The Background and Concept of Establishing a Novel Major by Merging Two Majors

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Significant developments in molecular biology materialized in the second half of the 20th century, leading to rapid progress in the fundamental understanding of organisms, which are systems based on genomes. In response, the 21st century is being called the age of life innovation - the age of applied life science. However, as biological phenomena are complex, they cannot be understood or applied simply by parsing them into numerous constituent molecules and fundamental processes and simplifying them in order to identify principles. Rather, it will be necessary to analyze complex biological phenomena as a whole, clarify the numerous elements that are involved and their relationships, and determine methods for their regulation. This is the kind of technological innovation that will be imperative in leading the way in the age of life innovation.

The rapid advances in technologies for DNA sequencing, omics analysis, and imaging in recent years have enabled comprehensive analysis of a wide variety of biological macromolecules for the first time, and paved the way for the analysis of complex biological phenomena as a whole. Moreover, massive data analysis of biological molecules, which was simultaneously realized, was found to be the focal point of life innovation. In the age of information-oriented life science, the innovation of information technology will be essential for understanding the numerous elements that are involved in biological phenomena and their interrelationships, as well as for examining their regulation.

Medicine has always been at the forefront of applied life science because of its urgent need, and there is no exception in the age of information-oriented life science. The marked progress being made in the acquisition of personal genomes in humans has enabled the rapid estimation of mutations related to diseases, and its clinical applications are being investigated. In addition, due to the accumulation of a substantial amount of phenotypic information in the form of medical care information, humans are thought of as the most suitable subjects of research involving novel information technology. Accordingly, in the age of information-oriented life science, it is expected that the field of medical science will lead the development of other fields.

Given this awareness of the modern age, the department of Medical Genome Sciences and the department of Computational Biology have been merged, resulting in the establishment of a unique new major that is unprecedented in Japan. The objectives of this new major are to lead the way in information-oriented life science while significantly contributing to life innovation, and to cultivate personnel capable of translating the results in the clinical setting. To this end, we believe that it is necessary to develop personnel with a novel specialty by actively employing on-the-job training in state-of-the-art informatics and medical science research settings and implementing a basic education environment for integrating information science and medical science. This kind of personnel is required not only in medicine, but also in other technical fields such as agricultural sciences, pharmaceutical sciences, environmental studies and biotechnology. The ideal objective of our new major, as the only major in Japan able to cultivate such personnel, is to extensively supply personnel who will contribute to information-oriented life science and life innovation while leading research in Japan in the 21st century, which has been called the age of applied life science.
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The Medical Sciences Group
INTRODUCTION TO THE MEDICAL SCIENCES GROUP

It has been more than 10 years since the first human genome sequence was unveiled. Since then, numerous genome sequences have been determined for both human and various other living organisms. Now, it is the time to transform life science into a "genome" based discipline. The research field that urgently requires such a transformation is medicine. Through the research in the field of molecular biology, it has been well-established that all living organism, including human, can be seen as a gene-based system, where the disease-state is the malfunction of it. Defects in some genes may cause human inherited disorders, or diseases such as cancer, and is also responsible for the susceptibility to even more diseases. Still, the entire and detailed picture of how one’s genome relates to diseases has yet to be revealed. Medical genome science is a new research field deciphering relationships between the variety of human genome and diseases, and translating those findings to advanced medical treatments.

The mission of our group is to lead medical genome research that explores the new frontiers in medical science, to cultivate translational research and to promote the advancement in medicine, contributing to human health and welfare. We welcome students from all disciplines who are interested in this field, with an adventurous spirit and the determination to contribute a global perspective that allows them to take a bird’s-eye view of the life sciences.

Our group offers research educational programs that integrates basic life sciences of genome, proteomics, and model animals, as well as advanced medicine, cooperating with the Human Genome Center and the research hospital, in the Institute of Medical Science, the University of Tokyo (IMSUT). Since academic year 2007, we have started the “Medical Genome Science Program” first supported by the Ministry of Education, Culture, Sports, Science and Technology, then, the program was established as a formal education program in the graduate school. Students who have completed this program are awarded an official certificate issued by the dean of Graduate School of Frontier Sciences. Many of our group staffs have actively collaborated with enterprises, government agencies, as well as other universities and bio-ventures that exploit the technological seeds generated by our basic research.
Protein synthesis is the most fundamental process in life. We address elucidation of a basic principle of translation systems derived various living organisms, such as bacteria, eukaryote and mitochondria. Based on cell-free translation system, we are challenging creation of artificial cell, one goal of Synthetic Biology. Moreover, the development of drugs discovery system using the PURE ribosome display method is addressed.

(1) Biochemistry of translation system

Using the reconstituted translation systems (PURE systems) originated of E. coli, yeast and mitochondria, we are promoting biochemical studies to elucidate more precise mechanism of translation process. Recently, yeast PURE system was successfully reconstituted and is now clarifying various regulation mechanism in translational process, such as mRNA-quality control. Studies on animal mitochondrial translation system are also in progress, which will provide us useful clues for the therapy of mitochondrial disease.

(2) Artificial cell based on the PURE system

All the proteins encoded on E. coli genome have been successfully expressed using the PURE system. We are also developing the cell-free system capable of producing complicated complex in cells, such as ATPase on membrane and ribosomal subunits. Through these bottom-up approaches, we would like pave the way to experimental constitution of cell.

(3) Development of medical probes using cell-free system

We are exploring protein-binders including antibodies by the ribosome-display method based on the PURE system. The peptide-drugs targeting GPCR synthesized by the PURE system will be developed by the in vitro evolution system.

References:

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Nat Protoc (2015) 9, 1328 – 1344
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Cells are composed of a number of biomolecular complexes and their networks. However, molecular details for their regulatory mechanism remain unknown. We seek to identify key molecular events and functions in cellular biological systems by molecular genetic approaches for microorganisms (e.g. Escherichia coli, Saccharomyces cerevisiae) combined with other techniques.

Research in our laboratory is focused on the protein synthesis apparatus, such as translation termination factors and mRNA quality control (mRNA surveillance) factors, as well as yeast epigenetic prion protein systems and membrane transporter systems.

Decoding mechanism of the stop codons and its versatile functions.

The mechanism of translation termination has long been a puzzle. The polypeptide-chain release factor (RF) plays a key role in terminating protein synthesis. Bacteria have two codon specific RFs, RF1 and RF2, to decipher three stop codons. Decades ago, an idea was formulated that RFs may be protein analogs of tRNA. This idea gained substantial support ten years ago by the identification of two classes of crucial RF peptide motifs, Peptide-anticodon and GGQ, in bacteria. These motifs are functionally equivalent to the anticodon and aminoacyl-CCA terminus of tRNA, although they are involved in different steps of translation. In eukaryotes translation termination is catalyzed by two classes of proteins, eRF1 and eRF3. eRF1 recognizes stop codons and hydrolyzes peptidyl-tRNA as a tRNA mimic, while eRF3, an elongation factor 1α (EF-1α) homolog, binds to and stimulates the activity of eRF1.

The roles of stop codons are known to be versatile. A number of essential genes with a premature stop codon in their protein coding regions are expressed by bypassing translation termination using the Sec (Selenocystein) insertion, translational frameshifting and so on. Such mechanisms are called translational RECODING (=Reprogrammed genetic decoding). Moreover, in eukaryotes, the premature stop codons in aberrant mRNAs are recognized differently from normal stop codons and trigger the NMD (=Nonsense mediated mRNA decay) system to avoid harmful protein synthesis.

The tRNA mimicry proteins provide a clue to elucidate the mechanism of stop codon recognition.

References:
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 Scientific Reports 6 (29295) (2016)
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 *review articles
In spite of the recent progress in preventive, diagnostic and therapeutic modalities, deaths due to various cancers are still increasing. The aim of our research group is “The prevention and control of cancer”. The major project in our laboratory is “the isolation of disease-related genes through genomic analysis”. Family history is acknowledged to be one of the strong risk factors for various diseases including cancers. To identify genes of medical importance, we conducted genome-wide association analyses using several thousands of samples. As a result, we have isolated various gene related with disease susceptibility, drug response, and laboratory test. We would like to achieve personalized medical treatment based on these findings.

The other project is “functional analysis of p53 tumor suppressor gene”. Mutations in the p53 gene are the most common genetic alteration observed in human cancers. Since about 90% of them were detected within its DNA-binding domain, the crucial function of p53 is considered as a sequence-specific transcription factor. We have identified a number of p53-target genes and elucidated the molecular mechanism whereby p53 regulate carcinogenic pathway. Our current project is identification of novel p53-target gene through proteome, transcriptome and genomic approach. Please refer to our home page for additional information.

References

RNA processing, which includes maturation process of functional RNAs and biogenesis and metabolism of RNAs, is important step for the regulation of gene expression in cells. RNA processing dysregulations are often associated with the human diseases.

The main interest in the Laboratory of RNA Biology is the mechanism and regulation of RNA processing machinery. In particular, our laboratory investigates the molecular mechanisms of synthesis, maturation and biogenesis of functional RNAs, by employing biochemistry, molecular cell biology, and structural approaches in complementary manners.

In the last decades, by structural and functional analyses of RNA processing enzymes, such as template-independent RNA polymerases (RNA-specific terminal nucleotidyltransferases), and viral RNA polymerases, we have contributed to solving classical and important problems in the RNA enzymology.

More recently, we have been studying function, structure and regulation of biogenesis and metabolism of small non-coding RNAs (sRNAs) in human cell. We focus on several enzymes, which include human terminal nucleotidyltransferases and modification enzymes, and their complexes with other regulatory proteins. These enzymes and the complexes with their regulatory proteins are involved in the biogenesis and metabolism of sRNAs, which are reportedly to regulate cell differentiation, proliferation, reprogramming, inflammation, cancer, and stress-responses. Our studies using techniques of biochemistry, molecular cell biology, and structural biology are expected to provide detailed molecular basis for development of drugs against human diseases.

You are welcome to join our laboratory as a graduate student. If you are interested in joining our laboratory and want to enjoy high-quality science together, please visit our web site, and contact us via e. mail to Kozo Tomita.

Web site of Laboratory of RNA Biology: http://www.park.itc.u-tokyo.ac.jp/rnabiology/

Related selected publications

Core Laboratories

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【Key Words】HTLV-1, ATL, epigenome, EZH2, tax

**Dr. Uchimaru’s Group**

In Prof. Uchimaru’s group, researchers in the Laboratory of Tumor Biology are in corroboration with Dr. Nakano in Laboratory of Viral Oncogenesis to study ATL (adult T-cell leukemia/lymphoma), which is caused by infection of human retrovirus, HTLV−1 (Human T-cell Leukemia Virus type−1). Our goal is to clarify the genetic and molecular disorders accumulated in the HTLV−1 infected T cells, which cause the onset of ATL, for development of new therapeutic approach to ATL.

HTLV−1 is mainly transmitted to infants from infected mothers through breastfeeding, and leads to malignant transformation of infected T cells 60〜70 years after the infection. The underlying molecular mechanisms of HTLV−1 pathogenesis and the genetic/epigenetic disorders responsible for the onset of ATL are poorly understood. Therefore, ATL is still one of the most aggressive T cell malignancies without effective cures. We speculate that genetic and molecular lesions at the time of HTLV−1 infection trigger further accumulation of molecular disorders in infected T cells, which cause immortalization and malignant transformation in these cells, followed by a monoclonal expansion of ATL leukemic cells. To uncover cellular events responsible for the ATL-onset, we focus on two aspects of this disease; (1) molecular disorders accumulated in ATL cells, and (2) deregulation of cellular pathways by HTLV−1 infection, and combine outcomes from those two approaches to understand the molecular mechanisms of ATL leukemogenesis triggered by HTLV−1 infection. Also, our research covers; (3) another human retrovirus HIV−1 to achieve the cure for AIDS and related diseases, as well as to further understand the molecular pathogenesis of human retroviruses, i.e., HIV−1 to AIDS and HTLV−1 to ATL (Fig. 1).

**Fig. 1. Research projects in Dr. Uchimaru’s group**

(1) Molecular dysregulation in ATL cells

In order to clarify molecular dysregulation in gene expression at various levels, we have been investigating mRNA and microRNA expression profiles, as well as splicing patterns in blood samples from ATL patients using various microarray technologies. Based on the comprehensive/comparative analysis of these data, we found abnormal overexpression of the epigenetic factor (EZH2), transcription factors (c-Myb, FoxM1), and a non-canonical Wnt ligand (Wnt5a), together with a complete loss of tumor-suppressive miR−31 in ATL cells. We also found a drastic accumulation of aberrant splicing mRNA variants in ATL cells. Our experiments show that accumulation of these genetic disorders is responsible for leukemogenesis and the malignancy of ATL cells (Yamagishi et al., 2012; Nakano et al., 2016) (Fig. 2).

We also focus on the pathological molecular network involving epigenetic deregulation in ATL cells. Particularly, we recently found through a genome-wide epigenetic analysis in ATL and HTLV−1 infected cells using the ChIP-on-chip technology that overexpression/disorder of polycomb family proteins EZH1/2 were responsible for reprogramming of epigenome causing abnormal gene expression profiles, thus downstream cellular signaling pathways in ATL cells.

**Fig. 2. Comprehensive analyses of ATL cells**
Therefore, EZH1/2 are promising therapeutic molecular targets for malignant neoplasms including ATL and other cancers (Fujikawa et al., 2016; Kobayashi et al., 2014; Yamagishi et al., 2012). Development and clinical trials of new drugs targeting EZH2 as well as EZH1 are in progress (Fig. 2).

(2) How does HTLV−1 infection affect the cellular homeostasis?

After HTLV−1 entry, the viral genomic RNA is reverse-transcribed and immediately integrated into the host human genome (provirus). Then, transcription and translation from the HTLV−1 provirus occur through the host cell machinery. We are particularly interested in the function of the viral transcription regulator, Tax, and mRNA transporter, Rex, in the HTLV−1 life-cycle, since they play major roles to utilize the host gene expression mechanism for viral replication. Rex is known to nuclear-export unspliced and partially spliced viral mRNAs. Further, we have found that Rex inhibits the cellular nonsense-mediated mRNA decay (NMD) to protect viral mRNAs and enhances production of viral proteins (Nakano et al., 2013). Tax strongly stimulates the viral promoter and transactivates viral expression. Our study has demonstrated that Tax also interacts with various cellular proteins, including EZH2. Thus, Tax is involved in the cellular epigenetic regulation (Fujikawa et al., 2016). Our study reveals that these viral proteins hijack and fine-tune the host cellular mechanism beneficial for viral replication (Nakano and Watanabe, 2016). We continue to investigate how Tax and Rex alter the cellular homeostasis, thus how trigger immortalization and leukemogenesis of HTLV 1 infected T cells (Fig. 3).

(3) Molecular pathogenesis of human retroviruses

We are also working on the molecular mechanism of AIDS-related problems, especially HIV−1 latency (Matsuda et al., 2015) and AIDS-associated malignant lymphomas (Yamagishi et al., 2015).

