cultured in three-dimensional condition. The HBV receptor molecule is visualized with fused green fluorescent protein.

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Lab URL *https://www2.infront.kyoto-u.ac.jp/HCV/*

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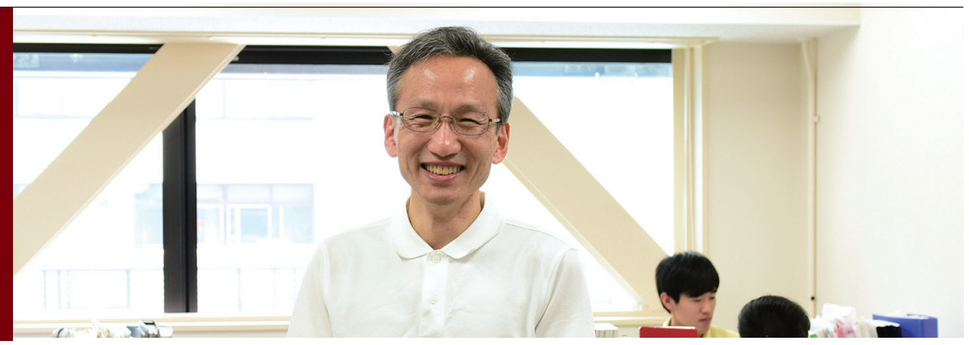

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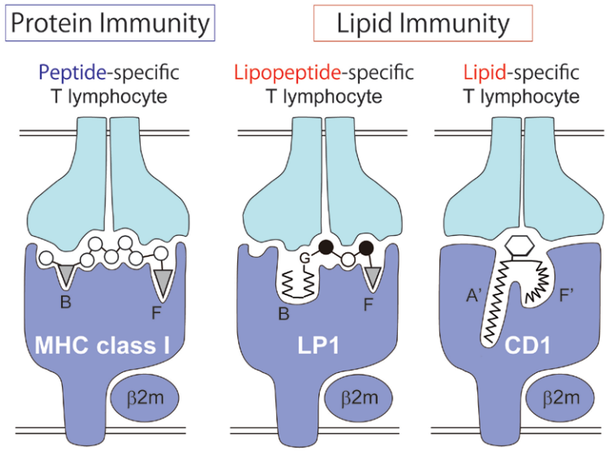
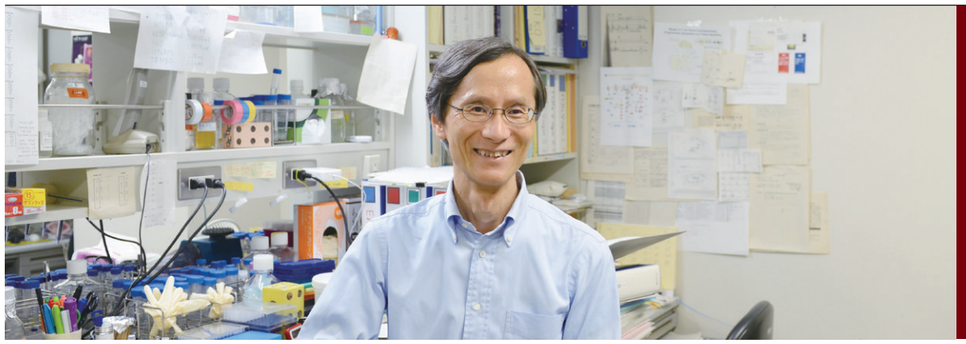
Lab. of Cell Regulation

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.



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 *https://www.infront.kyoto-u.ac.jp/ex_ivr/Lab/SugitaLab.html*



Lab. of Immune Regulation

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. Cytokines are a group of proteins important for controlling the immune system. Interleukin-7 (IL-7), one of the cytokines, plays important roles in differentiation, maintenance and response of lymphocytes and innate lymphoid cells, and is essential for organogenesis of lymphoid organs. We are pursuing research on development and response of the immune system, focusing on IL-7. We are now carrying out the following projects: (1) function of IL-7 receptor in differentiation, maturation and response of immune cells; (2) regulation of IL-7 receptor expression during lymphocyte development and immune response; (3) circadian control of dynamics and function of lymphoid cells by steroid hormones and sex difference in the immune system; and (4) visualization and local function of cytokine-producing cells, in relation with tumor immunity.

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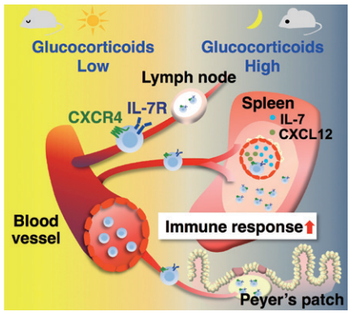


Figure 1 Immunoenhancing effects of glucocorticoids
Glucocorticoids drive diurnal oscillations in T cell distribution and responses by inducing IL-7R and CXCR4.

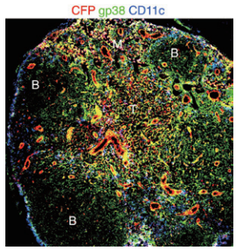
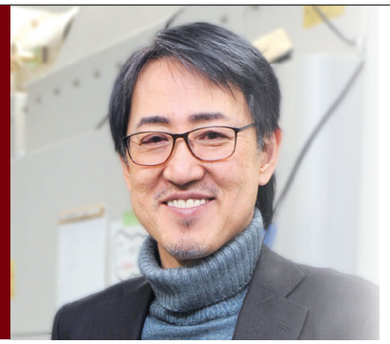


Figure 2 IL-15-expressing cells in lymph nodes
Immunohistochemistry of lymph nodes from IL-15-CFP knock-in mice. IL-15/CFP (red), fibroblastic reticular cells (green), dendritic cells (blue). IL-15 production is detected in stromal cells and blood vascular endothelial cells. B, B cell-rich follicles; T, T-cell zone; and M, medulla.

Lab URL *https://www2.infront.kyoto-u.ac.jp/Ikuta-Lab/*



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 addition, pandemic viruses appear about every ten years. In 2009, pandemic (H1N1) 2009 influenza arose and spread quickly around the world. Meanwhile, highly pathogenic H5N1 avian influenza viruses continue to circulate, and avian H7N9 and H9N2 viruses have infected humans. Therefore, we need to monitor these viruses. We study the mechanisms responsible for the high pathogenicity and transmissibility of influenza viruses, focusing on viral and host factors. To better understand pathogenesis and to improve the efficacy assessment of anti-viral drugs, we study influenza virus infection in a macaque model in the BSL-3 non-human primate facility at this institute. In addition, we are working on the development of new vaccines that are more effective than the current inactivated influenza vaccines., Lastly, we have developed a live imaging technique using two-photon microscopy.

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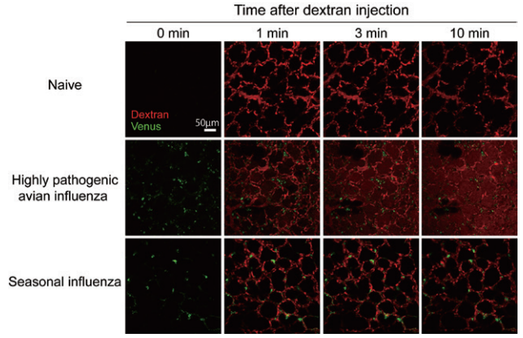


Figure 1 Pulmonary permeability in influenza virus-infected lungs of mice. Time-lapse imaging using 2-photon microscopy. Fluorescent dextran (red) was injected intravenous into the mice during image acquisition. In lungs infected with highly pathogenic avian influenza virus, we could observe that fluorescent dextran gradually leaked from blood vessels into the alveolar cavity. Green indicates virus-infected cells.

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)

Hepatitis viruses constitute a serious public health problem affecting more than 300 million people worldwide, which function as exogenous ligands inducing an inbalance of physiological condition to restricted hosts. We study these viruses to establish an experimental model evaluating infection and its cellular responses, to analyze spatio-temporal virus dynamics and its principle for survival during interaction with environment, and to develop a strategy for controlling these virus infections. We are also developing antiviral strategy against the novel coronavirus. Especially, our chemical genetics approach using chemical probes that manipulate virus infection enables to progress basic virology in concert with drug development.

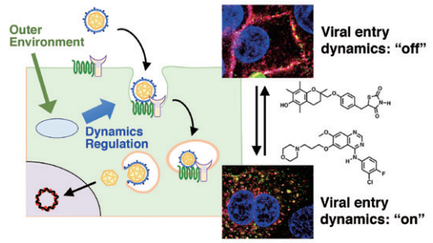
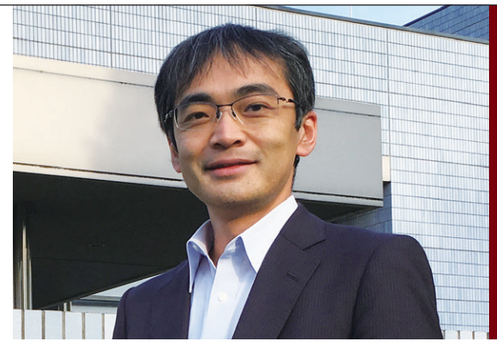


Figure 1 Chemical probes manipulating the dynamics of hepatitis B virus cell entry



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Topics

Lab. of Ultrastructural Virology

I joined the Hakubi Project in January 2020. My research theme is "Structural studies on RNA viruses".
I'm interested in the structure and assembly of viruses. There are many important human pathogenic RNA virueses such as influenza, Ebola, measles, rabies, corona, and Japanese encephalitis virus. The mechanism of viral assembly can be elucidated by determining the detailed structure of the viruses, which also lead to the development of anti-viral drugs. In addition, by comparing the structures of different viruses, we can further understanding of the viral evolution. Therefore, I would like to advance structural studies for existing, and new pathogenic viruses that may emerge in the future.

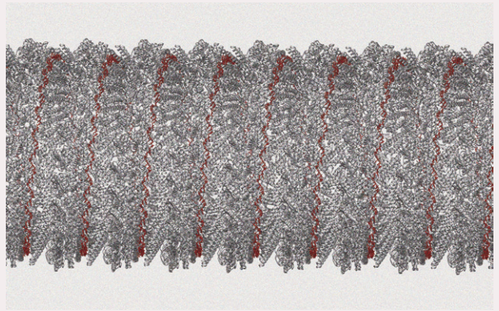

Figure 1 Core structure of the Ebola virus
An atomic model of the Ebola virus nucleoprotein-RNA complex (Red: RNA)
(Sugita et al. Nature 2018)

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Lab. of Viral Immunology (Visiting)

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:

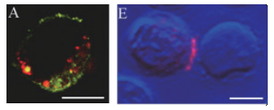
- why do some HTLV-1-infected people develop these serious diseases, while the majority remain healthy? and
- how does HTLV-1 persist lifelong in the individual, despite a strong immune response?

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.

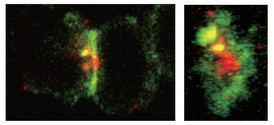
Continuing our collaboration with colleagues in Japan, we have discovered (Satou et al 2016: Proc. Nat. Acad. Sci. USA; Melamed, Yaguchi et al 2018: eLife) that HTLV-1 alters the structure and transcription of host chromatin. This highly unexpected observation raises new hypotheses about the pathogenesis of the leukaemia associated with HTLV-1 infection, and about the evolution of transposable elements in the mammalian genome. 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

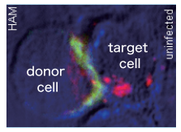
Gag protein complexes (red) polarize to the cell-cell contact area



- which contains organized adhesion domains (green)

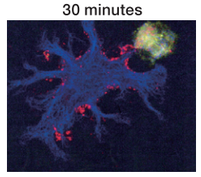


Gag is then transferred with the HTLV-1 genome to the target cell



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

30 minutes



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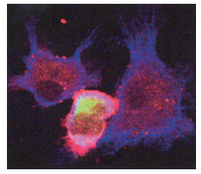


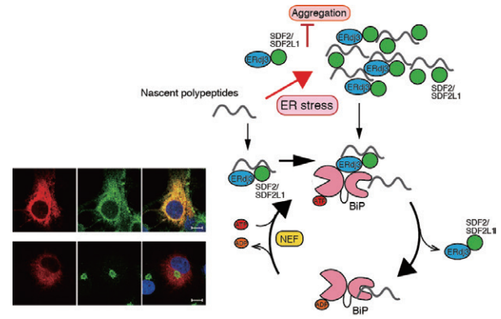
Dendritic cells (blue) can also be efficiently infected by contact with an HTLV-1-infected cell (green)

Lab. of Molecular and Cellular Biology

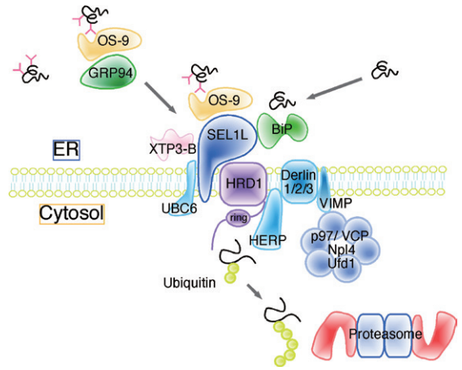
inFront

Our research focuses on the following three projects: Analysis of the quality control mechanism of proteins and the molecules such as chaperones and lectins that are involved in the mechanism (Hosokawa G); Analyses of transition stage from the formation of pre-initiation complex to elongation using RNA aptamer (HIrayoshi G); Analysis of illegitimate V(D)J recombination within T cell receptor β chain gene during normal T cell development in relation to tumorigenicity (Fujimoto G).

In Hosokawa G, we study 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 when cells are exposed to various stresses, or when mutations occur in the genes that endcode proteins. We are also analyzing the protein degradation mechanism named ERAD (endoplasmic reticulum-associated degradation), and the intracellular transport of proteins.



Chaperone protein complex in the endoplasmic reticulum (ER)
Newly snthesized proteins in the ER obtain their native conformations by the assistance of ER chaperon proteins. Some chaperone proteins make a complex to assist protein folding and to inhibit protein aggregation.



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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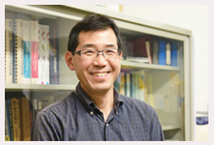

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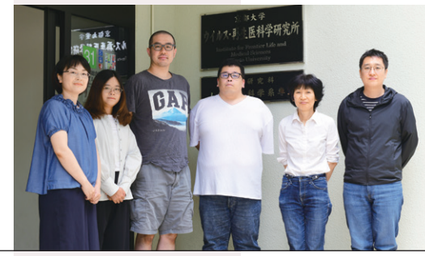

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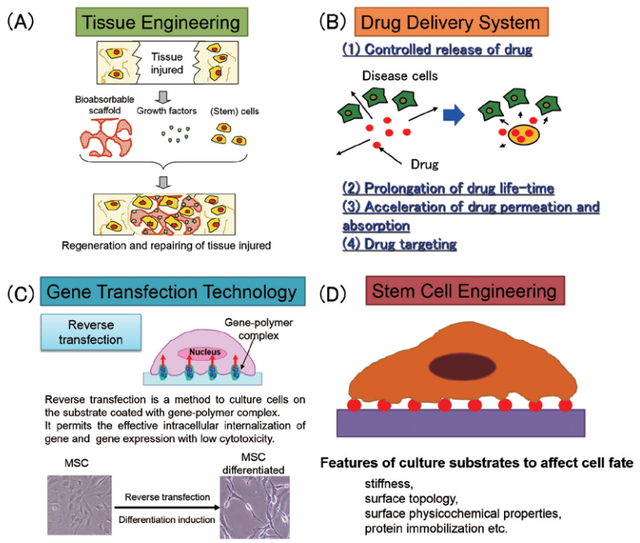
Lab. of Biomaterials

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 *https://www2.infront.kyoto-u.ac.jp/te02/index_en.html*

Lab. of Immunology

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.

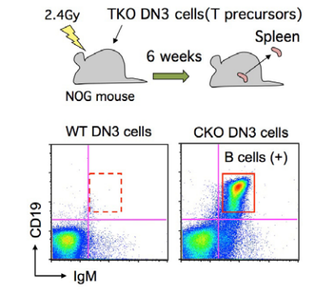


Figure1
Conversion of T cells to B cells by inactivation of polycomb-mediated epigenetic suppression
In T cell-specific Ring1A/B deficient mice, T cell development was severely blocked at an immature stage. We found that these developmentally arrested T cell precursors gave rise to functional B cells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

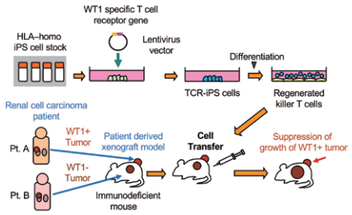


Figure2
Regenerated killer T cells showed efficacy in a PDX solid tumor model
iPS cells obtained from CiRA were transduced with WT1 antigen-specific T cell receptor that had been clinically tested, and killer T cells were regenerated from the iPS cells. The regenerated killer T cells were transferred to the PDX (patient derived xenograft) model mouse of renal cell carcinoma in which both of WT1 positive and negative tumor tissues had been transplanted, resulting in the suppression of the growth of solely the WT1 positive tumor.

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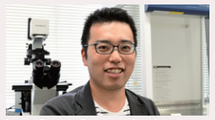

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inFront

Lab. of Tissue Regeneration

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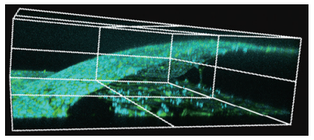
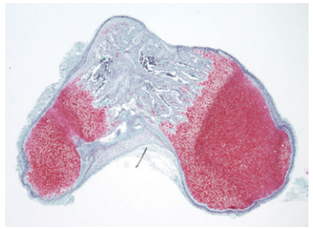
The objectives of our laboratory are to disclose the pathology of disorders in the musculoskeletal system at the molecular level and to develop new therapeutic modalities by understanding the physiological growth, differentiation, and transformation of mesenchymal cells. Following projects are currently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

1. Researches on mesenchymal stem cells
Mesenchymal stem cells (MSC), which exist in bone marrow stromal tissues, have a potential to differentiate to cells of various types in mesenchymal tissues. Many fundamental features of MSCs, however, are still unknown, which are crucial for the development of regeneration therapy using MSC as the evidence based medicine. We have analyzed the growth and differentiation potential of primary human MSCs.