Our recent publications


Dr. Satoh’s Group

Dr. Satoh is working on the molecular mechanisms of chromosomal translocations and functions of chimeric genes found in leukemias and lymphomas by combining cytogenetic techniques (FISH, CGH) and modern techniques in genome sciences such as next generation sequencing.
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**Key Words**  
Pathogen-host interaction, Antibody & T cell responses, Vaccine development, HIV

This laboratory is working on Microbiology and Immunology and analyzing pathogen-host interaction to elucidate the molecular mechanism of pathogen proliferation "in vivo". We have been focusing on HIV, a representative virus inducing chronic persistent infection, and examining viral replication, transmission and evolution, T-cell responses and B-cell responses.

We have established a non-human primate AIDS model using groups of macaques sharing individual MHC haplotypes. By using this model, we are analyzing virus-host immune interaction to elucidate the mechanism of virus control as well as virus persistence. Furthermore, we are working on HIV vaccine development and international collaboration projects are in progress for clinical trials. We are also attempting to develop vaccines against other pathogens including HTLV−1 and Dengue viruses.

We have currently started several projects for analyzing pathogen-host interaction in humans. First, we are working on the establishment of clinical genome database in domestic HIV-infected individuals. Second, we are conducting collaborative projects analyzing pathogen and host (and microflora) genomes in Vietnam and Ghana. These studies would contribute to elucidation of pathogen evolution under pathogen-host interaction as well as determination of host factors affecting pathogen proliferation and/or disease progression.

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**Laboratory of Innate Immunity**

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**Key Words**  
immunology, innate immunity, toll-like receptor, autoimmune disease, disease model

The immune system consists of adaptive immunity and innate immunity. Lymphocytes are key players in the former, whereas macrophages and dendritic cells have important roles in innate immunity. Macrophages and dendritic cells employ pathogen sensors for sensing microbial organism. Toll-like receptors (TLR) belong to the pathogen sensors in innate immunity. TLRs respond to microbial glycolipids, proteins, and nucleic acid, triggering innate immune responses. Recently, TLRs are reported to respond to self-derived products and have a role in non-infectious inflammatory diseases like autoimmune disease, allergy, obesity, and atherosclerosis. Our division focuses on molecular mechanisms underlying pathogens sensing by TLRs, and those regulating TLR signaling. Dysregulation of these mechanisms would lead to inflammatory diseases. Our goal is to understand molecular basis of the innate immune system.
Emerging infectious diseases pose a serious global threat. Although the mechanism of cross-species transmission is the most important question in virology, it remains still unsolved. We are studying Mononegavirales that contains many highly pathogenic emerging viruses. We have first established reverse genetics systems of several Mononegavirales, which enable us to generate infectious recombinant viruses. By using this technique with our animal infection models, we have been studying the mechanism of cross-species transmission, viral pathogenicity and virus-host interactions. These studies shed light on the cause of various pathogenicities, which could lead to development of novel therapies for viral infectious diseases.

Morbilliviruses including measles virus and canine distemper virus, which belong to Mononegavirales, are excellent vaccine vectors because of its lifelong immunity and strong induction of cellular immunity. Since there were no effective vaccines for leishmaniasis and Nipah virus infection, we have generated polyvalent vaccines for these pathogens and verified its efficacy in vivo. We have actively applied our new recombinant virus technique to develop polyvalent vaccines.

Nipah virus that emerged in 1999 is a highly virulent virus classified into biosafety level 4 (BSL4). It still breaks out frequently in South Asia, but there are no vaccines and treatment licensed for human use. Development of vaccines and antiviral drugs for Nipah virus is one of our goals.

Fig. 1. Development of bivalent leishmaniasis vaccine by reverse genetics system.

Measles virus is able to infect and kill cancer cells. Using reverse genetics technique, we have successfully produced an attenuated measles virus which maintains the infectivity and lethality to cancer cells. Additionally, we have proved its therapeutic effect for various types of cancer in vivo. Currently, we are utilizing this recombinant virus to develop a new cancer therapy and heading to translational research.

Nipah virus that emerged in 1999 is a highly virulent virus classified into biosafety level 4 (BSL4). It still breaks out frequently in South Asia, but there are no vaccines and treatment licensed for human use. Development of vaccines and antiviral drugs for Nipah virus is one of our goals.

Fig. 2. Localization of the recombinant measles virus in xenografted mice.

The themes pursued in our laboratory are related to “cancer”, “immunity”, and “bones”, since signal transducer TRAF6 and transcription factor NF-κB, which we are interested in, are profoundly involved in tumorigenesis, immune regulation, and bone metabolism. Upon cytokine stimulation, TRAF6 acts as an E3 ubiquitin ligase to generate Lys-63-linked polyubiquitin chains, which do not induce proteasomal degradation, but rather act as platforms for formation of active signal complexes leading to the activation of NF-κB. A number of serious human diseases are caused by various kinds of bone metabolism abnormalities and immunodeficiencies. We were able to reproduce diseases similar to these human diseases in TRAF6- or NF-κB-deficient mice, indicating that TRAF6/NF-κB signals are essential for normal bone formation and the establishment of immunity. Abnormal activation of NF-κB also plays a critical role in the onset and progression of various leukaeemias and many other cancers. We are trying to elucidate how dysregulation of TRAF6/NF-κB signaling leads to malignant transformation, immunoregulation, and bone metabolism at the molecular level and we are conducting numerous experiments on gene transfer into cultured cells and analyses of various knockout mice, aiming to put the results to use in drug discovery and the diagnosis and treatment of diseases. Details are shown in the Lab web site (URL: http://www.traf6.com).
Laboratory of Functional Analysis in silico

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【Key Words】 dry lab, bioinformatics, genome sequence analysis, transcriptional regulatory region, bio medical big data

The term “in silico” in the title of our laboratory is an analogy to more familiar terms such as “in vivo” (within the living) or “in vitro” (within the test tube), meaning “within the silicon chip” or “using computers”. Thus, the mission of our lab is to study bioinformatics or to analyze the functions of genes/their products through computational analysis of genomic information. More specifically, we have been motivated by a rather naive question: ”How genetic information is encoded as DNA sequences?” and have tried to decode these information, especially the regulatory information governing specific gene expression, in the genome sequence data. In addition to genomic data, we also conduct research on protein-protein interaction networks.

Although these studies are thus oriented to basic research, recent advances in DNA sequencing technology enables our activities applicable to various areas in medical sciences; we believe that our collaboration with renowned researchers in regenerative medicine, immunology, and developmental biology will make our lab attractive to students who wish to contribute to these areas from a new angle. Those who are not familiar to computers are also welcome.

Laboratory homepage: http://fais.hgc.jp/

Laboratory of Molecular Virology

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【Key Words】 virus, pathogenicity, homeostasis control factor

To date, approximately 250 herpesviruses have been identified, affecting most animal species. These viruses are associated with a variety of diseases such as encephalitis, malignancy and mucocutaneous diseases in human and animals. The objective of our research is to understand the mechanisms by which herpesviruses replicate in cells and manifest diseases in their hosts. Our goal is to apply our fundamental findings for the development of anti-herpetic drugs and vaccines for the control of these viral infections. Please refer to our homepage for more detail (http://www.ims.u-tokyo.ac.jp/Kawaguchi-lab/KawaguchiLabTop.html).

Laboratory of Cellular Therapy

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【Key Words】 leukemia, hematological malignancy, hematopoietic stem cells, epigenetics, molecular targeting therapy

Our laboratory is interested in the molecular, cellular, and genetic basis of hematologic malignancies, with a specific focus on Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML). Our research focuses on modeling hematological diseases using both mouse bone marrow transplantation (BMT) and human cell-based Xenograft assays. These models allow us to identify altered genes and signaling pathways, and understand the contribution of these alterations to the pathogenesis of hematologic malignancies. We are currently focusing on two of the most common types of myeloid neoplasms: ASXL1 – related and RUNX1 – related MDS/AML. We are also investigating factors to enhance the effect of immunotherapy against myeloid tumors. The ultimate goal of our lab is to eventually provide novel therapies to patients with MDS/AML.
Intra-University Cooperative Laboratories

**Laboratory of Virology does not recruit students for the academic year 2020**

**Laboratory of Virology**

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*【Key Words】* Influenza, Ebola virus, pathogenesis

Viruses can cause not only devastating diseases in humans, but also enormous damage to our society. The long-term goal of our research is to understand the mechanisms of virus replication in host cells and the molecular basis of virus pathogenesis in individuals, by using influenza virus infection as a model.

**Laboratory of Infectious Diseases**

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*【Key Words】* HIV infection, Viral hepatitis, Viral carcinogenesis, Life-style related diseases

Our lab has just started with new members.

Research in our laboratory is focused on the protein synthesis apparatus, such as translation termination factors and mRNA quality control (mRNA surveillance) factors, as well as yeast epigenetic prion protein systems and membrane transporter systems.

Our laboratory is a pioneer in HIV research in Japan, and we have published many basic and clinical reports. HIV infection is less likely to die of acquired immunodeficiency syndrome (AIDS) due to progress in treatment. Instead, new problems such as (1) malignant tumors based on immunodeficiency, (2) difficulty of eliminating HIV, (3) aging progresses faster than healthy people, leading to higher prevalence of life-style related diseases. Regarding (1) and (3), large-scale clinical and basic research has been started nationwide, and our laboratory plays the core of research. Also, preparation for (2) is also proceeding. In the future, we plan to develop translational research that returns the results of basic research to the clinical setting in collaboration with other laboratories of the institution.

We have also conducted fundamental research on hepatitis viruses so far. HBV, HCV are viruses with much in common with HIV. We have clarified viral factors related to the natural course of viral hepatitis and carcinogenesis. In the future, we plan to explore the relationship between hepatitis and other infectious diseases, various autoimmune phenomena caused by hepatitis, taking advantage of the features of the medical science research institute.

Chronic infection affects not only the main infected organs but also organs and systems of the whole body. I would like to conduct research with students who wish to enjoy such aspects of infectious diseases.

**Laboratory of Clinical Genome Research**

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*【Key Words】* cancer, genome, signal transduction, model mouse

Cancer results from accumulation of genomic and epigenetic alterations. These alterations comprised of a limited number of variants transmitted from parents and a large number of somatic changes acquired by aging and
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the exposure to environmental factors. Studies of inherited genetic factors will help the profound understanding of human tumorigenesis, and facilitate the development of preventive approaches. The acquired changes include not only driver mutations associated with proliferation, survival, and characteristics of cancer cells, but also passenger mutations irrelevant to carcinogenesis. Our group is working on the clarification of mechanisms underlying human tumors aiming for the application of genetic and epigenetic data in clinics, and challenging the development of diagnostic and/or therapeutic strategies and the precision medicine. Our challenges include 1) studies of Wnt signaling in tumorigenesis, 2) the development of assay system for the discovery of new molecular targeted drugs, 3) application of NGS and AI in the precise diagnosis of cancer in clinics, and 4) the establishment and investigation of novel mouse models of human cancer. Further information is available in our homepage. (http://www.ims.u-tokyo.ac.jp/furukawa/english/main_furu.html)

Laboratory of Advanced Genome Medicine

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【Key Words】gastroenterology, inflammation, cancer, stem cell, microbe, animal model

Our laboratory focus on the total pathogenic processes initiated at genome and extended to the whole body. The main object of our research is the inflammatory and malignant diseases developed in digestive systems.

As approaches against inflammatory digestive diseases, we investigate the pathogenesis of microbes and immune system. One of our research themes is how pathogens like Hepatitis viruses or Helicobacter pylori interact with host cells and trigger organic inflammation. We are also interested in the gut microbiota as the important component of host homeostasis. As researches for GI malignancies, we try to unveil the role of genetic mutations discovered in worldwide cancer genome research. By the use of genetically-engineered mouse model and organoid culture system of stem cells, we investigate the mechanisms of carcinogenesis and novel therapies against these cancers.

As shown above, the aim of our researches is to elucidate the pathogenesis of digestive diseases at each level of genes, cells, organs, and individuals, and to establish new therapy. We specifically apply mouse model, which enables analyses of complex interactions in the disease development and progression. Please visit our website for the details. http://www.ims.u-tokyo.ac.jp/dagm/english/home.html

Laboratory of Stem Cell Pathology

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【Key Words】Epigenetics, cancer, iPS cell, ES cell, mouse, developmental genomics

Epigenetic regulation plays a critical role for the cellular differentiation, the stable maintenance of cellular identity, and the reprogramming process. Accumulating evidence suggests that epigenetic abnormalities represented by abnormal DNA methylation have been involved in various diseases as well. We are interested in unveiling epigenetic regulation in the cellular differentiation, the maintenance of cellular identity, and the pathogenesis including age-related diseases such as cancer. Particularly, taking advantage of reprogramming technology to actively alter epigenetic regulation, we are investigating the role of epigenetic regulation on cancer development, maintenance, and progression. Finally, we will try to develop a novel approach targeting epigenetic regulation to treat cancer patients.
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【Key Words】Cell adhesion, Invasion and metastasis, Energy metabolism of cancer, Genome analysis, Development of novel approaches to diagnosis and treatment of cancer

Human cancers develop and progress toward malignancy through accumulation of multiple genetic and epigenetic alterations. Elucidation of these alterations is essential to provide molecular targets for prevention, diagnosis, and treatment of cancer. Our current interest is to understand the role of cell adhesion in cancer invasion and metastasis. To this end, an immunoglobulin superfamily cell adhesion molecule, CADM1, and its cascade were identified and are being characterized. Genetic and epigenetic abnormalities involved in human tumors, including cholangiocarcinoma, adult T-cell leukemia, lung, breast and urological cancers, are also being investigated. Furthermore, significance of the copy number variation in various cancers is being analyzed as an additional driving force to enhance genomic instability in cancer cells. http://www.ims.u-tokyo.ac.jp/hitogan/index.html

Laboratory of Rheumatology does not recruit students for the academic year 2020

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【Key Words】Glucocorticoid, Nuclear Receptor, Transcription, Metabolism, Muscle

Our division is founded in 2013 to tackle systemic autoimmune inflammatory diseases including rheumatoid arthritis, systemic lupus erythematosus and vasculitic syndromes, and manages increasing number of those in- and out-patients. We provide patients personalized and evidence-based medical service. We participate in cutting edge science of autoimmune, rheumatic and allergic diseases and novel treatments for patients with these disorders. We are interested in the mechanism of eukaryotic gene expression and development of novel therapy and/or drugs that target transcriptional machineries. For this purpose, our recent work is mainly focused on conditional regulation of transcription factors including the glucocorticoid receptor (GR) and inhibitory components of transcription elongation machinery including HEXIM1. Our recent achievement is now being applied in clinical settings in IMSUT Hospital.