2. Researches on mesenchymal tissues using induced pluripotent stem (iPS) cells
1) Investigation for the differentiation process of bone and cartilage cells using iPS cells We are establishing robust and efficient differentiation method of bone and cartilage cells from iPS cells, and investigate the prcise molecular mechanisms of differentiation.
2) Disease modeling and drug discovery using disease-specific iPS cells
One of the advantages of iPS cells is that it can be established from any individuals. We established iPS cells from patients with intractable hereditary bone and cartilage diseases, and using newly developed differentiation methods, we are performing the disease modeling and drug discovery for bone diseases such as fibrodysplasia ossificans progressiva and osteogenesis imperfecta, and growth plate disease such as multiple epiphyseal dysplasia.
3) Investigation for the cell-of-origin in sarcomas using pluripotent stem cells☒Sarcomas are malignant tumors developed in mesenchymal tissues and consisted of tumors with a variety of clinical and pathological features. Using iPS cells with drug-inducible driver mutations of each type of sarcoma, we analyze the effect of mutations in different stages of differentiation. This approach may help to explain the heterogeneity of tumors and also provide information for personalized medicine.



Bone-like nodules formed by GFP-labelled human iPS cells. The surface of nodules is covered by osteoblasts in a sheet-like structure and osteocyte with dendritic process migrate into the inside of nodules.

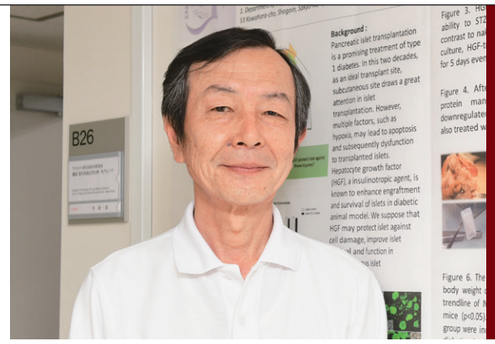


Growth plate-like tissues produced by the transplantation of osteochondral progenitor cells in somites induced from iPS cells. The tissue consists of Safran-O positive cartilage tissues and bone tissues.

Lab URL *https://www2.infront.kyoto-u.ac.jp/ca02/index-j.htm*

Lab. of Organ and Tissue Reconstruction

Our major mission is to develop regenerative medicine for endocrine (primarily diabetes) and metabolic (liver etc.) diseases. We are studying devices for 3D cell culture, 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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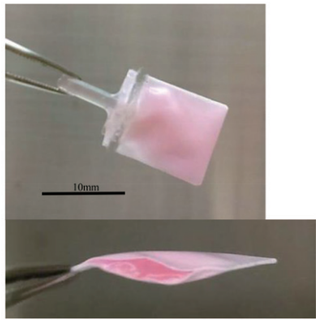

Highly histocompatible and porous EVOH bag that keeps cells inside securely (top) and immune-isolating chitosan hydrogel in it (bottom).

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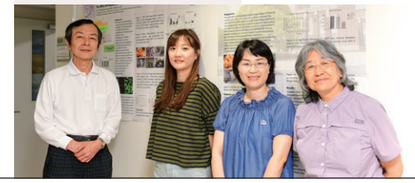


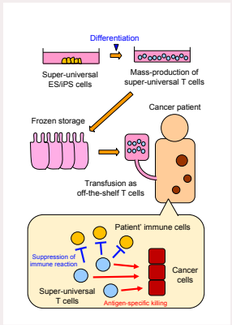
Lab URL *https://www2.infront.kyoto-u.ac.jp/ca03/en/g_info.html*

Topics

Lab. of Immunology

-Woking on the development of regenerated T cells for immune cell theray against cancer-

Mass production of T cells to be used for cancer immunotherapy can be achieved by regenerating T cells from iPS / ES cells in vitro. Currently, I am working on the development of technology to produce iPS / ES cells in which T cell receptor gene can be safely exchanged. This is one of the subjects of the project "Development of super-universal off-the-shelf T cells" which has been supported by AMED grant "Science and Technology Platform Program for Advanced Biological Medicine" for 5 years from 2019. To proceed with this research, it is necessary to make full use of genome editing technology and regenerative medicine technology.

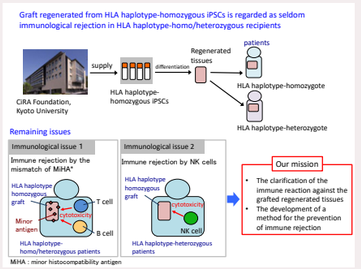


Program-Specific Assist. Prof.
Seiji Nagano

Lab. of Immunology

-Tackling immunological issues of the allogeneic transplantation in the regenerative medicine field-

Our research concerns the possible immune reaction occurring when regenerated tissues are transplanted. This research entitled as "Development of a method for the prevention of immune rejection against regenerated tissues using a novel in vivo human immunity-reconstitution model (PI: Kyoko Masuda)" has been supported by AMED in the program for Technological Innovation of Regenerative Medicine for 3 years from 2018. We expect our findings would contribute to advance the regenerative medicine in realizing transplantations with less or no immune rejection.



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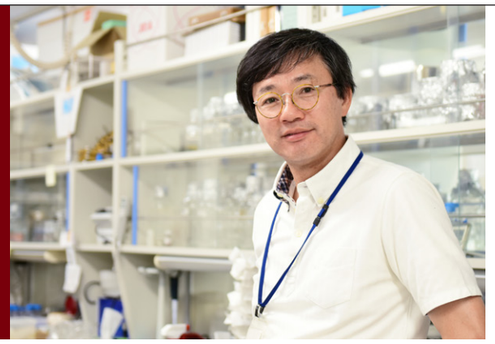

Lab. of Developmental Epigenome

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.

Lab URL ***https://www2.infront.kyoto-u.ac.jp/es03/index.html***

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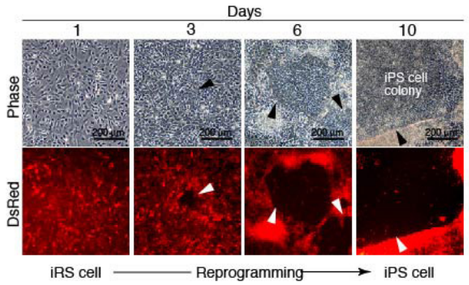
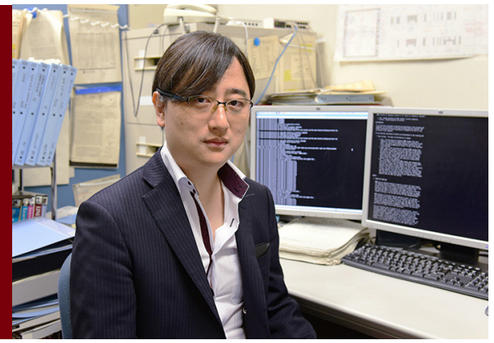


Reprogramming of iRS (intermediately reprogrammed stem) cell to iPS cell



Lab. of Chromosome Dynamics

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.

Lab URL ***https://www2.infront.kyoto-u.ac.jp/rc01/index-j.htm***

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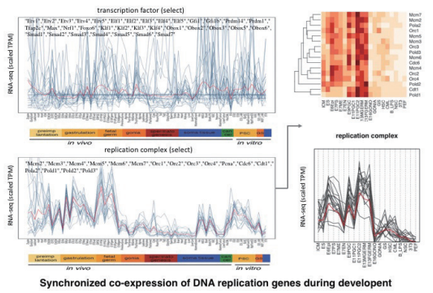
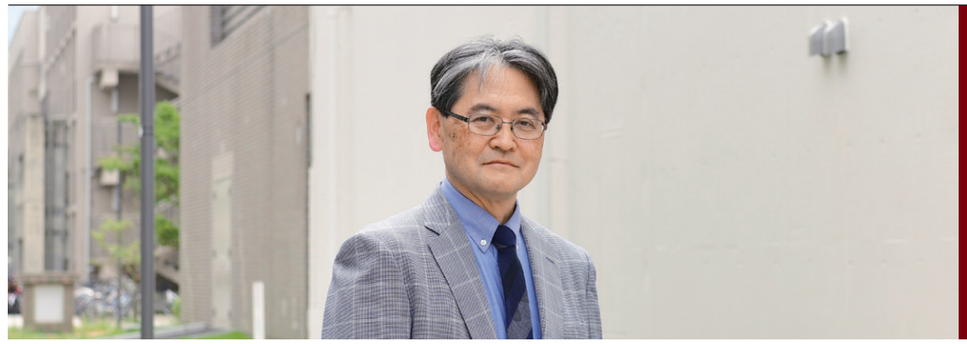
Tdrd1 and Tdrd9 protect the germline genome and epigenome from retrotransposon activity through the piRNA pathway

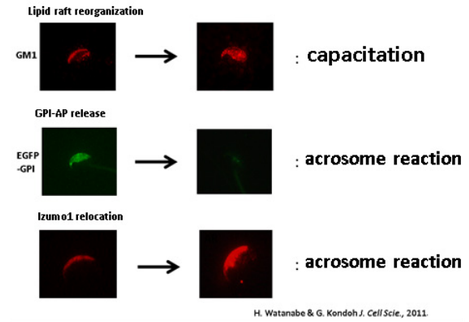


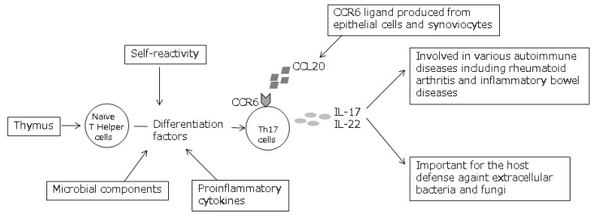
Synchronized co-expression of DNA replication genes during developent



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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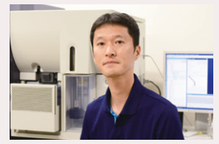

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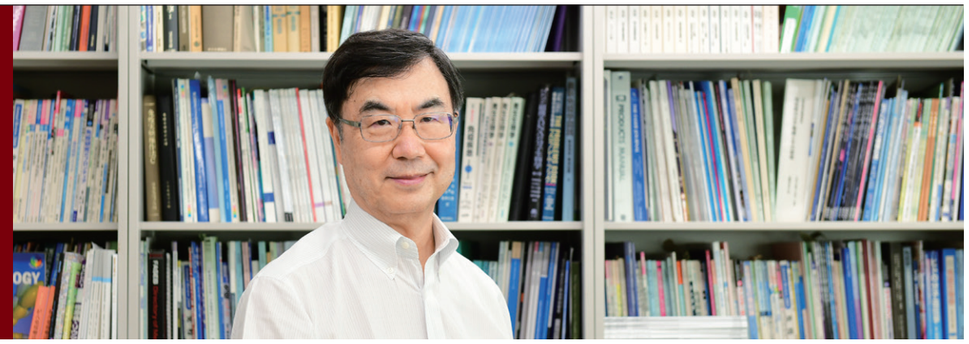

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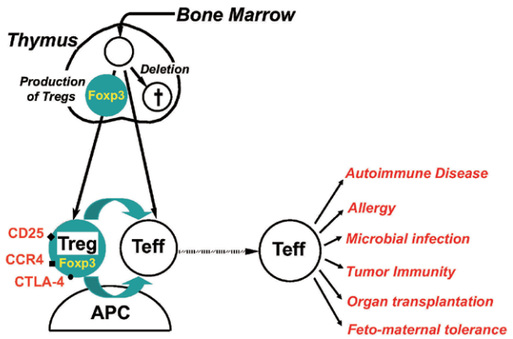
Lab. of Experimental Immunology (Visiting)

Our laboratory studies the mechanisms 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, genetic 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 the 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.

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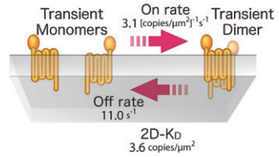
Lab. of Nano Bioprocess

A long-term goal of my laboratory is to uncover the mechanism of signal transduction process of receptors and molecules in the plasma membrane, leading to elucidate the conserved general feature of signal processing. We perform this research by applying the advanced optical microscopy techniques. Therefore, the new imaging techniques and analysis methods for image decoding have been developed, which allow us to directly observe elementary processes organized by single molecules in the plasma membrane. We' re particularly interested in G-protein coupled receptors or GPCR, and its signal transduction. By applying our imaging methods, we can now directly detect the association and dissociation of receptor molecules as well as other signaling molecules at the single molecule level.



Dynamic equilibrium between monomers and dimer of G-protein coupled receptor in the live plasma membrane

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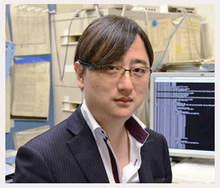
Topics

Lab. of Developmental Epigenome

In multicellular organisms, the genome DNA of individual cells starting from fertilization accumulates mutations as the cells divide, and such alterations in the genetic information is thought to cause future dysfunction, cancer, aging, etc. of the individual. Interestingly, genetic stability during development is not uniform and is regulated differently depending on the stage of development and cell type. For example, early embryos and embryonic stem cells derived from them show a high genetic instability due to rapid cell proliferation and large-scale chromatin remodelling. However, basic understanding of molecular crosstalk between developmental program and genetic stability of individual cells, and systematic search for artificial reconstruction of the genetic stability of cells and individuals have not yet progressed. Our research group focuses on (1) the elucidation of molecular mechanisms underlying the genome stability control in pluripotent stem cells and germline stem cells and (2) artificial manipulation of genome stability of stem cell resources. We are also working on (3) the development and implementation of quality control system for human ES cell and other stem cell resources.



Assoc. Prof.
Shinichiro Chuma

Lab. of Biomechanics

Biological phenomena, such as development, growth, and environmental adaptation are coordinately regulated by complex molecular and cellular interactions. However, specific mechanisms through which molecular/cellular dynamics orchestrate physiological structure and function of biological tissues/organs are not fully understood. The major focus of my research is to clarify the self-organized regulatory mechanism in biological systems toward application to regenerative medicine. Specifically,I have been working on mathematical modeling and computer simulation of bone remodeling and brain morphogenesis from the view point of multiscale biomechanics.

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Lab. of Biomechanics

The Laboratory of Biomechanics aims at clarifying the self-organized regulatory mechanisms of a diverse biological phenomena through interdisciplinary approaches encompassing mechanics, life science, and medical sciences. The major goal of our research is to understand how well-organized dynamics emerge from complex molecular and cellular interactions in living systems. Specifically, we are focused on highlighting the roles of “adaptation to the mechanical environment” and “hierarchy of structure and function” in living systems based on integrated biomechanics and mechanobiology studies using experiments and mathematical modeling and simulation. Our research topics cover developmental processes (cell differentiation, morphogenesis, and growth) and functional adaptation to the environment by remodeling and regeneration of tissues and organs.

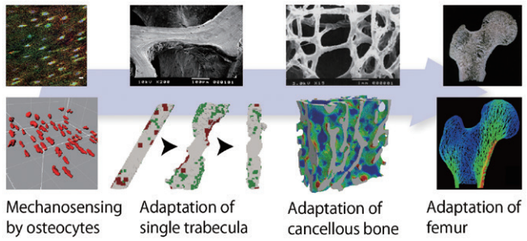

Figure 1 Bone can remodel its outer shape and inner structure to adapt to the surrounding mechanical environment. This study aims to clarify the mechanism of bone functional adaptation achieved by cooperative cellular activities.

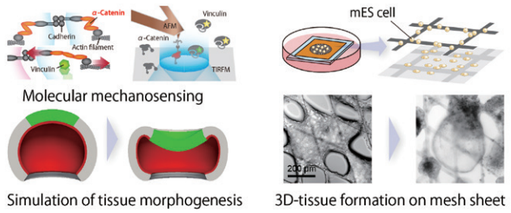

Figure 2 Morphogenesis of biological tissues is regulated by mechanical forces generated through multicellular interactions. This study aims to clarify the mechanism of tissue morphogenesis using experiments and simulations.

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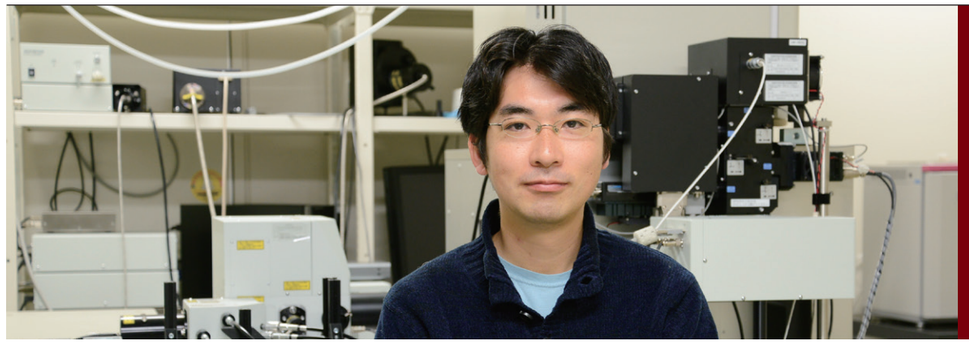

Lab. of Developmental Systems

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.

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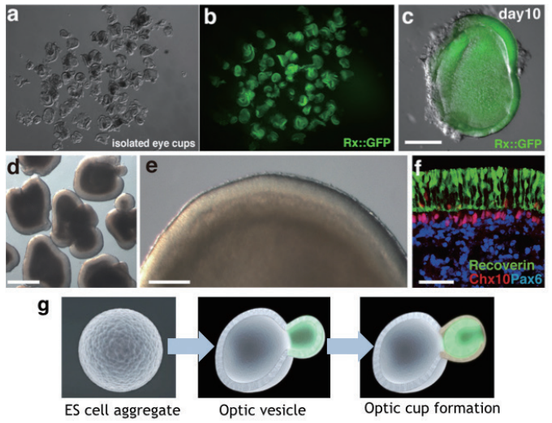

in vitro formation of optic cup and layered retina from ES cells
a-c, Isolated optic cup structure generated from mouse ES cells. d-f, ES cell-deirved optic cup differentiate into layered retinal structure. g, Scheme of in vitro optic cup formation in ES cell culture.

Lab URL *https://www2.infront.kyoto-u.ac.jp/bs01/*

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Lab. of Systems Virology

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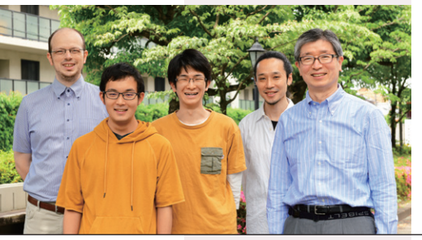
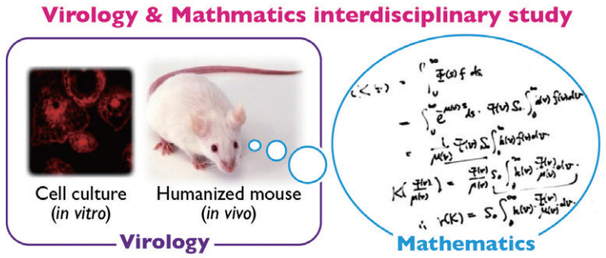


Virus infects cell and replicates. Viral genome transmits from infected cell to adjacent naive cells. This is a most significant characteristic of virus. The mechanism of this infection event is a primary theme of our laboratory. It has been found that various cellular factors positively and negatively 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. We address the mechanism of virus replication 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.