Laboratory of Medical Proteomics
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【Key Words】proteomics, network analysis, cancer, signal transduction, translation control

Signal transduction systems are known to regulate complex biological events such as cell proliferation and differentiation via sequential phosphorylation/dephosphorylation reactions all over cellular networks. Previous in-depth cell signaling analyses under a variety of experimental conditions revealed many of the key molecules and related events leading to each biological effect. Although the widespread association of signaling molecules contributes essentially to cellular regulation, their network-wide behavior is mostly yet to be analyzed.

Recent technological advances regarding high resolution mass spectrometry-based quantitative proteomics, in combination with phosphorylation-directed protein/peptide
enrichment methodology, have enabled us to grasp the dynamic status of phosphorylated signaling molecules in a comprehensive and unbiased manner. In our previous studies, phosphoproteomics-based numerical modeling was applied to evaluate regulatory network elements from a statistical point of view and further integration with transcriptome dynamics led us to uncover regulatory hubs at the transcriptional level. Currently, we mainly focus on establishment of theoretical platforms for comprehensive evaluation of drug targets regarding disease-related signaling networks to understand and regulate aberrant cellular responses from a systems perspective.

Laboratory of Genetics
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[Key Words] signal transduction, mouse model, gene/molecular targeted therapy, neoplasia/immunity, ageing/neuromuscular disorder

The major interest of this laboratory is in molecular signals that regulate a variety of cellular activities. Our aim is to address how dysregulated cellular signals give rise to neoplastic, immune, neural, metabolic, developmental and/or age-related disorders. Our goal is to understand the molecular bases of tumorigenesis and the development of other intractable diseases as a path toward uncovering therapeutic targets. For example, we identified Dok−7 as an essential protein for neuromuscular synaptogenesis and found DOK7 myasthenia, a recessive hereditary neuromuscular synaptopathy. We further demonstrated that elevated Dok−7 expression, or any equivalent method that safely enlarges neuromuscular synapses, has potential as a therapy for a range of neuromuscular disorders with structural defects in neuromuscular synapses.

Currently, we are investigating regulatory mechanisms in protein-tyrosine kinase-mediated signaling pathways, their pathophysiological roles and the potential for therapeutic intervention.

Our website:
http://www.ims.u-tokyo.ac.jp/genetics/html/home.html

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[Key Words] signal transduction, cancer, non-coding RNA, stress response, MAP kinase

The aims and ongoing research projects in our laboratory are to elucidate molecular mechanisms that underlie the regulation of signal transduction systems, such as "MAP kinase cascades" and "Stress granules", which are responsible for cell-fate decisions including cell growth, differentiation, and apoptosis.

The MAPK signaling cascades are well conserved in all eukaryotes and consist of three tiers of protein kinases (MAPKKK-MAPKK-MAPK). In mammals, there are at least three subfamilies of MAPKs, named ERK, JNK and p38. The ERK subfamily members are activated by mitogenic stimuli and are associated with proliferative responses. In contrast, JNK and p38 are activated by environmental stresses (e.g., DNA-damaging reagents, UV irradiation, or osmotic shock) and by cytokines (e.g., TNFα), and are associated with inflammatory, reparative, and/or apoptotic responses.

Stress granules are recently discovered cytoplasmic punctate foci (composed of mRNA and proteins) that appear when the cell is under stress. We have recently identified a novel role of stress granules in the regulation of apoptotic cell death. Formation of stress granules suppresses the activation of p38 and JNK pathways, thereby inhibiting stress-induced apoptosis. However, the precise function of stress-granule formation, particularly its role in the regulation
of cellular stress responses, remains to be elucidated. Perturbation of these critical signaling systems is involved in a variety of life-threatening diseases, including cancer, autoimmune diseases, neurodegenerative disorders and type 2 diabetes. Therefore, these signaling systems are of clinical importance. Our laboratory also aims to develop new diagnostic and therapeutic tools for currently intractable disorders in which these pathways are involved. Techniques employed in our lab include: molecular and cell biology, biochemistry and genetic engineering (including knockout mice and yeast). For more details regarding our laboratory, please visit our Web site: http://www.ims.u-tokyo.ac.jp/dcsmm/DCSMM/Top-E.html
**Laboratory of Stem Cell and Molecular Medicine**

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【Key word】hematopoietic stem cells, hematological malignancies, aging, epigenetics

Research Topics
1. Molecular mechanism of stem cell self-renewal  
2. Epigenetics of stem cell aging  
3. Epigenetics of cancer

Stem cells have the remarkable capacity to both self-renew and give rise to many types of more specialized cells in the body, which explains their great therapeutic potential in regenerative medicine. But that’s not the only reason stem cells have become such a hotbed of scientific inquiry. These cellular transformers also offer an invaluable research tool for probing the disease mechanisms that underpin cancer, aging and a host of other health problems. Our major interest is to elucidate various life phenomena through stem cell research. We focus on the mechanisms of self-renewal and multi-lineage differentiation of hematopoietic stem cells (HSCs). We are also interested in how the deregulated HSC functions are associated with aging of our body and the development of age-related hematological malignancies. We approach these issues mainly from the view point of epigenetics, such as DNA and histone modifications and higher order chromatin architecture.

http://www.ims.u-tokyo.ac.jp/molmed/

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**Laboratory of Regenerative Medicine**

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【Key word】regenerative medicine, iPS cell, organoid, cancer organoid

Regenerative medicine is a challenging scientific field that aims to convert the pioneering knowledge of developmental biology and stem cell biology to clinical application. For patients with end-stage organ failure, organ transplantation is the only effective treatment; however, the paucity of organ for transplantation hinders the treatment of most patients. Therefore, regenerative medicine with transplantable organs has attracted attention. Our laboratory has established novel organoid culture technologies to reconstruct human organs from stem cells, including human induced pluripotent stem cells (iPSCs). We are currently developing a novel therapeutic strategy to substitute organ transplantation. Furthermore, we have applied our established technologies to cancer research and have reconstructed artificial refractory cancer tissue (cancer organoid) with tumor microenvironment. Based on this unique cancer organoid, we are currently developing a new drug-screening system to impede cancer relapse and metastasis.
Our laboratory is interested in the mechanism of maintenance DNA methylation during cell proliferation. DNA methylation is one of the best known epigenetic modifications and plays an essential role in many biological events such as transcriptional regulation, development, differentiation, suppression of retrotransposons, and maintenance of genome stability. Therefore, the DNA methylation pattern needs to be accurately inherited to daughter DNA when the replication of genomic DNA occurs, and dysregulated DNA methylation causes various diseases including cancer. However, we still do not know the entity of the molecular mechanism maintaining the DNA methylation pattern, due to its complexity. Particularly, it is unclear what triggers the collapse of maintenance DNA methylation machinery and, consequently, genome instability or diseases. To answer this critical question, we utilize a cell-free system that can reproduce the chromosomal replication in vitro to advance our research. Besides, we aim to develop novel DNMT inhibitors based on the new molecular mechanisms that we discovered.

In addition, in our laboratory, we are exploring the molecular basis of tumorigenesis and aging. For more information on our laboratory, please visit our homepage.
(http://www.ims.u-tokyo.ac.jp/cancer-cell-biology/hp2018/01index.html)
Most genetic information encoded by the genomic DNA is first transcribed as messenger RNAs (mRNAs), followed by translation to proteins to exert their functions. Coined by Francis Crick in 1958, this flow of genetic information—called the Central Dogma—has been widely accepted as a basic principle in molecular biology. However, recent studies have revealed many important exceptions to this principle. Our laboratory is investigating one such exception called non-coding RNAs (ncRNAs), which act as functional RNA molecules without being translated to proteins.

Well-known ncRNAs such as rRNAs (ribosomal RNAs), tRNAs (transfer RNAs) and snRNAs (small nuclear RNA) were all discovered at the dawn of molecular biology. These canonical ncRNAs play pivotal roles in fundamental processes of the Central Dogma including mRNA processing and translation, and as such, their functions and actions have been studied extensively. However, recent studies revealed that a much wider variety of ncRNA species are in fact expressed in eukaryotic cells. For instance, miRNAs (microRNAs), siRNAs (small interfering RNAs) and piRNAs (piwi-interacting RNAs) are tiny ncRNAs of 20–30 nucleotides discovered from the 1990’s onward. These small RNAs recognize their target mRNAs through base pairing and regulate the fundamental flow of the Central Dogma at post-transcriptional and transcriptional levels. More recently, transcriptome analyses have identified numerous long non-coding RNAs (lncRNAs) with diverse functions including epigenetic regulation. These newly discovered ncRNAs are thought to play essential roles in complex biological processes by dynamically and finely modulating gene expression. Yet, our knowledge on production and function of these ncRNA species is still very limited. We are challenging this new frontier of the RNA world by combining biochemistry, biophysics, and cellular and developmental biology.

http://www.iam.u-tokyo.ac.jp/tomari
Intra-University Cooperative Laboratories

Laboratory of Immunology and Infection Control

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【Key Words】 antibody, somatic hypermutation, gut microbiota, mucosal immunity

The immune response has evolved to protect us from pathogenic infectious agents and toxic foreign substances. In acquired immune response, antigen stimulation of B cells induces two distinct genetic alterations in the immunoglobulin (Ig) loci: somatic hypermutation (SHM) and class switch recombination (CSR), both of which require an enzyme, activation-induced cytidine deaminase (AID). After these processes, among diversified Ig repertoire, selected high-affinity Igs efficiently defend host. AID plays a crucial role in host defense but it introduces DNA cleavage into Ig loci and aberrantly into non-Ig loci causing lymphoma. Our aim is to answer ‘how AID’s activity targets Ig loci specifically’ using AID mutant protein and mutant knock-in mice and to understand the precise molecular mechanism of SHM and CSR.

Recently dysbiosis (gut commensal microbial imbalance) is frequently reported to be associated with illnesses such as inflammatory bowel disease (IBD), obesity, cancer, etc. We found that the high-affinity intestinal IgA produced by SHM is important to control non-pathogenic gut bacteria as well as pathogens. Our main question is how intestinal IgA recognizes and targets a huge variety of gut bacteria. We have isolated a useful monoclonal IgA to modulate gut microbiota leading to symbiosis (balanced host-microbial relationship in gut).

We aim at applying the findings of our basic research to practical medicine.

Major Research Topics

1. Mechanism of gut microbial regulation by intestinal IgA

We generated hybridomas from IgA producing cells in small intestine of wild type mice. We selected W27 monoclonal IgA as a best gut microbial modulator because of its strong binding ability specifically against colitogenic bacteria. We are analyzing the bacterial target molecule for W27 to control microbial community, and will elucidate the reason why IgA selects that target in the point of physiological view. We aim at the development of therapeutic W27 IgA antibody.

2. Molecular mechanism of SHM

We have found that a N-terminal mutant AID (G23S; glycine to serine mutation at the 23rd AA) showed defective SHM but relatively intact CSR both in vitro and in vivo, suggesting the N-terminus of AID may be the domain responsible for SHM-specific co-factor binding. Through the search of SHM-specific co-factor, we will understand how AID distinguishes SHM from CSR.

3. Search for IgA CSR inducer

Upon antigen stimulation B cells can undergo CSR to IgG, IgE or IgA isotype. However, what induces B cells to each isotype specifically is not completely understood. We focus on searching a novel IgA CSR inducer, which may drive IgA CSR instead of IgE CSR at mucosal surface, helping prevent allergy, as well as enhance the mucosal immunity.

Homepage address:
http://www.iam.u-tokyo.ac.jp/lab/shinkura/

High-affinity IgA produced through SHM is important to control gut microbiota
Laboratory of Structural Biology of Macromolecular Complexes does not recruit students for the academic year 2020

Laboratory of Structural Biology of Macromolecular Complexes

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Key Words: protein, structural analysis, ubiquitin, neuroscience, signal transduction

Biological macromolecules are folded to exert their specific functions. Therefore, three-dimensional structure determination is necessary to elucidate how the biological macromolecules work. X-ray crystallography is a powerful structure determination method in terms of resolution and applicable molecular weight. The mission of our laboratory is elucidation of regulatory mechanisms for molecular signaling and reactions inside or outside cells at atomic resolution by X-ray crystallography of biological macromolecular complexes. We further perform functional analyses using site-directed mutants in vitro and/or in vivo to support the principle of the complex formation and the functional mechanism which are revealed by the three-dimensional structure of the macromolecular complex.

Laboratory of Stem Cell Regulation

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Key Words: stem cell, liver, fibrosis, regeneration, cell death

Liver is a central organ for homeostasis by performing numerous functions such as metabolism, drug detoxification and production of plasma proteins. Liver is composed of hepatocytes and non-parenchymal cells that include endothelial cells, hepatic stellate cells (HSCs), biliary epithelial cells (BECs), blood cells and so on. During liver development, hepatoblasts proliferate and differentiate into both hepatocytes and BECs. Thus hepatoblasts are considered as liver stem/progenitor cells (LPCs) in the fetus. We have previously identified many cell surface markers for fetal liver cells and uncovered the cell-cell interactions regulating proliferation and differentiation of LPCs using flow-cytometric analysis, cell culture system and mutant mice. Meanwhile in adult liver, "oval cells" have been considered as LPCs contributing to regeneration when liver is severely damaged. Although the nature of oval cells remained unclear for a long time, we have identified two cell surface markers for oval cells, EpCAM and TROP2, and shed light on it by the use of a cell sorter and cell culture system. However, the precise mechanisms regulating LPCs in adult liver are poorly understood. We are trying to understand the mechanisms regulating LPCs in liver diseases from the perspective of cell-cell interactions. Among the newly identified LPC markers, we recently found some genes involved in inflammation, fibrosis and liver cancer. Currently, we are also investigating the relationship of LPCs with liver fibrosis and carcinogenesis.
The ubiquitin-proteasome system (UPS) plays a pivotal role in proteostasis and controls almost all of cellular functions by selective protein degradation. As the maintenance of protein homeostasis is essential to human health, dysfunction of the UPS due to stresses, age-associated changes, or gene mutations causes various diseases such as cancers, inflammation, and neurodegeneration. However, we do not yet know the overall principle of the ubiquitin signaling and decoding mechanisms, the proteasome, and mitophagy. We aim to elucidate the fundamental mechanisms of the ubiquitin code as well as proteasome function and to integrate it into pathophysiology, and then to develop therapeutic strategies for UPS-related diseases.

Research Projects

1. Proteasome Dynamics and Pathophysiology (Figure 1)
   The proteasome is a highly organized proteolytic machinery that degrades ubiquitylated proteins in an ATP-dependent manner. We have characterized the structure, assembly pathway, and substrate targeting mechanism of the proteasome. We also found that the proteasome dynamically changes its intracellular localization and its accessory proteins under various stresses to restore proteostasis. Currently, we are generating knock-in mice to visualize proteasome localization and activity to analyze physiological changes of the proteasome accompanying stress and aging. Furthermore, we have generated model mice of proteasomal gene mutation derived from patients with neurodevelopmental disorders. Using the mutant mice, we will elucidate the pathophysiology of the proteasome mutation at the whole-body level.