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 *https://www2.infront.kyoto-u.ac.jp/Koyanagi_HP/*

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Lab. of Growth Regulation System

Somatic stem cells actively proliferate and give rise to different types of mature cells (active state) in embryonic tissues while they are mostly dormant (quiescent state) in many adult tissues. Notch signaling is known to regulate both active and quiescent states of somatic stem cells, but how it regulates these different states is unknown. Recent studies revealed that the Notch effector Hes1 is expressed differently between the active and quiescent states during neurogenesis and myogenesis: high in the quiescent state and oscillatory in the active state. When the Hes1 expression level is high, both the neurogenic factor Ascl1 and the myogenic factor MyoD expression are continuously suppressed. By contrast, when Hes1 expression oscillates, it periodically represses Ascl1 and MyoD expression, thereby driving Ascl1 and MyoD oscillations. High levels of Hes1 and the resultant Ascl1 suppression promote the quiescent state of neural stem cells, while Hes1 oscillation-dependent Ascl1 oscillations regulate their active state. Similarly, in satellite cells of muscles, known adult muscle stem cells, high levels of Hes1 and the resultant MyoD suppression seem to promote their quiescent state, while Hes1 oscillation-dependent MyoD oscillations activate their proliferation and differentiation. These findings will be useful to application to tissue regeneration in the near future.

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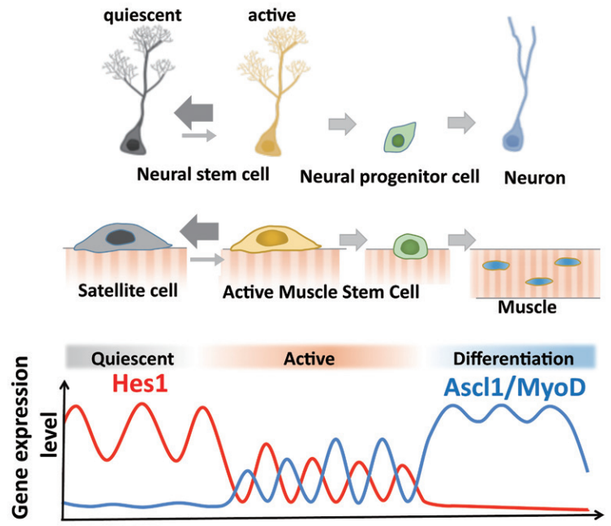

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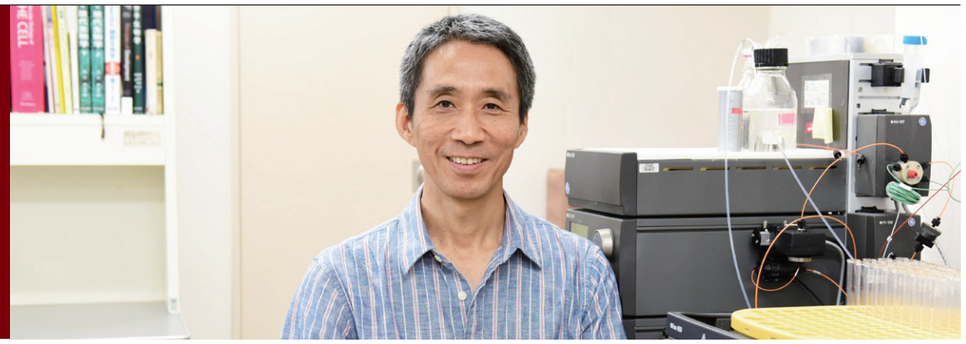

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Lab. of RNA System

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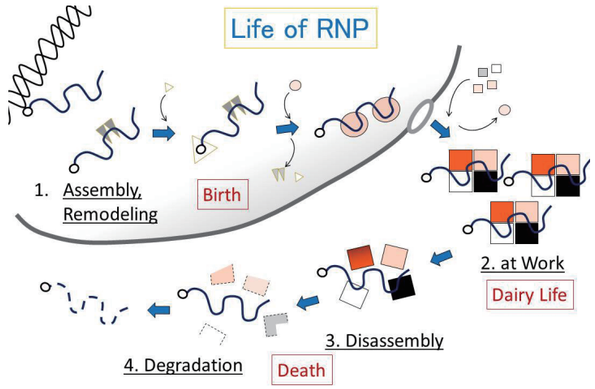
RNA in the cell is not naked but bound by various proteins. Specific RNA binding proteins gather onto the newly-made RNA and thus specific RNP (ribonucleoprotein) is born. RNA component usually undergoes maturation from its primary form through RNA processing. RNP frequently changes its protein composition. 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 *https://www.infront.kyoto-u.ac.jp/ex_ivr/Lab/ohnolab.html*

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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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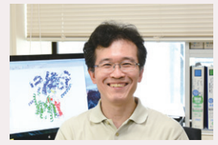

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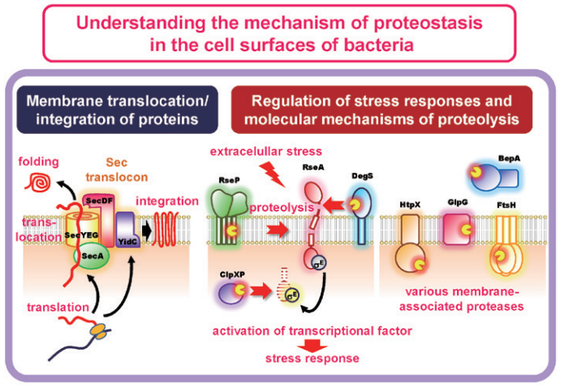
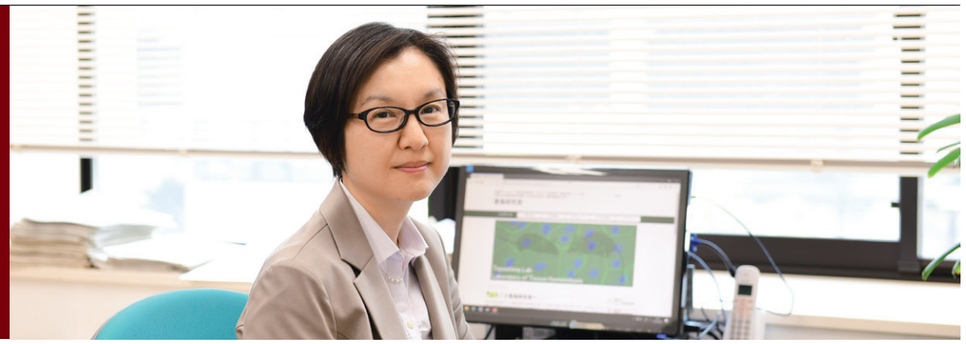


The research prejects carried out in the laboratory of Biological membrane system.

Lab URL *https://infront-biomembrane.jp*



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Lab. of Tissue Homeostasis

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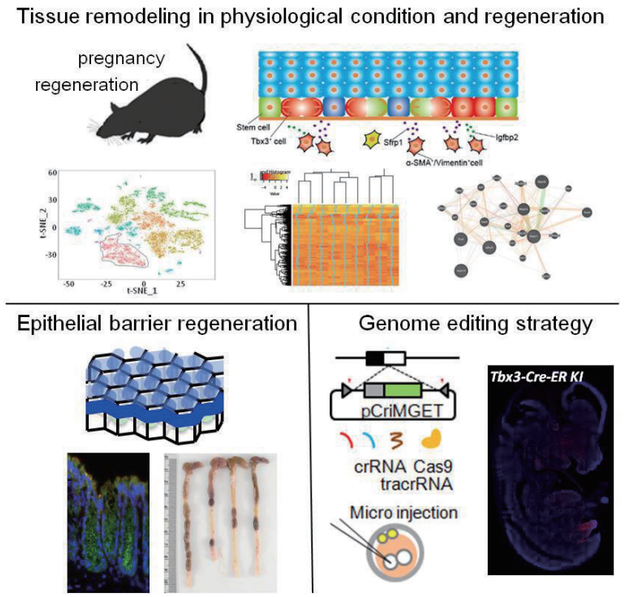
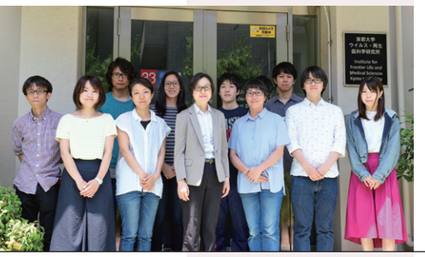
Each organ in the adult body responses to tissue damage or physiological changes of the body through regulating the multicelullar network by which organ size and functions are determined. Our laboratory studies the mechanisms of tissue remodeling especially focusing on a regenerating organ from acute and chronic damage, as well as maternal remodeling organ during pregnancy. How the tissue mechanics and secretory molecules affect the transcriptional network in the multicellular systems is one topic in the projects. These endogenous tissue remodeling mechanisms would be applied for regenerative medicine. We also interested in how the maternal tissue remodeling contributes to fetal growth or developmental origin of health and disease (DOHaD).





Lab URL *https://www2.infront.kyoto-u.ac.jp/Toyoshima-HP/*

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Lab. of Mathematical Biology

The progress of modern biology revealed that biological phenomena are governed by complex network systems including many molecules, cells or organs. For the aim of understanding the functions of complex systems, we adopt mathematical and computational methods. By theoretical approaches we decipher huge amounts of experimental information, and to give integrative understanding for the biological systems. Our final goal is to open a new bioscience which will progress by the repeats of the theoretical predictions and the experimental verifications. We are promoting multiple projects of collaborations with experimental biologists. One of our recent projects is studying dynamics of complex network systems in biology. We developed some theoretical frameworks to extract the important aspects of dynamics from network structure alone, without assuming other quantitative details. By combining our theory with experimental measuring and controling, we will determine mechanism of dynamical behaviours and understand the principles for the biological functions.

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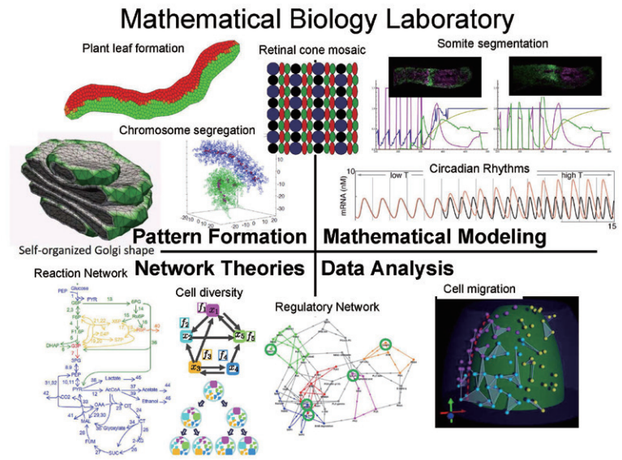
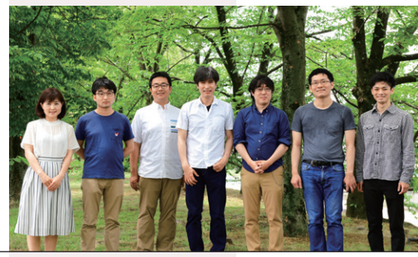


Research topics in lab. of Mathematical Biology



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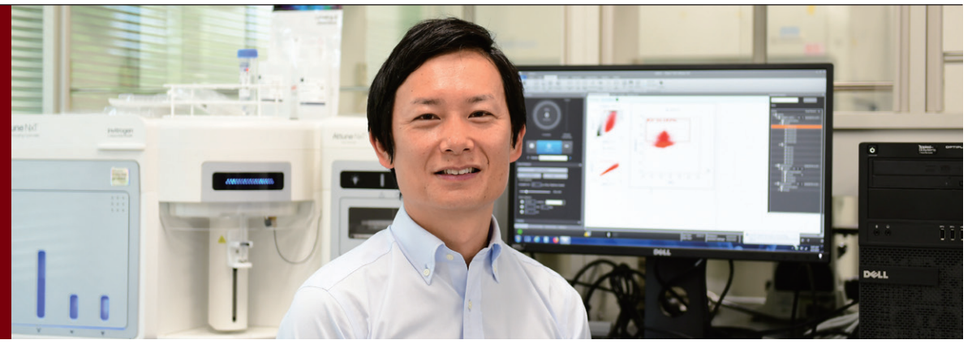

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Lab. of Stem Cell Genetics

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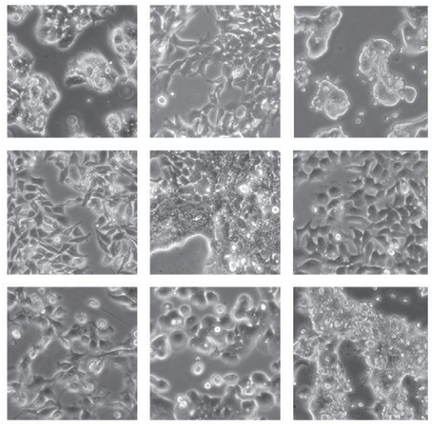
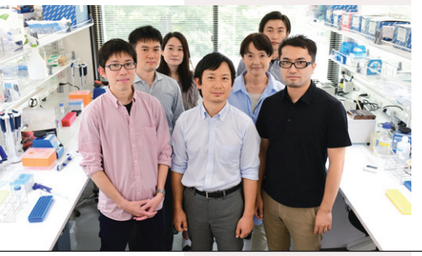
Forward genetic approach can comprehensively reveal genes involved in a phenotype of interest. This approach was frequently applied in lower model organisms such as yeast, Caenorhabditis elegans and fruit fly to identify genes involved in fundamental biological processes. In contrast, forward genetic approach had been hampered in mammalian cultured cells as there was no efficient way to inactivate all copies of every gene. Our research has been focusing on developing novel genetic tools that enable us to apply powerful forward genetics in mammalian cells. We have recently developed a functional genetic screening method using the CRISPR-Cas9 system, which is highly efficient to genetically dissect a wide range of mammalian biology. Our current work focuses on molecular function studies of genes identified through CRISPR-based genetic screening in the following two research area: 1. Molecular mechanisms of pluripotency maintenance and differentiation of human pluripotent stem cells and 2. Genetic vulnerabilities in cancer cells and drug development. For the latter, we have recently completed an analysis of the CRISPR screening dataset of >300 cancer cell lines and identified a number of promising drug targets. We will conduct detailed molecular studies of these candidates to further narrow down the list to the most promising drug targets.



Colorectal cancer cell lines showing various cell morphologies. This cancer type can be classified into a few sub-groups based on gene mutations and gene expression profiles. Drug targets that show specificity in certain groups are most valuable as these targets are associated with biomarkers that can be used for patient stratification, and prioritised in follow-up analysis and subsequent drug development process.



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Lab. of Cell Fate Dynamics and Therapeutics

My laboratory studies the molecular basis of cell fate regulation in normal and malignant stem cells. We are currently investigating several pathways of hematopoiesis and skeletal muscle systems in mice and human. Stem cells have a remarkable ability to propagate themselves, self-renewal. It allows tissue regeneration and repair damaged tissue after injury. But this ability is a double-edged sword; the same mechanism of self-renewal can be a target of malignant transformation and lead to cancer development. In the past decades, we have learned a great deal about the mechanisms of cancer-causing transformation, and yet finding effective ways to eradicate cancer cells has remained an elusive goal in many types of cancers. This is partly because tumors are often complex and heterogeneous mixtures of neoplastic cells with different self-renewal and differentiation capacities. Unlike many differentiated cells within a tumor, some cancer cells have the ability to self-renew. These self-renewing cancer cells, or cancer stem cells, are therapy-resistant and can drive tumor relapse and metastasis following treatment cessation. Recent studies, including our own work, suggest that the normal and malignant stem cells operate on cell fate regulatory signals that are common or specific to each population. Our research program seeks to improve our understanding of stem cell and cancer biology, and to apply this knowledge to the development of novel and effective approaches to treat human disease and cancer.

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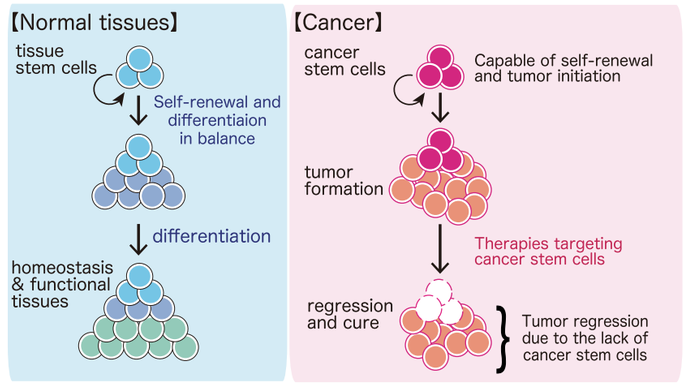
Stem cells in tissues and cancer



Stem cells in tissues and cancer. Stem cells maintain both normal and malignant tissues, and we seek to uncover the molecular basis of cell fate regulation essential for the stem cell functions.

Lab URL *https://www.infront.kyoto-u.ac.jp/research/lab41/*

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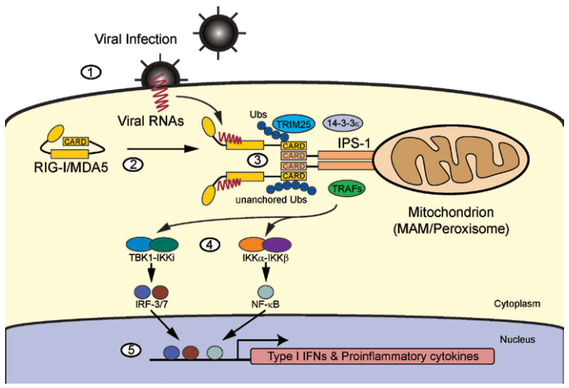
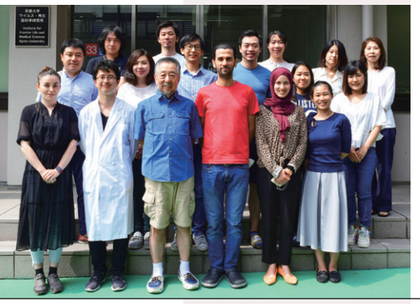
Lab. of Regulatory Information (Visiting)

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.