2. Deciphering the Ubiquitin Code (Figure 1)
   Different polyubiquitin chain linkages direct substrates to distinct pathways, as referred to as ‘ubiquitin code’. We have developed a highly sensitive MS/MS-based quantification method for ubiquitin chains. The method allows us to analyze linkage-type selectivity of ubiquitin decoder proteins at endogenous experimental setting. We recently identified the main pathway targeting the K48-linked ubiquitylated substrates for proteasomal degradation. We also identified more complexed ubiquitin chains branched at K48 and K63, which act as a unique coding signal to enhance NF-κB signaling. We are further analyzing the decoder proteins throughout the ubiquitin-mediated pathways to reveal the ubiquitin network.

3. Mechanisms of Mitophagy (Figure 2)
   Ubiquitin is also important for quality control of mitochondria. Mitochondria with decreased membrane potential show impairments in ATP synthesis and protein import into matrix. Such low quality mitochondria should be degraded, and thus are marked with ubiquitin for selective degradation in cells. A mitochondrial kinase PINK1 and a ubiquitin ligase (E3) Parkin are key factors in this mechanism. Interestingly, PINK1 and PARKIN are responsible genes for hereditary recessive Parkinson’s disease. We have focused on molecular functions of PINK1 and Parkin, and revealed that when the mitochondrial membrane potential decreased, PINK1 accumulates on damaged mitochondria, phosphorylates ubiquitin at Ser65, and the phosphorylated ubiquitin functions as an activator for E3 reaction of Parkin. Moreover, phosphorylated poly-ubiquitin chain catalyzed by PINK1 recruits Parkin to damaged mitochondria by functioning as a Parkin receptor. Consequently, trio of PINK1, Parkin, and phospho-ubiquitin rapidly tag outer membrane proteins on depolarized mitochondria with ubiquitin. The ubiquitin chain is also recognized by RABGEP1, and it directs the downstream Rab proteins, RAB5 and RAB7A, to damaged mitochondria for degradation by lysosomes. Impairment of the aforementioned process predisposes to familial PD. However, the detailed mechanisms how “Parkin ubiquitylates damaged mitochondria for degradation” remained unknown, and we are studying to elucidate the molecular mechanism of the system.
Precise duplication of genetic materials is central to the stable maintenance of genomes through generations. Defects in the genome copying processes would generate genomic instability which could ultimately result in various diseases including cancer. The goal of our studies is to understand the molecular basis of how huge genomes are accurately replicated and the precise copies of the genetic materials are inherited to the next generation. Three billion base pairs of the human genome (2 meter long) are replicated with almost no errors during the 6−8 hr time span of the cell cycle. This requires an extreme level of coordination of temporal and spatial arrangements of chromatin organization and signaling events for initiation of DNA replication (16).

We recently discovered novel and crucial roles of non-standard DNA structures in regulation of DNA replication and transcription. Notably, we found that G-quadruplex structures (Fig. 1), which are widely present on genomes (estimated to be at more than 370,000 locations on the human genome), regulate organization of chromatin architecture and initiation of DNA replication (Fig. 2; 9). Recent reports indicate crucial roles of these non-canonical DNA/RNA structures in diverse biological reactions as well as in pathogenesis of diseases. One of our major goals is to establish a novel principle of the genome by elucidating the fundamental and universal functions of G-quadruplex and other non-B type DNA structures in regulation of various genome functions. Through these efforts, we will also explore the possibility that mutations found in various diseases including cancer are related to alteration of these non-B DNA structures, which are likely to be essential components of genomes but somehow have been disregarded in the past.

Our other major projects include 1) Maintenance of genome integrity and its failure as a cause of diseases: molecular dissection of cellular responses to replication stress, a major trigger for oncogenesis, and elucidation of mechanisms by which stalled forks are processed and the genome is protected from various insults, to understand how the failure of this process leads to diseases and senescence (7,8,11). 2) Chromosome dynamics that determines cell fate and regulates cell proliferation: elucidation of mechanisms regulating temporal and spatial regulation of genome duplication as well as coordination of replication, repair, recombination and transcription (2,4,6,10,12,13). 3) Unraveling the universal mechanisms of origin firing and its regulation (genetic and enzymological studies using E.coli as a model). 4) DNA replication and development: understanding the roles of replication factors or replication timing regulation during development/ differentiation processes or during the functioning of various tissues and organs. We have recently found potential novel and critical roles of Cdc7 kinase in development of brain. 5) DNA replication as target of anti-cancer drugs: we have developed specific inhibitors of a replication factor as novel anti-cancer drug, and try to find a highly efficient and side-effect-free therapy for cancer patients by novel combination of reagents that modulate cell cycle.

To achieve these goals, we are using E.coli, fission yeast, ...
Inter-Institute Cooperative Laboratories

various mammalian cell lines, embryonic stem cells and model animals. We would like ultimately to apply the basic knowledge on the mechanisms of stable genome maintenance to the diagnosis and therapy of the relevant diseases including cancer.

We are recruiting highly motivated and interested individuals who are communicative and can share excitement with us in the laboratory. We have had students from many foreign countries including Korea, Malaysia, Taiwan, China, Canada, Italy, France, USA and Germany and have been excited to have many different cultures in our laboratory. Please feel free to contact us at any time through e-mail or by telephone.

Selected publications
8 Yang, C-C. et al. (2016) Nature Communications 7: 12135

[Key Words] mental illness, mind, brain, molecular biology, genome

Why is homo sapience suffered from mental illnesses? Numerous numbers of people in field of religion or philosophy had ever investigated the maze far past. Only three hundred years have passed since medical sciences involved in this theme. We are challenging to resolve the twister interwoven with brain and mind by using methods and tools of biology.

Functional psychiatric disease is the brain disorder causing emotional and thinking difficulty without any abnormal sings in electric encephalography or brain imaging. Schizophrenia is the major one of those as well as mood disorder.

We perform genomic and metabolome analysis using blood samples from patients with schizophrenia in order to reveal pathophysiology of the disease. We create animal and culture cell-based model utilizing genetic polymorphisms and aberrant metabolism seen in the patients.

Human iPS cells induced from a schizophrenic patient carrying the rare genetic variation were differentiated to neural cells to be analyzed for investigation of pathophysiology of the disease.

Schizophrenia is a common disease that the prevalence is around 1% of population at any region of the world. Why has schizophrenia survived natural selection during human evolution? We are also seeking answer of the question by using our models of animals and culture cells.

Ego-function such as self-identity is also disturbed in patients with schizophrenia. We challenge to reveal ego and self-consciousness, the fields that had ever been investigated by religion or philosophy far past, by using tools and methods of molecular biology.

Oxidative stress is a central mediator of advanced glycation end product (AGE) formation, and pyridoxamine [vitamin (vit)B6] (biosynthesized from pyridoxal in vivo) is known to detoxify reactive carbonyl compounds (RCOs) via carbonyl-amine chemistry. Cellular removal of AGES hinges largely upon the activity of the zinc metalloenzyme glyoxalase I (GLO1). We detected idiopathic carbonyl stress in a subpopulation of schizophrenia. We first found an interesting case carrying genetic defect of glyoxalase
1 (GLO1) that increased AGES and decreased vitamin B6 since GLO1 detoxifies AGES and vitamin B6 is carbonyl scavenger. We obtained 20% of patients showing carbonyl stress by the manner expanding concept of the case over the general schizophrenic patients. This manner can resolve the problem of research on schizophrenia derived from the heterogeneity of the disease. Genetic defect of GLO1 contributes to the stress by 5 times higher risk compared to that of intact gene. AGES level was significantly correlated with negative symptoms of the patients. Pyridoxamine, active vitamin B6, could be the first medicine for negative symptoms of schizophrenia as most of the antipsychotic medicines are not effective for negative symptoms. We here present unique report of resolution of research difficulty due to heterogeneity of schizophrenia and possible discovery of the drug for negative symptoms of the disease.

http://www.igakuken.or.jp/schizo-dep/

References

Laboratory of Functional Biomolecules Engineering
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[Key Words] protein engineering, evoloutional molecular engineering, synthetic biology, biologics, therapeutic proteins

The excess of imports over exports of pharmaceutical products exceeds 2 trillion yen in Japan. Thus, most of national medical expenses finally flow abroad. This unfavorable balance of trade in medical economy must be solved so that such an expenditure leads, for example, new capital spending and creates the healthy employment. Therefore, the achievement of the pharmaceutical products with 'Japanese flag' through the domestic innovation in drug development and manufacture, especially for biologics, is demanded among other things. Hence we aim at the construction of fundamental technologies to contribute to innovative development and manufacture for biologics, and push forward a research of protein engineering and synthetic biology with the both theoretical and experimental approaches.

As concrete subjects, we are conducting the following theme: analysis of the molecular evolution of proteins using a cross profiling method that is the computational technique developed by us, development of designing software for an artificial protein based on the energy landscape sampling, synthesis of artificial proteins with novel structure and high function by evoloutional molecular engineering method, engineering yeast cells having a synthetic genetic circuit for drug development screening, analysis of the tolerance acquisition mechanism of drug-resistant genes, development of the pharmacokinetics improvement technology of biologics, stabilization of pharmaceutical protein using post-translation modification mechanism, construction of the library for screening drug-like molecules having a non-immunoglobulin scaffold, and advancement of the quality control technology for biologics using the artificial affinity protein. Through these, we aim at the holistic understanding of biological system in association with evolution and the offer of valuable industrial applied seeds of engineering. We welcome every person who wants to spend his or her student life in the atmosphere of National Institute which is different from that of universities. Please refer to a homepage for the details.

http://unit.aist.go.jp/biomed-ri/biomed-mcb/ci/honda_lab/

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[Key Words] evoloutional molecular engineering, metagenomics, ribosome engineering, synthetic biology, white biotechnology

Research in my group focuses on (i) functional metagenomic, (ii) evolutionary engineering of enzymes and (iii)
ribosome engineering. These technologies are integrated to develop microorganisms (mostly Escherichia coli) to diversify or improve microbial functions.

**Functional metagenomics.** It is known that more than 99% of microorganisms are thought to be unculturable or difficult to culture in a laboratory using standard cultivation methods. We apply functional metagenomics approach to screen for industrially relevant enzyme-coding genes that are otherwise difficult to be discovered.


**Evolutionary engineering of enzymes.** Enzymes are environmentally friendly biocatalysts that are widely used in modern life. One roadblock to more widespread use of enzymes in industry is their lack of stability under non-native conditions, e.g., extremes of pH, temperature, and ionic strength that are common to industrial bioprocesses. This problem can be partly solved by genetically modifying the protein via rational design or directed evolution. Such protein engineering may also improve other enzymatic properties (e.g., enhanced substrate specificity, expression level, and reduced product inhibition, etc.) that are crucial to industrial bioprocesses. We develop various genetic engineering techniques that are valuable for directed evolution and apply them for improving enzyme’s functions.


**Ribosome engineering.** The ribosome is an extremely complex molecule in its structure and function. Because of this complexity, it was considered that the molecule is difficult to engineer. Recently, we have shown that ribosome can be modified for its function by replacing one of the central components 16S rRNA. We apply this technique to address the question on the robustness of life (or ribosome) and to use thus engineered organisms for industrial applications.


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**Key Words** Chronobiology, Biological clock, Circadian rhythm, Chrono-nutrition, Sleep

Endogenous oscillators control the variety of physiological and behavioral circadian rhythms of almost all life forms from bacteria to humans. The suprachiasmatic nucleus (SCN) is the master circadian pacemaker that controls most physical circadian rhythms such as sleep/wake cycles, body temperature, blood pressure, heart rate, hormonal secretion and metabolism, as well as behavior in mammals. Numerous studies at the molecular level have suggested that the circadian oscillator in the SCN is driven by negative feedback loops consisting of the periodic expression of clock genes. Studies of clock genes in mammals have implied that oscillatory mechanisms function in various peripheral tissues such as the heart, lung, liver, kidney, and circulating blood cells, and that they are entrained to the SCN. Although the peripheral oscillators seem to play an important role in regulating various physiological functions, the circadian oscillatory mechanism in peripheral tissues remains vague. We are trying to understand the circadian regulation system in the organism at the molecular levels.

Recent studies on the clock genes reveal the relationships between the circadian clock and the appearance or symptom of various diseases. Moreover, increases in the sleep disorders, depression, and the neurosis etc. are also thought to be associated with the circadian clock disturb in the 24 hours society. Development of a novel treatment method through a circadian clock regulation seems to become possible, because strong connections exist between the circadian clock disruption and the metabolic disorders under various diseases. We are aiming to pay attention to not only the contribution to the time-dependent medical treatment and the chronopharmacology fields but also the relationships between the lifestyle (especially, feeding habit and mental stress) and circadian clocks at a molecular level, and to contribute from a preventive viewpoint to the public health medical treatment.

1) Molecular mechanisms of the circadian rhythm generation by the biological clock in culture cells to animals.
2) Search for functional molecules that potentially regulate the circadian clock.
3) Relationships between the circadian clock and various diseases such as metabolic diseases (diabetes, obesity, and thrombosis), cancer, sleep disorders, depression, and other mental stress.

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【Key Words】bio-standards, bio-measurement technogoly, nucleic acid related enzyme

We develop novel bioanalytical technologies for the characterization of nucleic acids and proteins. Further, we are working with biomolecule standard materials and contributing to biotechnology standardization. We aim toward the industrial application of the developed technologies in collaboration with private companies. Our laboratory is an environment where you can experience research work and obtain knowledge regarding industrial applications and standardization techniques.

Development and standardization of bioanalytical methods.

We develop standard materials for the validation and evaluation of bioanalytical methods. These standard materials are used in medical engineering and genetic testing fields. In these fields, non-SI-traceable methods are used to determine the amount of nucleic acids and proteins. In order to overcome such situations, our laboratory is trying to use digital PCR and fluorescence correlation spectroscopy, which can directly quantify the number of biomolecules such as nucleic acids and proteins, to establish SI-traceable methods. Moreover, the development and evaluation of nucleic acid reference material are conducted in our laboratories and we are standardizing bioanalytical methods to facilitate the global use of biotechnology in many fields. To facilitate the standardization of biotechnology, we have constructed a framework for cooperation with domestic industrial bodies and foreign governmental/research institutes.

Development of drug-screening techniques targeting nucleic-acid-related enzymes.

Nucleic-acid-related enzymes such as helicase, nuclease, polymerase, and ligase are indispensable for all organisms. These enzymes play vital roles in the cell life cycle of all organisms and it is important to elucidate the mechanisms underlying their effects. We focus on the toxin-antitoxin (TA) systems, a nucleic-acid-related enzyme that is widely conserved among microorganisms. It is known that toxin molecules can cause growth arrest and death of microorganisms under stress conditions. Thus, the TA system is considered to be a potential drug target. We are conducting 1) expression and purification of toxin/antitoxin proteins and 2) development of screening methods for functional molecules that potentially regulate TA systems.