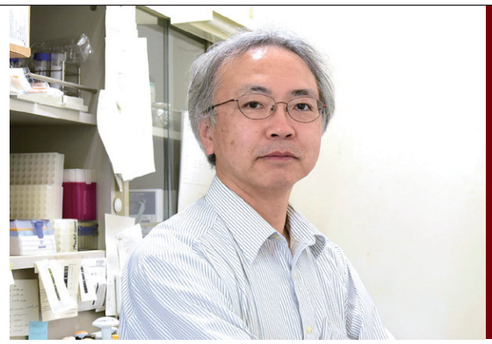


Sensing viral dsRNA and activation of RLR
When cells were infected with virus (1), viral dsRNA is sensed by RIG-I or MDA5 (2). CARD of RIG-I and MDA5 interacts with another CARD-containing protein expressed on mitochondria, termed Interferon Promoter Stimulator-1 (IPS-1) (3). AS a result of these molecular 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. 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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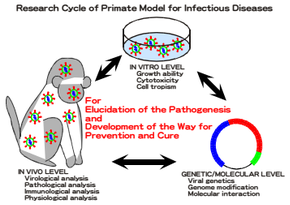
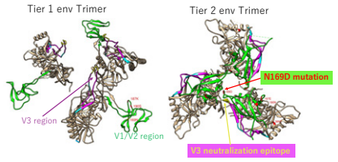


We will elucidate the pathogenicity and develop preventive and therapeutic methods of infectious diseases by comprehensive analysis at the level of molecules, cultured cells, and infected individuals.



• N169D is a key substitution for gaining neutralization resistance.

The virus mutated in monkeys acquired neutralization resistance by structural shield of the target site.

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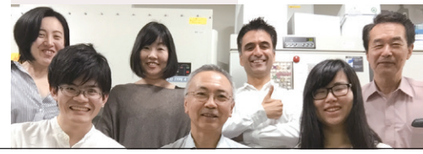
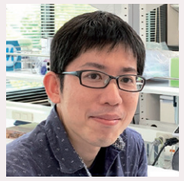


Lab URL ***https://www2.infront.kyoto-u.ac.jp/primatemodelHP/***

Topics

Lab. of Stem Cell Genetics

Transcriptional networks are important keys of cell fate determination and are frequently dysregulated in diseases. The aim of our research is to elucidate transcriptional networks in leukemia development to identify potential therapeutic target(s) by using CRISPR-based genetic approaches and transcriptome/epigenetics analyses. We also pursue understanding of transcriptional regulations in pluripotent stem cells and relationship with stemness of cancer.



Assist. Prof.
Yusuke Tarumoto

Lab. of Stem Cell Genetics

Whereas there are around 30 to 40 trillion cells in our body, genetic information of individual cells are basically identical. The character of individual cells is defined by combination of expressing gene and each expression level and obtained by multiple “epigenetic” mechanisms. We are developing new research tools using genome editing technology to understand epigenetics in stem cells and cancer cells more detail. To tackle this, I am trying to clear epigenetic features of Acute Myeloid Leukemia by proteomic approach.

Assist. Prof.
Gohei Nishibuchi

Lab. of Stem Cell Genetics

In vitro genome-wide CRISPR screening has been employed to identify therapeutic targets for hematological cancer. Recently, it has been shown that hematopoietic cancer cells receive important signals for growth or survival from hematopoietic microenvironments that usually maintain and regulate normal hematopoiesis in vivo. We therefore aim to identify genes essential for growth or survival of hematological cancer cells in vivo by in vivo genome-wide CRISPR screening.

Assist. Prof.
Kazunari Aoki

inFront

Lab. of Infectious Disease Model

Prof. Hirofumi Akari
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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.

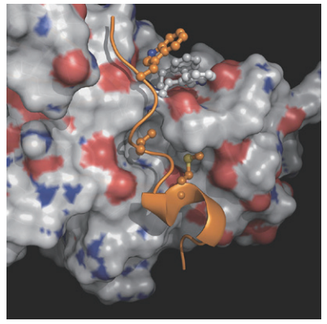


Figure 1 Interaction between HIV-1 Nef N-terminus and mu-1 subunit of adaptor protein-1

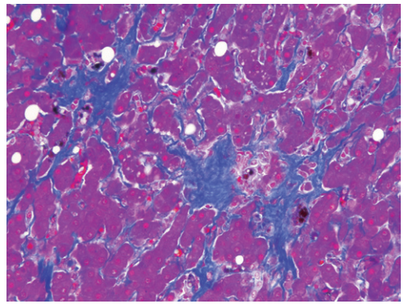
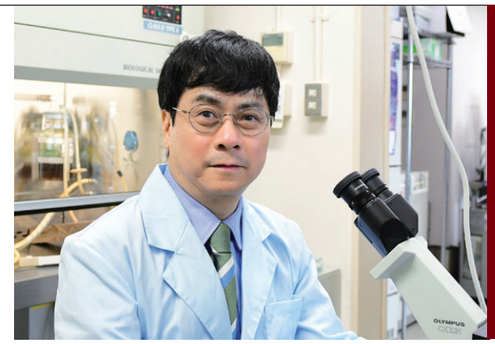


Figure 2 histopathological analysis of liver fibrosis in a tamarin persistently infected with GBV-B (Masson's trichrome staining)

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.



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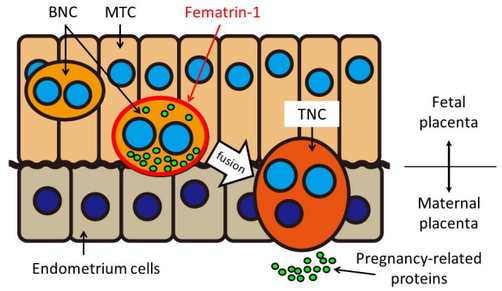

Fematrin-1, a bovine endogenous retrovirus K1-derived protein, is involved in the formation of trinucleate cells (TNC) appreared in bovine placenta. BNC: binucleate cells; MTC: mononucleate trophoblast cells.

Assoc. Prof.
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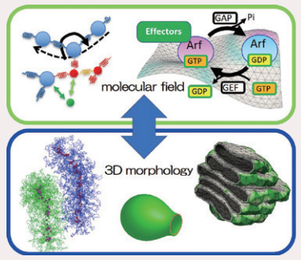
Lab URL *https://paleovirology.jimdo.com/*

Topics

Lab. of Mathematical Biology

Complex behaviors of eukaryotic cells depend on the functions of organelles. They consist of various molecules assembling in self-organized manners and individually display characteristic shapes and behaviors. Their functions depending on the shapes and behaviors are difficult to reduce to the activities of molecules and much remains unrevealed. Using statistical mechanics, soft-matter physics, and complex systems science, we construct mathematical models of organelles and aim to understand their shapes, behaviors, and functions.



Assoc. Prof.
Masashi Tachikawa

Lab. of Cell Fate Dynamics and Therapeutics

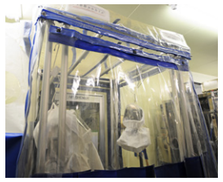
Our lab is working on cell fate decision in cancer and stem cells. Among them, my research focuses on metabolism and cancer. Cancer cells utilize cancer-specific metabolic pathway that is different from normal cells. However, it is still unclear how such metabolites upregulate cancer cell proliferation. I'm interested in protein modification with the metabolites, and the regulation of cancer cell proliferation and malignant transformation by it. Eventually, I would like to contribute to find a way to cure cancer that is incurable by current therapy.

Assist. Prof.
Kenkyo Matsuura

Research Center for Infectious Disease

Non-human Primate Experimental Facility

In our experimental facility, BSL3 level infected animal experiments that allow experiments with blood born virus are in operation. Collaborative researchers and technical staff (veterinarian) of our institute perform management and experiments under prior consultation. What is the purpose of this facility? Development of vaccine against human pathogenic virus and elucidation of pathogenicity.



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.

Center for Animal Experiments

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.

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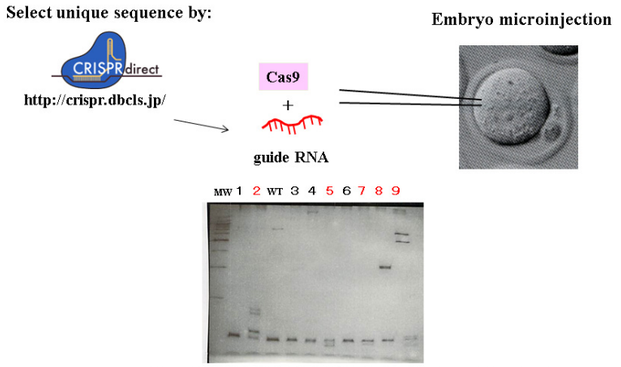


Our strategy for developing genome-edited mice using CRISPR-Cas9 system.

Lab URL *https://www2.infront.kyoto-u.ac.jp/an/newpage1.html*

About us

Our mission

The center for human ES cell research was newly established in April 2020, with a mission of promoting the establishment and distribution of human ES (ES) cell lines and the advancement of applied studies on them. ES cells are a type of pluripotent stem cells, known as widely as induced-pluripotent stem (iPS) cells, and human ES cells precede human iPS cells in the history of their first establishment. There are two institutes in Japan approved for the generation of hES cell lines, one being the national center for child health and development and the other being our institute, and currently we are manufacturing human ES cell lines for clinical use in our MHLW approved cell processing facility. Regarding the importance of human ES cells in academic researches and their potential benefits in clinical applications, a robust and stable supply of high-quality human ES cells is essential for the advancement of regenerative medicine as well as basic researches. To realize the clinical application of human ES cells, we strengthen our current facility of ES cell production and, through further cooperation with other research organizations and hospitals inside and outside of Japan, we accelerate the progression of stem cell research and regenerative medicine.