We welcome students who are interested in the development of bioanalytical technology, international standards for biotechnology, and the unique TA systems in microorganisms. We promise that you will have an excellent experience with us.

Laboratory of RNA Systems Biology (RIKEN)

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【Key Words】RNA, translation, ribosome, next-generation sequencer, biochemistry, bioinformatics, ribosome profiling

Since Nobel prize laureate Francis Crick has proposed in 1950s, the central dogma of life: DNA makes RNA makes protein, has been most basic principle in life. We are investigating "translation", which lies at the core of central dogma, focusing how translation is control and how its control impacts on life, by following two major approaches.

Analysis with Next-Generation Sequencer

Recent development of next-generation deep sequencer allows us to identify and measure the RNA in cells. Using
this technology, we are using “ribosome profiling”, which allows one to survey which RNAs are translated and which codons are decoded by ribosome, among transcriptome comprehensively. Indeed, this technique is revolutionizing our understanding of translation dynamics in cells.

Simultaneously, we also use the other deep-sequencing based technologies to investigate RNA-protein interaction, which regulates translation. Combining those techniques, we tackle to reveal ternary relationship among RNA, RNA-binding protein, and translation.

**Classical Biochemical Methods toward detailed mechanism**

Translation is complicated and multistep reaction. Simultaneously, those steps are targets of regulation. To understand the mechanism of translation control, we need to dissect the reaction into fundamental processes. We used conventional but super powerful biochemistry to address molecular mechanism of RNA and its translation.

Our approaches encourage ones to learn both wet experiment and dry analysis. Anybody is welcome to stop by our lab anytime. Let’s tackle to the mystery of RNA and translation together!

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**Laboratory of Molecular Target Therapy of Cancer**

(The Cancer Chemotherapy Center of Japanese Foundation for Cancer Research)

Research on molecular target therapy of cancer has come to play a central role in anticancer drug development. As the clinically launched molecular targeting drugs have proved themselves more effective and relatively safer than conventional anticancer drugs, expectation to molecular targeting drugs is growing much bigger than ever. **Laboratory of Molecular Target Therapy of Cancer** aims to develop new molecular cancer therapeutics. This **Laboratory** consists of three independent labs, which are investigating mechanisms of cancer metastasis and anticancer drug resistance (Fujita lab), cellular adaptation to tumor microenvironment (Tomida lab), and telomere maintenance and cancer stemness (Seimiya lab), respectively. Based on these basic researches, they are also conducting applied researches for new drug development.

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Tumor metastasis, drug resistance, and development of new therapies.

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**[Key Words]** Drug Resistance, Tumor Metastasis, Cancer Stem Cell, Tumor Evolution, Immuno-Oncology

Although cancer treatments have gradually improved during past decades, we are still facing problems to surmount in prevention and therapy of cancers. Recent advances in molecular-based understanding of cell proliferation have provided the rationale for the molecular-targeted therapy to control cancer. The aim of Fujita’s Lab is to identify possible targets, to clarify the function of molecular targets, and ultimately to develop effective molecular targeted therapies of cancer. For this purpose, we are investigating
the molecular mechanisms of podoplanin-induced tumor metastasis, resistance to molecular-targeted drugs, and stemness in cancer cells. In addition, we are developing podoplanin-targeted neutralizing antibodies and small compounds for clinical applications.

(\url{http://www.jfcr.or.jp/english/chemotherapy/department/fundamental/index.html})

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**[Key Words]** Tumor Microenvironment, Drug Discovery, Tumor Metabolism, Unfolded Protein Response, Autophagy

Cancer cells in solid tumors are often surrounded by the stressful microenvironment, such as hypoxia (low oxygen) and low glucose, due to insufficient blood supply. The stressful microenvironment is thought to be a major cause of tumor progression and chemotherapy resistance. However, such stress conditions are not observed in normal tissue, and therefore, can be exploited for selective killing of tumor cells. To identify new molecular targets, we are studying the molecular mechanisms of the cellular adaptive response to microenvironmental stress, by using the genome technologies. Specifically, we are interested in unfolded protein response, hypoxic response, glucose metabolism, autophagy and epigenetic regulation. We are also studying inhibitors of the adaptive response and their mechanisms of action to develop a new class of molecular cancer therapeutics.

(\url{http://www.jfcr.or.jp/english/chemotherapy/department/genome/index.html})

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**[Key Words]** Molecular Target, Drug Discovery, Telomere, G-quadruplex, Cancer Stem Cell

Unusual maintenance of chromosome ends, telomeres, supports infinite cancer cell growth. This system will also support so-called cancer stem cells, which contribute to initiation, metastasis, and recurrence of the disease. We are investigating the molecular mechanisms for telomere maintenance, cell immortality, and cancer stemness. Based on these basic researches, we are also developing druggable seeds. First, we are developing telomere-targeting drugs, such as G-quadruplex ligands, which preferentially attack glioma stem cells. Second, we are developing inhibitors for the poly (ADP-ribose) polymerase called tankyrase. This enzyme promotes telomere elongation by telomerase and Wnt/\(\beta\)-catenin signaling in cancer. Third, employing functional genomics and comprehensive gene expression analysis, we are pursuing therapeutic targets of cancer stem cells.

(\url{http://www.jfcr.or.jp/english/chemotherapy/department/molecular_biotherapy/index.html})
The Biomedical Innovation Course
Introduction to the Biomedical Innovation Course

In the field of medical science, new research outcomes are sprouting continuously, and we regard the whole attempt to combine these with other scientific and technological achievements to provide society with new medical solutions as "medical innovation." Medical innovation includes all activities from basic research through to actual utilizations in medical settings, and re-evaluation their effectiveness and safety.

In order to design these activities, it is important to train researchers to have a bird’s-eye view of multiple aspects including bioethics / medical ethics, intellectual property, industry-university collaboration, technical standards, regulation, business, science and technology policy, and health policy. Basic science researchers in the field of medical and life sciences are required to understand the social mechanisms and their tasks in developing the results of advanced science into medical and industrial applications. In the biomedical innovation course, we aim to develop human resources that contribute to medical innovation from aspects of both education and social science research.

<Curriculum>

In our course, we aim to provide life science graduate students with knowledge that is essential for researchers in understanding social issues both inside and outside their majors through lectures and exercises. We especially focus on providing the following basic knowledge and skills that are essential regardless of whether the students plan to work in the academia, companies or public agencies in the future:
1) Research ethics and medical ethics
2) Intellectual property
3) Analysis and design of medical innovation by framework thinking
4) Policies related to medical science

In the advanced curriculum, students will train in practical exercises such as writing patent claims for bio-intellectual properties, conducting bibio-metric analyses for overlooking research fields of their own interests (data mining of papers), furthering their knowledge on advanced policy studies concerning medical science, learning about the R&D activities of various companies, and acquiring knowledge of how to design university-originated start-ups.

<Research Activities on Social Science>

Graduate students belonging to laboratories of the Biomedical Innovation Courses conduct "social scientific research" on medical innovation. We welcome students with various backgrounds regardless of their past majors. Graduate students with natural science backgrounds who have no experience in social science will receive an introductory education when entering social science field; basic training is carried out in the first half year to understand "What is social-scientific thinking?"

Currently, the biomedical innovation course consists of a core laboratory and two collaborative laboratories (intra-university cooperation). For detailed research contents, please find the activities of each laboratory in later pages.

Characteristic to the social science field, there are flexibilities in selecting research topics or approaches in research activities that convert social problems occurring in medical care and life science to "research themes" and verify through social scientific approaches, knowledge and experience as a working adult are also beneficial. Although our faculty does not provide a special selection for adult student applicants, administrative considerations will be made so that adult students may commit to research while working. Currently, a large number of adult students are enrolled and participate in their research part-time.
Laboratory of Bio Innovation Policy

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[Key Words] Innovation Policy, Intellectual Policy, Technology Standard, Regulation

In our laboratory, we conduct social scientific research on innovation in life science and medicine. All research subjects of the students fall within this category. The theme selection is based on the student’s autonomy. The student, mentors and lab members work together to reconstruct the “vague awareness of the issue” of the student as “Research Questions” to establish the theme as something acceptable as a thesis by thoroughly examining the backgrounds and methods. An introduction of the research areas is as follows (for more detailed examples of themes, please refer to our homepage).

Regarding the efforts to make use of intellectual properties for the development of industries in the field of life science, the key conundrum is the system design; how should we design a value chain of the “National Innovation System” that would connect the various stakeholders in basic research and development of products together? Beyond empirical case studies, a new framework is required for effective IP strategies, technology transfer systems, translational researches, regulatory designs, corporate strategies, and science & technology policies in order to link research outcomes to industries. Based on these perceptions, we realize the importance to readdress the basic question of how innovation itself could or should be measured. Furthermore, in order to plan future innovation policies and corporate strategies, we believe that it is essential to analyze the relationships or interactions between subjects that are responsible for innovation activities; organizations and institutions; innovators and regulators; innovators and users.

Researches in our lab involves the three following areas:

(1) Knowledge Management (KM) in the life science field

Knowledge Management is the basis for discussing intellectual property strategies, corporate strategies, and science & technology policies in the field of life science. To give an example of our research in this area, we have studied the relationship between products and patents (Product-Patent Linkage) in the pharmaceutical field, and an empirical analysis has been conducted on the life cycle management (LCM) of drugs by testing combinations of patent strategies and regulatory strategies. We have also generalized the results by modeling and analyzing the interaction between corporate knowledge managements and science & technology policies by utilizing knowledge cycles in other fields such as genetic engineering. The overall aim in this area is to develop new and workable “knowledge management cycles” for facilitating the utilization of research outcomes.

(2) Measurement of Medical Innovation (MMI)

Measurement of Medical Innovation is a research area aimed at grasping the actual state of innovation in the advanced medical field. As a means of conducting empirical analyses of patent strategies, industry-academia collaborations, and corporate strategies, we use patent-metrics and bibliometrics utilizing patent data bases and literature data bases) with a focus on specific technologies, products or companies. We aim to empirically analyze innovation activities through developing methods for measuring R&D activities. In the current age of analytics, the need to establish or introduce various data-scientific methods for the acquisition and analysis of data is significant. Our laboratory conducts collaborative researches with data scientists in order to increase the efficiency and validity of our research. The data generated in advanced medicine includes research data on papers, patents, various databases, regulatory documents (e.g. guideline documents and documents generated in the process of reviewing/approving medical products), real world data, et cetera. Although we have experienced great improvement in data access over the years, the development of analytical frameworks and analytical models has been slow to catch up (i.e. we still need a lot of trial-and-errors about what and how we should analyze in order to achieve the intelligence we need). By combining orthodox and unique measurements, we work on data-oriented measurements of innovation.

(3) The National Innovation System (NIS)

We are conducting research on institutions/organizations, industry-academia cooperation, regulation, technical standards, science & technology policies which are all part of the National Innovation System. For example, technical standards and regulations need to be developed timely and efficiently for newly emerging science & technology; if not, they may become obstacles to practical applications, and may bestow direct and negative impacts on industrial competitiveness.

In our laboratory, we regard regulatory systems as a critical subject in the NIS. We have redefined regulatory science as policy process of regulation, and have conducted analyses on the interactions between innovation and regulation. We are currently conducting research on the relationship between technology forecasting activities and the establishment of regulatory guidelines/technical standards; the composition process of technical standards/regulatory guidelines; the relationship between technical standards and regulations; the choice of regulatory paths in medical products and services; international comparison of regulations; and boundary organizations responsible for composition of rules.
Intra-University Cooperative Laboratories

Laboratory of Public Policy

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【Key Words】bioethics, research ethics, medical law, public policy, medical sociology

Laboratory of Advanced Medicine Promotion

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【Key Words】biostatistics, medical research design, big data, clinical trials, clinical epidemiology, epigenetics, bioinformatics, DNA methylation, machine learning, social medicine

Research activities in our laboratory: A lot of works are published as collaborative research by being in charge of research design and statistical analysis in clinical trials or clinical epidemiological research. Analyzing confounding and correlations between variables, creating prediction models, we always try to find true relationships by finding and correcting pseudo correlation, and create statistical models useful for medicine and society. We are also involved in environmental epidemiology research and epidemiological research with multi-omics data, and incorporates analyses using machine learning methods such as LASSO and Random Forest in addition to the basic analysis method used in biostatistics. This makes it possible to predict more accurately than conventional methods while maintaining simplicity. We are attempting to predict the onset of future diseases for specific diseases from various environmental pollutants and metabolic products in the blood.

Another important interest of us is epigenetics. In particular, we have studied DNA methylation, using large-scale data. In a recent study, integrating DNA methylation microarray data, gene expression arrays data, and micrRNA expression data, we summarized gene expression control system using statistical models, and reported epigenetic changes and its importance in cancer tissues (Nojima et. al, Mol Cancer 2016). Moreover, we are also involved in social medicine research based on questionnaire survey (e.g. nursing research field). We always try to provide easy-to-understand analyses for collaborators and readers of publications by using simple model, and promote new medical development from the standpoint of “statistics”.

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The Computational Biology Group
Goals of the Computational Biology Group

Computational biology is a cutting-edge field, a fusion of life science and information science. The Computational Biology Group is dedicated to promoting a wide range of research that aims at understanding life as a system, and toward fostering the talent that carries this field into the future.

Computational biology has come to be widely recognized as a field that is indispensable in uncovering the secrets behind biological phenomena. Methods and approaches from the information sciences allow not only genomic sequences but also a wide variety of biological data such as gene expression, biomolecular interactions, biomolecular structures, biological pathways, genetic and cellular networks, and ecosystem structures to be analyzed. Computational biology is leading to new understandings and discoveries in the life sciences, setting now a global trend.

One of the primary driving forces behind this trend is the revolutionary advancement in the comprehensive measurement of life science data, the so-called “omics” fields of genomics, proteomics, transcriptomics, metabolomics, epigenomics, and metagenomics. Also attracting increased attention is systems biology, which uses mathematical models and quantitative experiments to tie together the components of life with the dynamic behavior of biological phenomena.

These fields exist in close association with one another, and cannot be easily separated. Our group’s goal is to afford system-based understanding of biological phenomena through using cutting-edge information technology and experimental techniques, as well as to nurture the talent who employ any technology for groundbreaking work in the life sciences.

Our curriculum is designed so that students with backgrounds not only in biology and information science, but also in areas such as physics, chemistry, mathematics, and engineering can study computational biology. In addition to core courses, our department offers coursework performed in cooperation with the University of Tokyo’s Institute of Medical Science, as well as courses at AIST and RIKEN. With these distinguished faculty members, we offer a balance of coursework related to both information science and life science. Twice in a row the Ministry of Education, Culture, Sports, Science, and Technology has selected us in its Center of Excellence programs (once for our 2004–2008 program, "Elucidation of Language Structure and Semantics behind Genome and Life Systems," and once for our 2009–2013 program, "Deciphering Biosphere from Genome Big Bang"), marking our educational program as one of the world’s best.

Entering into the 21st century, computational biology is moving beyond just uncovering mysteries of biological phenomena, toward becoming a principal method in applied researches in the life sciences. Topics to be addressed include medical applications with the aim of personalized medicine, and examination of genomes of microbes from places as diverse as extreme environments to the human gut, for finding solutions to health, environmental, and energy problems.

We eagerly look forward to the participation of students who bring fresh ideas and talents to our field.
**DNA, one of the fundamental building blocks of life, shapes its sequences and chromatin structures dynamically during evolution and cell differentiation. These changes occur on a broad scale:**

- Large-scale reorganizations of chromosomes over hundreds of millions of years
- Relatively small genetic variations after speciation
- DNA modifications during development and differentiation

Such variations enhance gene functionality and bring about diversity in organisms, but are also factors for disease. It is therefore vital to investigate the details of the nature of immutable and invariant DNA.

Collecting and analyzing massive amounts of DNA data is a promising approach to understand these fundamental questions, demanding a computationally efficient method of analyzing numerous data rapidly with a high accuracy.

**Large-scale chromosomal changes**

We have studied chromosome evolution in vertebrates and insects over the past 600 million to 1 billion years, comparing the DNA of humans, chickens, killifish, and puffer fish. We confirmed the Ohno’s conjecture (1970) on the two rounds of whole genome duplications in early vertebrates (Fig. 1).

**Personal DNA analysis for disease-associated genes**

On scales of decades to millions of years, we see relatively small genetic variations, such as substitutions, insertions, and deletions. These contribute to phenotype differentiation, and in turn to issues such as genetic diseases. Decoding individual genomes allows us to detect these changes; however, reading the approximately 3 billion base pairs that constitute human DNA is no trivial task. We have developed a system using ultra high-speed sequencers and parallel processing computers to analyze variations in one person’s DNA in about a day on average. Aided by this technology, we are working with the University of Tokyo Hospital to search for genes and genomic regions that are specific to ethnic Japanese, developing a DNA reference of a typical Japanese. We are also looking for genetic changes linked to brain and other diseases.

**Chromatin structure, DNA methylation, and genetic variation**

DNA is wrapped around histone octamers, bundled tightly enough to fit within a 10 μm nucleus, though human DNA is nearly 2m long if stretched out. This leads to some fundamental questions: How is it that such a three dimensional structure doesn’t become tangled when it is copied and distributed into two nuclei? If two genes that work in concert are encoded far apart, does this imply that they come into proximity after DNA folding?
One interesting phenomenon that we have reported on with regard to chromatin structure is ~200bp periodicity of genetic variations such as single nucleotide variations and short indels downstream of transcription initiation sites and its association with nucleosome positioning (Fig. 2). In vertebrates, the methylated C in CpG is highly mutated into a T. We have observed that mutations are more likely to arise in areas around methylated Cs (Fig. 3)—further proof that the mechanism inducing changes in DNA is shrouded in mysteries.

**Image analysis of gene-disrupted strains**

Once the DNA of a species is sequenced, it becomes possible to modify DNA so that a given gene is knocked out or forcibly expressed. Disrupting essential genes is generally lethal, but knocking out non-essential genes results in slight changes to phenotype. Analysis of fluorescent microscopic images of disruptants of non-essential genes makes it possible to treat morphological variations as quantitative traits. Our image analysis server is available through WWW (Fig. 4).
Labratory of Genome Informatics

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【Key Words】 Genome Informatics, RNA informatics, Sequence Design, Stochastic Model

The research goal of Asai-lab is understanding life from a viewpoint of information science. We put our basis on mathematical theory, especially stochastic models, to develop new algorithms and software.

Genome Information Analysis

Genome sequences are not merely simple strings, but hidden behind them are real molecules with real structures that hold information about complicated biological mechanisms. 'Meanings' are hidden behind the 'visible' sequences. Recent research has revealed that genomes are dynamically controlled — for instance there are relations between cell differentiation and the structural change of genome.

We have been developing software for genome sequence analysis, especially for large amount of data from high-throughput sequencers, in order to extract information based on stochastic framework.

RNA informatics

Since the discovery of RNA interference and micro RNAs, a number of functional non-coding RNAs have been found. They are transcribed but not translated to proteins, play various roles in cells, not limited to repression of translation.

We have developed theories and leading software in the field of RNA informatics, such as CentroidFold, one of the most accurate tools for the secondary structures prediction of RNAs (http://www.ncrna.org). The probability of a specific RNA secondary structure, even if it is the most stable structure, is astronomically small, because RNA structures undergo thermodynamic fluctuation. We are developing various methods to extract useful information from the probability distribution of the RNA secondary structures.

Recently, it has been shown that the modification of genomic DNA is essential to the regulation of processes such as cell differentiation. The modification plays important role also in RNA. In order to predict the structures of RNAs which include modified bases, we are trying to identify the energy parameters of modified bases by combining MD simulations and melting temperature scaling experiments. The results will be implemented to various analysis tools of RNA secondary structures.

Genome Sequence Design

We are studying the design of genome sequences for efficient production of target materials by micro-organisms. We have designed clusters of genes of anti-body in the AMED project. In the NEDO project, we are trying to optimize the DNA sequence for efficient production by machine learning, based on a large number of combinations of DNA sequences experimentally produced. In such a design, the efficiency of the translation of mRNA as well as that of transcription, should be optimized to improve productivity. This area has an abundance of wide-ranging research subjects, such as the relationship between the efficiency of translation and the structure of mRNA.

Privacy Preserving Calculations

From large amount of data, including DNA sequences of personal genomes, we expect that valuable information can be extracted using AI technologies such as machine learning. Recently privacy data mining technologies, which safely process sensitive data in the encrypted form, have become important. In CREST project, we develop a general framework of delegate calculation that enables easy implementation of various privacy preserving services.

Research Projects

KAKENHI Innovative Area, "Advanced Genome Analysis Platform"
KAKENHI Kiban(A), "RNA informatics for Epitranscriptome analyses"
NEDO P16009, DNA design
CREST "General framework of safe privacy preserving data processing agent"

Research environment

We respect autonomy of the members, and develop our research through discussions. Students can develop their research depending on their ability while learning mathematical theory and programming. It should be also noted that a student lacking biological knowledge can find suitable research subject.

We collaborate with Artificial Intelligence Research Center (AIRC), AIST, where the researchers and students of Asai-lab are studying. We can communicate with the researchers in AIRC without barriers between the labs and participate in seminars and research discussions.
It is still remaining mostly unknown which of the variations or mutations occurring in the human genomes contribute to etiology of diseases. We employ versatile applications of next generation sequencing technologies, such as Whole Genome/Exome Seq, RNA Seq, ChIP Seq and Bisulfite Seq to understand the biological meaning of the identified genomic mutations. 

Advent of the next generation sequencing technologies has enabled us to analyze thousands of human genomes. Consequently, a rapidly increasing number of mutations have been identified and associated with various diseases, such as cancers. However, it still remains elusive how these mutations invoke changes in epigenome, transcriptome, or proteome functions. For the diseases as exemplified below, we are conducting an integrative analysis of multi-omics data, namely DNA methylation, histone modifications, binding patterns of transcriptional regulatory factors and gene expression patterns. Furthermore, to complement currently undetectable layers of transcriptome regulations, we are developing novel methods, based on the latest genomic technologies, such as next generation sequencing, single cell analysis and single molecule sequencing technologies. Also, as one of the representative sequencing centers in Japan, we are distributing the next sequencing platforms and the related technologies widely to the research community. 

**Theme 1 Cancer genomics**

As collaboration with several hospitals and laboratories of clinical sequencing, we have analyzed the mutation patterns of various types of cancers, including lung, colon and stomach cancers. We have found that the mutated genes are mostly distinct depending on patients and cancer types, with rare exceptions of the TP53, KRAS and EGFR genes. With rare mutual overlaps, it is difficult to statistically discriminate so-called driver mutations, which serve as a direct driving force to carcinogenesis, from so-called passenger mutations, which occur in the human genomes as a consequence of chromosomal instability in cancers, thus, have no functional relevance. Moreover, in spite of supposed importance, almost no clue has been obtained for the mutations which invoke abnormal transcriptional regulations. To address these issues, we have established an experimental system to collect genome, epigenome and transcriptome data from the same cellular material and have started the data production. By integrating such multi-omics data, we are investigating epigenomic and transcriptomic consequences of the genomic mutations.

**Theme 2 Technology development and modeling**

Recent genome-wide analyses have revealed that gene expression regulations, such as the regulations at transcriptional elongation, RNA logistic and RNA degradation, play no less important roles than transcriptional initiations. We are trying to develop a new method to evaluate the contribution from these factors, using the latest genome-related technologies. We have constructed an experimental system in which correlation between DNA mutations at every base position can be associated with promoter activities for thousands of genes simultaneously. Generated data is further processed to construct a model, using machine-learning and statistical inference technologies, to predict eventual transcript levels. We are also including the data obtained from the emerging technologies measuring post-transcriptional regulatory factors to the model. Eventually, we believe such a model should be essential to understand biological meaning of the genomic variations of regulatory roles in the humans.

**Theme 3 In field analysis of infectious diseases**

Frequently, behaviors of human immune systems in responds to pathogens are significantly different in field from those in laboratory conditions. We have a field base in Indonesia and are analyzing the mutual correlation between the host-pathogens at every omics layer, particularly focusing on malaria parasites.

**References**

Suzuki et al. Nucleic Acids Research. 2015  
Irie et al. Nucleic Acids Research. 2011  
Yamagishi et al. Genome Research. 2014
Our lab aims to develop novel algorithms to discover new knowledge from large and heterogeneous data. As a center of data-centric science in Japan, we collaborate with top researchers of different disciplines including life sciences, chemistry, pharmacology, material and environmental sciences. Students are expected to develop important data analysis skills that are indispensable in current scientific protocols.

**Multiple tests for combinatorial effects**

More than three transcription factors often work together to enable cells to respond to various signals. The detection of combinatorial regulation by multiple transcription factors, however, is not only computationally nontrivial but also extremely unlikely because of multiple testing correction. The exponential growth in the number of tests forces us to set a strict limit on the maximum arity. We developed a novel statistical test called LAMP (limitless-arity multiple testing procedure) [1]. LAMP counts the exact number of testable combinations and calibrates the Bonferroni factor to the smallest possible value. LAMP lists significant combinations without any limit, while the family-wise error rate is kept under the threshold. In the human breast cancer transcriptome, LAMP discovered statistically significant combinations of as many as eight binding motifs.

**Automatic design of molecules and materials**

Design of new molecules and materials are of scientific and industrial importance. We apply machine learning and artificial intelligence methods to accelerate the design of new molecules and materials. To this aim, we are developing new methods involving Bayesian optimization and Monte Carlo tree search. Recently our lab developed a python package COMBO [3] that automatically selects promising candidates for simulations and experiments.

**References**


Laboratory of Large-Scale Bioinformatics

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【Key Words】sequence algorithms, probabilistic models, genome evolution, genome regulation, repeats

This lab is based partly at the University of Tokyo in Kashiwa, and partly at AIST in Odaiba, central Tokyo.

Our ultimate aim is to decipher the functional and historical information in genome sequences. We do this using statistical models (such as hidden Markov models) and computational methods (such as enhanced suffix arrays and dynamic programming). A major approach is “the comparative method”, which is widely used in biology and philology to understand where things come from, and thus “what they are”. Another planned approach is to look for co-evolution, as a signal of interacting genomic loci.

One recent focus is characterization of genome rearrangements in evolution and disease. We recently published a new method that identifies rearranged orthologous regions in a statistically rigorous fashion [1]. This should help us to understand how genomes and genes have evolved.

Another interest is “simple sequences”, which occur in all genomes. Simple sequences evolve extremely rapidly, and thus contribute strongly to phenotypic variation and disease (e.g. Huntington’s disease). I developed a method to identify them, named tantan, which appears to capture them much better than other methods [2].

Collaborations
I collaborate with friends in many places: NCBI (USA), Waseda University (Japan), University of Paris VI (France), Leiden University (Netherlands), etc. The lab participates in the FANTOM project, which is a large international consortium [4]. Students joining the lab are welcome to take part in these collaborations, and especially to interact with other labs in Kashiwa and Odaiba.

Research environment
Lab members are encouraged to pursue their own original ideas. We learn from discussions and journal reading together with other labs. Students are welcome from all over the world, and will have a chance to learn Japanese or English, and experience a rich culture.

References
Core Laboratories

Laboratory of Biological Network Analysis

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【Key Words】Bioinformatics, Computational Biology, Artificial Intelligence, Machine Learning, Biological Science

Our laboratory is focusing on making biological discoveries through the application of statistical methods to genome-scale data such as genome sequences, microarray data, and next-generation sequencer data. We are also working on developing new probabilistic and mathematical tools that are necessary for such analysis.

Since the first successes in the 1990s, researchers have succeeded in decoding the full genome of thousands of species. The information generated from those efforts is not limited to genome sequences, but also includes other building blocks of life such as RNA, proteins, metabolites, and DNA modifications. However, integrated analysis of such extremely heterogeneous data has only just begun, and many problems await solutions. We are applying statistical techniques to detect faint signals in the noise that will lead to a deeper understanding of life.

Function and evolution of RNA structures

Various RNA molecules such as messenger RNA, transfer RNA, and micro RNA are involved in the expression of proteins. Most RNA molecules form secondary structures through base pairs such as A-U and C-G. The stabilizing energies of secondary structures are relatively large, and have a significant impact on the regulation and efficiency of gene expression. There exist very accurate models of RNA secondary structures that use a concept from the information sciences called stochastic context-free grammar, which allow for computer-based investigations of RNA structures. By intensively using such models, we are studying various biological processes involving RNA, such as molecular interactions of micro RNA and RNA-binding proteins, alternative splicing, and messenger RNA translation (Fig. 1). We are also investigating RNA structural evolution using genome sequences of human and vertebrate populations (Fig. 2).

Evolution of cancer genomes

Cancers are diseases in which cells multiply uncontrollably, and are often caused by accumulation of DNA mutations. In many types of cancer, each cell division causes various types of mutations to genome sequences. Since such changes in cancer genomes are similar to the genome evolution during speciation, we can use various evolutionary and genetic tools to study cancer progression. We are using tools from population genetics such as Markov processes and the coalescent theory to estimate growth of cancer tissues. We are seeking for methods that allow for computing the probabilities of cancer metastasis or recurrence from the estimated quantitative data.