History

Institute for frontier life and medical sciences first succeeded in establishing human ES cell lines in 2002, and since 2017, directed by the the former laboratory of embryonic stem cell research, has been serving as the supplier of clinical-grade human ES cell lines in Japan (as of April, 2020). In order to enhance our capability and performance in research and development of human ES cells for clinical use, the facility underwent a reorganization in 2020, and the center for human ES cell research was newly founded.


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


Cell Processing Room


Liquid Nitrogen Suppy System


Monitoring System


Supply Room


Cell Storage Room

Division of Clinical Basis for ES Cell Research

Lab. of Embryonic Stem Cell Research	Associate professor Suemori (full time)	・Establishment and distribution of hES cell lines ・Library construction of hES cell lines
Lab. of Embryonic Stem Cell Application	Associate professor Chuma (concurrent)	・Quality control of hES cell lines ・Comparative analyses of genome/epigenome regualion

Division of Basic Technology Development for ES Cell Research

Lab. of Organoids Technology	Professor Eiraku (Center Director/concurrent)	・Generation of organoids from hES cells ・Regenerative medicine & drug discovery by organoids
Lab. of Regenerative Immune Cell Therapy	Professor Kawamoto (concurrent)	・Regenetation of T cells from hES cells ・Cancer immunotherapy by regenerative T cells

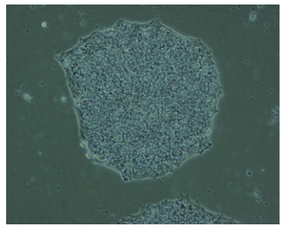
Organization overview

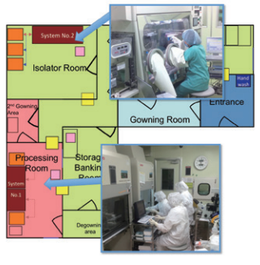
The center for human ES cell research comprises two divisions, namely, the division of clinical basis for ES cell research and the division of basic technology development for ES cell research. The division of clinical basis for ES cell research consists of two groups: the laboratory of embryonic stem cell research (led by associate professor Suemori), which is responsible for the establishment and distribution of human ES cell lines, and the laboratory of embryonic stem cell application (led by associate professor Chuma), which takes charge of quality control of and comparative genome/epigenome analyses of human ES cell lines. The division of basic technology development for ES cell research consists of two groups, which aim for research and development, with mid-to long-term vision, intended for clinical applications of human ES cells: the laboratory of organoids technology (led by professor Eiraku, Center Director) and the laboratory of regenerative immune cell therapy (led by professor Kawamoto). Together, our center works toward the establishment of an international and stable research facility for human ES cell distribution, as well as the development of basic technologies required for its clinical application, such as quality control and cell/organoid culturing methods.

Division of Clinical Basis for ES Cell Research

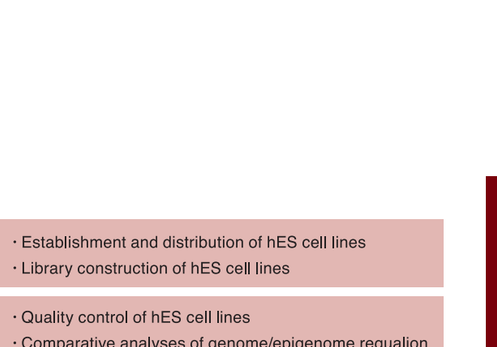
Lab. of Embryonic Stem Cell Research

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 human embryonic stem (hES) cell lines.


Human Embryonic Stem Cell



Clinical-grade hESC Processing Facility



Lab URL ***https://www2.infront.kyoto-u.ac.jp/es01/top.htm***

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Program-Specific Sr.Lect.
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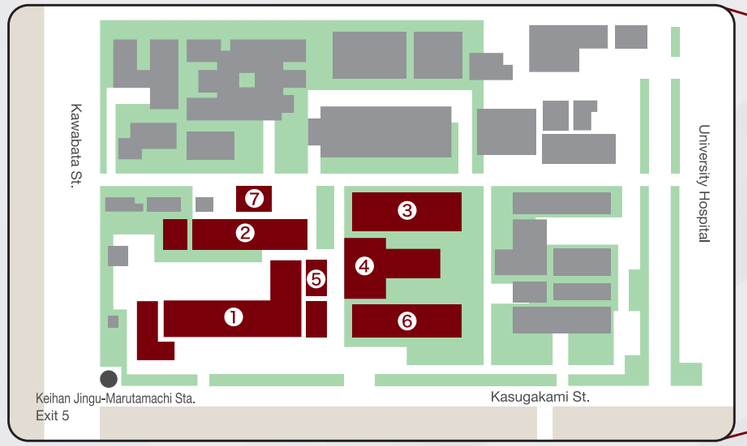
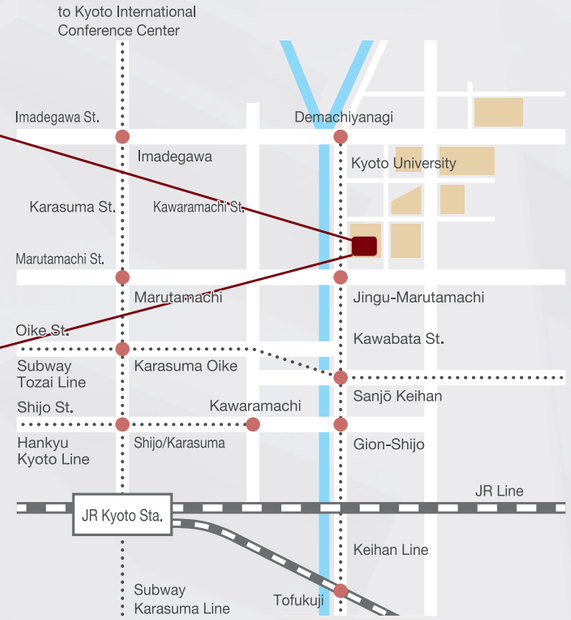
Map & Access





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 Biomaterials
- Lab. of Immunology
- Lab. of Tissue Regeneration
- Lab. of Organ and Tissue Reconstruction
- Lab. of Developmental Epigenome
- Lab. of Integrative Biological Science
- Lab. of Experimental Immunology
- Lab. of Nano Bioprocess
- Lab. of Biomechanics
- Lab. of Developmental Systems
- Lab. of Stem Cell Genetics
- Division of clinical basis for ES cell research
- Administration Office

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

- Lab. of Tumor Viruses
- Lab. of Cell Regulation
- Lab. of Immune Regulation
- Lab. of Systems Virology
- Lab. of Growth Regulation System
- Lab. of RNA System
- Lab. of Biological Membrane System
- Lab. of Tissue Homeostasis
- Lab. of Regulatory Information
- Lab. of Primate Model
- Lab. of Virus-Host Coevolution

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

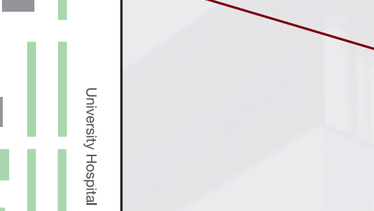
- Lab. of RNA Viruses
- Lab. of Ultrastructural Virology
- Lab. of Systems Virology
- Lab. of Mathematical Biology
- Lab. of Cell Fate Dynamics and Therapeutics
- Reproductive Engineering Team
- Center for Animal Experiments

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 Integrative Biological Science
- Lab. of Developmental Systems
- Division of clinical basis for ES cell research



❻ Molecular Biology Research Bldg.

- Non-human Primate Experimental Facility

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

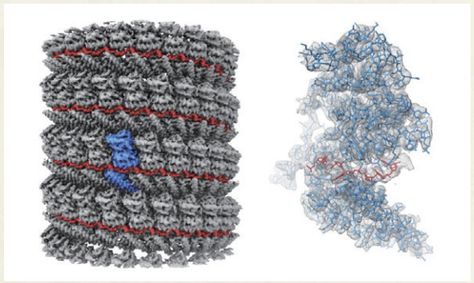
- Lab. of Systems Virology
- Lab. of Infectious Disease Model

Frontier Life and Medical Sciences Research Fund

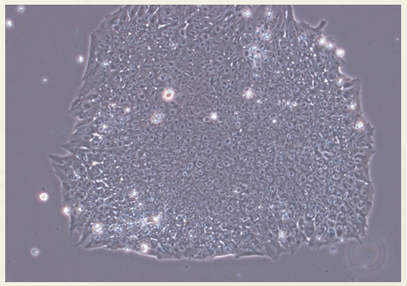
Uncovering the secrets of vital activity to shape the future of medical sciences

The Institute for Frontier Life and Medical Sciences, Kyoto University is known for its brilliant research findings in medical sciences, including the discovery of the human leukemia virus and regulatory T cells. Your contribution will help us move forward.

◆Please visit the Frontier Life and Medical Sciences Research Fund website.
http://www.kikin.kyoto-u.ac.jp/en/contribution/infront/



Core structure of Ebola virus as captured by cryo-electron microscopy.



Human ES cell line was produced for clinical purposes at the first time in Japan (KthES11). It has been already distributed to various research institutions.