Simulating embryonic development and cell differentiation

Embryonic development in animals begins with the cleavage of fertilized eggs, followed by gastrulation and mesoderm differentiation, which results in the formation of organs, bones, and muscles. Such macroscopic changes of animal morphology are precisely controlled through complex interactions between transcription networks and signaling molecules. However, the technologies for making predictions about those mechanisms from cell-level data such as transcription factor bindings and histone modifications are still in its infancy. We are developing methods that combine differential equations for embryonic development from mathematical biology with Bayesian analysis of gene regulatory networks from bioinformatics, in order to associate macroscopic stages of embryonic development with microscopic sequencing data. We are aiming to simulate animal developmental processes by using sequencing data.

Joint research and research partners

We perform our research in close association with the Computational Biology Research Center at the National Institute of Advanced Industrial Science and Technology.

Research at our lab

As we are a “dry” laboratory with no experimental facilities, we analyze public data and the experimental results of collaborating labs using computers, rather than generate our own experimental results.
Core Laboratories

Laboratory of High-performance Analysis System

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【Key Words】Genome Informatics, Genome Assembly, High-Performance Science, Distributed Parallel Programming

The International Human Genome Project started in 1990, spending 13 years and 3 billion US dollars to map the human genome of a single haploid (equivalent). Since then, the cost of DNA sequencing has been reduced by a factor of 3 million over the past two decades. In January 2014, Illumina announced a new DNA sequencer, HiSeq X Ten, that can decode the genomic sequence of one human genome at only about 1,000 US dollars. Imagine if we saw satellite images in Google Map via the Internet only 20 years after Christopher Columbus found America. We are seeing such a rapid technological advance in reality, being excited about what we will find from new technologies.

Furthermore, in October 2016 Oxford Nanopore announced a surprisingly improved version of the USB flash memory shaped DNA sequencer that cost 1,000 US dollars. It is portable and easy to use, so even amateur researchers can buy and use it, although Illumina HiSeq X Ten requires a several million US dollars for upfront, which hindered the amateur use completely. Oxford Nanopore also says they plan to release SmidgION, a DNA sequencer that can be used and attached with smartphone. They claim a single sequencing run would cost only tens of dollars.

Such rapid and drastic advancements in DNA sequencing technology affect not only to how we do research but also to our daily life. If I tried to add a camera to mobile phones in 1997, everyone might have thought I went crazy and I was doing a pointless thing, but no one would think so today. I believe that DNA sequencers will be used in a daily life in 2025 as smartphones with camera are today. We are seeing such a rapid advance in DNA sequencing, being excited about what we will find from new technologies.

New technologies, new algorithms

We are developing algorithms and software for new technologies in molecular biology such as PacBio Sequel, Oxford Nanopore MinION, 10X Chromium. More specifically, we are developing a variety of fundamental genome analysis software/algorithms for sequence alignment, genome assembly, genome comparison, graph genome analysis, construction of genetic maps, genotype caller, and so on.

Private cloud middleware for large-scale analysis of sequence data

The processing speed of computers improves slower than the growth of data generated by DNA sequencers. We need to address it in part by parallel computation, but it increases programming costs significantly. Previously, researchers in High Performance Computing (HPC) made efforts to efficiently use computational resources. It was totally fine for researchers to spend a few years to write efficient code that utilizes transistors in CPU. However, for sequence analysis in which we see a new problem setting every three months due to rapid improvements in technologies, it is pointless to optimizing code spending a few years.

In order to better explain the situation, we propose a new term ‘High Performance Science (HPS)’ in contrast to the traditional HPC. What we want to maximize is scientific knowledge we obtain, not the utilization of transistors in CPU. To this end, we are developing middleware (software that sits between users and the OS, allowing easy creation of applications) that will allow efficient utilization of parallel processing over huge datasets for rapid verification of hypothesis in life sciences.

Research at our lab

We have collaboration projects with other laboratories so that students are excited about real experimental data (if they wish) from recent technologies. We welcome foreign students with programming skills and interests in biology.
Intra-University Cooperative Laboratories

**Laboratory of Bioinformatics and Systems Biology**

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**Key Words** Systems biology, trans-omics, metabolism, diabetes

**Systems biology of cellular signaling**

Our research is aimed to the understanding of the features of signaling pathways and examining them as a type of “channel” for communication to the extracellular environment. In particular, we first proposed the concept of “temporal information coding,” which embed information to the time pattern of molecular activation. Since information processing is performed through the molecular interactions too complex to understand with conventional methods we therefore create models that replicate the behavior of signaling pathway by the cooperation and feedback between simulation models and the actual measurements of cell behavior (Fig. 1).

![Fig. 1 Strategy of Systems Biology](image)

**Information coding of signaling pathways**

1. **Insulin action**

Insulin is the only hormone that lowers blood sugar levels. Blood insulin concentration varies in temporal patterns and the physiological significance of this has been reported in the past, while the molecular mechanism is poorly understood. From the view point of “temporal information coding,” it is possible that information is encoded in these time patterns, and target organs responses are individually controlled in a time-dependent manner. Our research has hown that the information encoded in the insulin time pattern is multiplexed in the AKT time pattern, allowing downstream molecules to be individually controlled (Fig. 2). In the future we hope to perform animal experiments to give an *in vivo* demonstration of temporal information coding and to uncover the mechanism behind it. We also hope to improve our understanding of insulin’s actions by combining various layers of comprehensive measurement technologies to automatically detect signal pathways that straddle multiple hierarchies.

![Fig. 2 Temporal coding of insulin action](image)

2. **Mechanisms of cell fate determination**

Signal transduction networks including ERK elicit multiple cellular functions. One of the critical properties of the signal transduction system is that the same signaling networks can code multiple cellular functions. We have recently found that the distinct temporal coding of ERK signaling networks regulate cell growth and differentiation in PC12 cells in response to EGF and NGF. We are currently trying to explore the decoding mechanism of distinct temporal patterns of ERK activation via downstream molecular networks.

3. **Trans-omics of insulin action**

We explored signal flows of insulin, an important hormone for metabolic homeostasis. We reconstructed the static signal flow of insulin based on time-series phosphoproteome and metabolome data together with multiple databases and found where an insulin signal flowed through a global transomic network. We analysed the dynamic signal flow using kinetic modelling together with model selection and model reduction, and found when specific phosphorylation and allosteric regulation selectively control temporal patterns of metabolites. Thus, we demonstrate a global landscape for the signal flow of insulin, which reveals the large-scale mechanism of metabolic homeostasis.

Systems biology requires fundamental knowledge from a wide variety of fields, including the life sciences, physics, information science, and mathematics. We therefore do our
best to maintain a multidisciplinary research staff with highly diverse backgrounds.

Fig. 3 The large-scale trans-omic networks

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【Key Words】 genome information, miRNA, siRNA, thermodynamics, epitranscriptome

In the cells, RNA is transcribed from genomic DNA, and is translated into protein with specific biological function. Such principle information flow from DNA→RNA→protein is called as the central dogma. For many years, RNA has been considered to act as the simple carrier of genetic information from DNA to protein in the central dogma, but the recent researches focused on RNAs have revealed that RNAs are not simply an intermediary tool of information delivery; they instead serve many unique and important functions by themselves. RNAs which are not translated into proteins but function as RNAs are called non-coding RNAs (ncRNAs). We focused on the ncRNAs, especially on their genome-wide functions on the regulation of gene expression.

Mechanisms of genome-wide regulation of gene expression by non-coding RNAs

There are many different kinds of ncRNAs, from short double-stranded RNA with only about 20 bases to very long ones with tens of thousands, and they are involved in a wide variety of biological phenomena. In RNA silencing performed by microRNA and small interfering RNA (siRNA), both with approximately 20 bases each, the nucleotides approximately one-third of the full length of these small RNAs identify the target genes using the sequence complementarities, and suppress the expression of hundreds to thousands of messenger RNAs at once. Analyses related to such genome-wide regulations are important in ncRNA researches. We are performing such comprehensive studies by microarray or next generation sequencing analyses. We have also revealed that the thermodynamic stabilities in the microRNA duplex and microRNA-target RNA duplex can determine the extent of silencing efficacies (Fig. 1). We are working with the goal of using these molecular biological and physicochemical properties to learn about mechanisms for controlling genome-wide genetic expression, and better understand important biological phenomena.

Functional analysis of RNA binding proteins

RNA binding proteins are important proteins related to a wide variety of biological functions, including RNA silencing, target gene identification, RNA editing, and even immune system response to RNA viruses. We are working to learn how these proteins function, by using large-scale sequencing or microarray analyses to perform comprehensive identification of their binding regions and their effects on gene expression.

Analysis of gene networks using RNA interference

RNA silencing via siRNA is called RNA interference (RNAi), and has become one of the most important tools in modern functional genomics. Since RNAi does not damage genomic DNAs, its clinical applications are expected. However not only a target gene with complete complementarity to siRNA but also non-target genes with partially complementary
sequences are found to be suppressed in RNAi. By the mechanistic studies, we established target-specific RNAi procedure for suppressing only a single target gene without affecting the expression of non-target genes (Fig. 2). Such method has been applied for various studies, such as functional genomics, protection against virus infection, or clinical applications. Furthermore, we would like to hopeful apply such specific RNAi procedure for the analysis of gene network.

Laboratory of Bioinformatics and Systems Biology

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【Key Words】bioinformatics, genome evolution, ecosystem, metagenome, animal behavior

Providing new insights into life

Our laboratory aims at providing new insights into life through bioinformatic approaches.

Technological innovations in the life science domain have enabled us to obtain and analyze massive amount of data that can unveil the underlying principles of Life and its evolutionary history. While genomic data provide an overview of the history of life over hundreds of millions of years, other omic data illustrate how genomic sequences perform their functions about, for example, gene expression, regulation, and interactions. Pathway and network data represent diverse biological knowledge in a machine-understandable manner that permits large-scale computational analyses. Bioimaging and biologging data provide ways to quantitatively characterize phenotypes and behavior of organisms. Last but not least, metagenomic, ecogenomic, and environmental DNA data illustrate complex interactions between Life and environments.

To understand life, it is fundamentally important to integrate and analyze these data comprehensively, not partially. In this context, utilizing deep understanding of both biology and informatics, we aim to uncover new concepts, insights, and laws behind life systems.

Evolution of genomes and their functions

Genomic information reflects the long history from our ancient ancestors to the current day while also serving as the foundation of all biological activities. The analysis of genomic evolution is a scientific endeavor that aims at answering questions such as how Life has evolved from the common ancestor, and how the genomes and the biological systems they encode have been developed.

Transcriptomic data tell us about the identity and expression level of genes that exist within genomes, and metagenomic data provide a compositional view of complex microbial ecosystems. Both are treasure troves of information. By analyzing the dynamics between these omic datasets over various environmental conditions, we aim
to understand how Life responds to environmental changes and what kind of interactions and inter-relationships exist between them.

**Other frontiers of bioinformatics**

Bioimaging and biodogging data are important resources for quantitatively analyzing phenotypes and behavior of organisms. In our laboratory, new information technologies for analyzing those types of data are being developed. Other related research topics involve data visualization, text mining, and bibliographic analysis.

**Joining our laboratory as a graduate student**

We welcome students who are eager to learn and understand both biology and informatics and to conduct interdisciplinary researches. In particular, those who majored bioinformatics and/or were involved in research projects related to bioinformatics during their undergraduate or master courses, and aim at earning a Ph.D will be welcome. If you are interested in joining our laboratory, please send an email to PI first.

Notes: We have experience in accepting students from outside of Japan. Japanese language is not mandatory if you have enough English skills; however, a will to learn Japanese would be necessary because it makes you enjoy Japan more and many optional classes are held in Japanese. As the University of Tokyo provides Japanese language classes, we usually encourage colleagues from abroad to take them. You may obtain further information on our laboratory website.
Laboratory of Bioinformatics and Systems Biology

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Intra-University Cooperative Laboratories

Through the analysis of biomedical big data, we conduct research to better understand biological phenomena, e.g. immunity against, and to overcome, disease such as cancer. In the near future, it is expected that medical care will shift towards patient specific optimal therapies and drug dosages to treat and prevent disease. To achieve this, we apply data mining techniques to biomedical big data such as genomics, image, and clinical data accumulated at medical institutions, and determine the underlying causes of disease -cancer, common, and intractable ones. By reconstructing the multilayered biochemical network of organs and tissues, we can understand the disease mechanism as a whole. For example, by correlating the relationship between cancer and the surrounding microenvironment, such as immune response, we will be able to predict the response, side effects, and tolerance of different cancer treatments for each individual. In this way, we conduct research on biomedical science, making full use of state-of-the-art omic profiling technology, mathematics, and computational science.

Cancer Immunology Research

Recently, we analyzed the whole genome sequence of liver cancer cells from 300 patients and found a cluster with mutations within a novel cancer-related gene [1]. Patients in this cluster are less likely to have cancer recurrence after surgery and have good prognoses. We also found that the population characteristics of cancer cells and their relationships with microenvironments, such as immune response, are different across clusters. Cancer cells originally stem from our own cells, but are altered, and therefore, they are non-self. Our immune systems are always eliminating such cells, although the cancer cells are under constant change and escape. That is, the subsequent behaviors of cancer cells will differ depending on the characteristics of cancer cells as well as the microenvironments and treatments. In addition to understanding the mechanisms that will make these differences, we will construct a predictive model of treatment effect aiming for establishment of precision medicine to optimally treat each patient.

Analysis methodology with machine and deep learnings

Artificial intelligence includes machine learning and deep learning techniques as the backbone.

We research their ability to process not only images, but also non-image data, particularly omic data. They could be applied to analysis of image data such as pathological and biomolecular images, analysis of omics data, and integrated analysis of both datasets. As an example, we have been conducting research to convert non-image data, such as transcriptome data, to image data, so that they could be input to deep learning and fully utilize the advantage of deep learning methodologies.

Various people gather and research

Our laboratories are also located in Tokyo Medical and Dental University and in RIKEN, in addition to the University of Tokyo, and we involved in much collaborative research. Our lab includes bioinformatics researchers, clinical doctors, researchers who like genetics, sequence analysis staff, network analysis researchers, and mathematics researchers from Japan and abroad, sharing their expertise and knowledge to further our research every day.

References:

Trans-omics Research

In order to further understand the interaction between the cancer cell and the local microenvironment, it is very effective to analyze not only the cancer genome but also their epigenome and transcriptome. This methodology can be used not only for cancer but also for other common diseases. For example, we recently participated in an international project on asthma and found many genes related to asthma in the human genome [2]. Considering epigenome and gene expression quantitative loci (eQTL) in order to evaluate the function of the genes, we discovered that most of them are involved in immunity. In another study, to investigate the cause of Alzheimer’s disease, we integrated and analyzed the genomic data of dementia patients and gene expression data in a Alzheimer mouse model, and discovered two new candidate causative genes for Alzheimer disease [3]. In this way, the trans-omics research makes it easier to understand the mechanisms of our bodies and disease. In the future, we will understand more detailed mechanisms of them through network system analysis.
Rapid accumulation of sequence and structure data of biological macromolecules has increased the need for rapid computational analysis of those data. Our laboratory develops new methods used for analysis of those data to acquire new biological knowledge. Most of our work is related to computational structural biology and protein bioinformatics, but we also cross into a wide range of academic fields.

**Protein structure prediction**

Our lab has developed and released FORTE (http://www.cbrc.jp/forte/) (Fig. 1) [1], which implements a profile-profile comparison method that is applicable to predict protein structures. We have applied this method in elucidating the TOM complex [2], and also in CASP and CAPRI, a community-wide experiment for predicting protein structure and protein complex [3].

**Protein ligand-binding site comparison**

We have developed a method for performing an exhaustive pairwise comparison of known and putative ligand-binding sites in PDB. We have created a database, called PoSSuM (http://possum.cbrc.jp/PoSSuM/) to compile comparison results [4]. We have also developed an effective method for ligand-binding site comparison based on a reduced vector representation derived from multidimensional scaling of generalized description of binding sites [5].

**Protein evolution and design**

Learning about the mechanisms behind protein structure formation is one way to deepen our understanding of proteins. We have devised an efficient amino acid substitution matrix, called MIQS, based on a set of typical existing matrices [6]. We have also succeeded in comparing protein profiles related to sequence (evolution) and structure to discover common sequential and conformal characteristics between unrelated proteins [7].

**Research at our lab**

Our lab is in Artificial Intelligent Research Center (AIROC) at the AIST Tokyo Waterfront Research Center in Odaiba, Tokyo.

**References**

Structure-based drug design (SBDD) – in which new pharmaceuticals are designed based on the three-dimensional structure and known interactions of a target receptor protein – has attracted increased attention due to the development of structural genomics. Yet conventional computer-based SBDD requires precise 3D coordinates for the target protein structure, and compound docking simulations require high-precision structural search and interaction energy calculations. However, there are almost no crystalline structures in pharmaceutical target protein families such as G-protein coupled receptors (GPCRs), so there are high expectations for computerized methods of molecular modeling. While other common target proteins such as the tyrosine kinase family have relatively many crystalline structures, structural deformations near the binding compound call for optimization and evaluation of the structure’s suitability for SBDD.

Against this background, we conduct research with an aim at developing methods for molecular modeling of target proteins and docking simulations, as well as virtual screening methods.

**Molecular modeling of target proteins**

We are investigating methods of molecular modeling specific to the structure of the target protein, focusing on methods for comparative modeling and molecular dynamics simulations for the GPCR and tyrosine kinase families. For example GPCR is a target protein with seven transmembrane helices, and we are attempting predictions from sequence analysis of the amino acid residues required for stable existence between helices, reflecting the results in structure predictions. Figure 1 shows an example of molecular modeling for a histamine receptor.

**Compound modeling**

There are many previously reported methods for simulating docking between proteins and compounds, and many software packages that can perform such simulations. However the precision of docking simulations depends on the protein or compound, and other problems remain, such as searching for candidate binding compound structures and needed improvements to compound evaluation functions. We are developing a method called CoLBA for evaluating compound binding by simulating active site docking for representative compounds such as inhibitors after target protein structures are formed. CoLBA is advantageous in that considerations of candidate structures obtained through docking simulation occur not only based on interaction energy, but also by using results from multiple compounds to mutually compare molecular interaction profiles with the target protein, thereby arriving at a consensus determination of the binding state. This allows flexible and intuitive screening that does not depend on interaction energy alone (Fig. 2).
compound docking simulation. The hit ratio is simulated for a group of compounds known to be active toward the target protein, and a group of non-active compound randomly selected from a library. The results of this evaluation are fed back into molecular modeling of the target protein and in the docking simulation process, helping to optimize the target protein–compound model.

In future joint research we hope to evaluate physiological activities by selecting compounds with models created from libraries of millions of compounds.

Laboratory of Computational Systems Biology (AIST)

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【Key Words】Protein design, Protein structure prediction, X-ray ab initio phasing, Cryo-EM structure refinement, Computational drug design

The complex biological functions of proteins are determined by their equally intricate three-dimensional structures. The correctly folded native structure is critical for the proper function of a protein in a cell. Small deviations from its native structure can often lead to malfunction of the protein and cause diseases. We are interested in understanding the protein functions through computational studies of their structures. Our research interests are on the following areas:

●Protein folding and design
●Ab initio phasing with de novo models
●Virtual screening and drug design

1. Protein folding and design

Understanding the principles of protein folding especially the energetics will enable us to predict protein structures from their sequences. We have developed an efficient conformational sampling method for fragment-assembly based de novo protein structure prediction called EdaFold that uses an Estimation of Distribution Algorithm. This method has achieved top performance in the template-free modeling category of CASP10. We have developed one of the fastest exact cluster method called Durandal that can be used to identify a good protein model among many decoys.

Protein design allows us to explore large regions of the protein universe not yet observed in nature. Recently, we have developed a very efficient method and have used it to design the first perfectly symmetric β-propeller proteins that self-assemble according to simple arithmetic rules. We are interested in applying the protein design principles to create proteins with novel architectures, new biological functions or effective therapeutics.

2. Ab initio phasing with de novo models

We are developing new computational methods to solve the X-ray crystallographic phase problem for protein structure determination. Our efforts are focused on improving de novo models predicted computationally so that they can be used as templates for structure determination by molecular replacement. We have developed an error-estimation guided model rebuilding method that can efficiently improve de novo models with increased success rate for molecular replacement. Recently, we have developed a fragmentation and assembly method that can use low accuracy de novo models for ab initio phasing.

3. Virtual screening and drug design

Drug discovery is a long and costly endeavor that involves many stages of multidisciplinary collaborations. Our effort focuses on using computational tools to identify initial hit compounds for a given protein target (lead discovery) and optimize them into potent lead compounds (lead optimization). We also develop novel methods for the identification of
small molecule inhibitors. We collaborate with biologists to validate our identified hit compounds by experimental assays. We also collaborate with structural biologists to understand the binding mode of hit compounds for lead optimization.

References:
Laboratory of Cancer Medical Informatics (NCCHE)

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【Key Words】Bioinformatics, Transcriptional regulation, Translational regulation, Microbiome, Multiomics analysis, cancer genome analysis

Laboratory of Cancer Medical Informatics (National Cancer Center Hospital East)

In order to advance the research and treatment of cancer, clinical information that is guaranteed quality is absolutely required. In addition, data for multilayer omics analysis such as genome, transcriptome, and metabolome from patient or cell specimens is also required in order to investigate the cancer mechanism and the effects of drugs. Moreover, microbiome information which comprehensively examines the bacteria present in humans has also been accumulated, and the relation with cancer is one of the hot topics. The amount of data generated by such analysis has increased day by day. Bioinformatics is essential not only for combining biology and medicine but also for integrating these to derive novel knowledge. We are now trying to extract helpful medical and biological knowledge based on not only designing efficient pipelines for data processing but also constructing database servers for cancer genome, transcriptome including non-coding RNAs, and microbiome. We are also aiming to 'translational informatics' that contributes to cancer research taking advantage of valuable clinical multilayer-omics data accumulated in the National Cancer Center.
## DEPARTMENT MEMBERS
### (COMPUTATIONAL BIOLOGY AND MEDICAL SCIENCES)

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### MEDICAL SCIENCES GROUP

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### INTER-INSTITUTE COOPERATIVE LABORATORIES

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<td>Yusuke INOUE</td>
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<td>Shinichi MORISHITA</td>
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<td>Kiyoshi ASAI</td>
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<td>Tatsuhiko TSUNODA</td>
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<td>Shinya KURODA</td>
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<td>INFOMATICS OF MOLECULAR FUNCTIONS (AIST)</td>
<td>Kentaro TOMII</td>
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<td>Takatsugu HIROKAWA</td>
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<td>Susumu GOTO</td>
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Applying for the Master Course

Eligibility for Application
- Please refer to "the Guidelines for Applicants to the 2020 Master Course" (the Guidelines, hereafter), which is distributed from Graduate School of Frontier Science (GSFS), the University of Tokyo.

Submitting Documents
- Please submit all the designated documents including “the Application Form” and “the Inquiry Sheet (Master Course)” attached to this book. Please make sure that all required fields are filled in.
- Applicants might be required to submit certificates as well as the application documents. Please read the Guidelines carefully. Before you submit documents and certificates, use “the Checklist” attached to this book so that all the necessary documents and certificates are included in an envelope.

Admission Quota and Choosing Your Laboratories
- The admission quota for our department is 53, including a few for the Biomedical Innovation Course.
- Choose one of the Groups or Course: (1) the Medical Sciences Group, (2) the Computational Biology Group, (3) the Biomedical Innovation Course.
- Choose laboratories you wish to join. Applicants to the Medical Sciences Group must choose at least 2 and at most 3 laboratories. Applicants to the Computational Biology Group must choose at least 2 and at most 5 laboratories. Applicants to the Biomedical Innovation Course must choose exactly one laboratory. Note that your request may not be met depending on the capacity of individual labs.
- Note that you cannot choose more than one Group or Course; if you choose more than one laboratory, they all must be in the same Group (or Course).

Selection Procedure
GSFS has two types of admissions, the Ordinary Examination, and a Special Selection for Applicants with Overseas Education. Nonetheless, our department, Department of Computational Biology and Medical Sciences (Dept of CBMS) does not provide a Special Selection for Applicants with Overseas Education.

(Ordinary Examination)
Applicants are selected by the result of the following examinations: (1) Written examination on specialty subjects, (2) Written examination on foreign language (English), and (3) Oral examination.

Written Examinations
- **Foreign Language (English):** All applicants must take the TOEFL-ITP exam (the foreign language exam type E1 in the Guidelines).
- **Specialty Subjects:** Applicants to the Medical Sciences Group or the Computational Biology Group must answer four questions out of twelve in biology, information science, and related fields. Applicants to the Biomedical Innovation Course must answer two questions out of six in intellectual property, bioethics, medical statistics, and related fields. The problem descriptions are provided either in Japanese or in English. Please choose on Inquiry Sheet (Master Course) your preferred language for problem descriptions. Note that you must choose either language, not both. You can answer in English and/or Japanese regardless of your choice for the problem descriptions.

Oral Examination
Applicants who passed screening based on the written examinations take an oral examination. Academic achievements as well as your motivation for research will be evaluated.
Examination Schedule
The following is the examination schedule. All the written examinations will be held in the Kashiwa campus. The detailed information including venues will be provided when examination admission tickets are sent to applicants in late July.

August 6, 2019 Tue. 9:30-11:30 Specialty Subjects
12:30-14:50 Foreign Language (TOEFL-ITP)
August 7, 2019 Wed. 13:00- Oral exam (the Biomedical Innovation Course)†
August 8, 2019 Thu. 10:00- Oral exam (the Medical Sciences Group and the Computational Biology Group)†

† Only for those who pass the screening based on the written examinations.

Announcement of Results and Admission Procedures
Written exams: The announcement of the screening results (pass or fail) based on the written examinations will be made at noon on August 7 (Wed) both at the bulletin board in the entrance hall of Transdisciplinary Sciences Building on the Kashiwa campus, and on the web page of our department.
Oral exam: Please refer to Section 10 (Announcement of Results and Admission Procedures) and Table 2 (A−12, A−13, A−14, A−15) of the Guidelines.

Miscellaneous
Enrollment in September: If you wish to enroll in September 2019, please indicate so on the Inquiry Sheet (Master Course). You must have already graduated or are expected to graduate from a college or university by September 2019. Please be aware that you cannot change the time of enrollment from September 2019 to April 2020 even if you fail in graduating from a college or university by September 2019.

Past Examinations: Past written examinations for Specialty Subjects are available on our department website (http://www.cbms.k.u-tokyo.ac.jp/).

General Note: Please make sure that you read the Guidelines carefully. It can be downloaded from our department website (http://www.cbms.k.u-tokyo.ac.jp/).

Personal Information Statement
The school shall use personal information of applicants such as names and addresses only for the purpose of selecting successful applicants (e.g., processing applications, conducting screening), announcing accepted applicants, and conducting admission procedures. The personal information of admitted students shall be used for the purpose of student affairs (school registration, schooling, grading and other administrative matters), student assistance (healthcare, career support, tuition exemption, scholarship applications, the use of libraries, etc.), and tuition payments. The examination results may be used in future studies for improving both the entrance examination system and the education at the University of Tokyo.

Contact
Student Affairs,
Graduate School of Frontier Sciences, the University of Tokyo
5-1-5 Kashiwanoha, Kashiwa, Chiba pref., JAPAN 277-8561
Phone: +81-4-7136-4092
Applying for the Doctoral Course

Eligibility for Application
- Please refer to “the Guidelines for Applicants to the 2020 Doctoral Course” (the Guidelines, hereafter), which is distributed from Graduate School of Frontier Science (GSFS), the University of Tokyo.
- Those who have graduated from or are expected to graduate from a six-year undergraduate course in medicine, dentistry, veterinary medicine, or pharmacy, and those who wish to qualify by ⑥ to ⑧ indicated in “(1) Ordinary Examination” in the applicant eligibility section in the Guidelines, are subjected to individual screening. Please contact us for details. Note that those who are subjected to individual screening cannot apply for schedule B.
- Applicants who have completed or are expected to complete a Master course at the department other than our department, and those who wish to enroll in the Computational Biology Group, may not apply for schedule B.

Submitting Documents
- Please submit all the designated documents including “the Application Form” and “the Inquiry Sheet (Doctoral Course)” attached to this book. Please make sure that all required fields are filled in.
- Applicants might be required to submit certificates as well as the application documents. Please read the Guidelines carefully. Before you submit documents and certificates, use “the Checklist” attached to this book so that all the necessary documents and certificates are included in an envelope.

Admission Quota and Choosing Your Laboratories
- The admission quota for our department is 24, including a few for the Biomedical Innovation Course.
- Choose exactly one laboratory on the Inquiry Sheet (Doctoral Course).
- We strongly recommend that you contact a (prospective) supervisor before you apply, but it is not mandatory.

Selection Procedure
GSFS has two types of admissions, the Ordinary Examination, and a Special Selection for Applicants with Overseas Education. Nonetheless, our department, Department of Computational Biology and Medical Sciences (Dept of CBMS) does not provide a Special Selection for Applicants with Overseas Education. The problem descriptions of written examinations are provided either in Japanese or in English. You can answer in Japanese and/or English regardless of your choice for the problem description.

〈Ordinary Examination〉
Applicants are selected by the result of the following examinations: (1) Written examination on specialty subjects, (2) Written examination on foreign language (English), and (3) Oral examination including presentation of your Master thesis (See Table 1). Those who have completed or are expected to complete a Master course in the University of Tokyo are exempt from the written examinations (Foreign Language. Specialty Subjects), except for those who have completed or are expected to complete a Master course in different department from the Department of Computational Biology and Medical Sciences in the University of Tokyo AND wish to enroll in the Computational Biology Group.

Written Examinations
- **Foreign Language (English)**
  - **Schedule A:** Please choose one or more options from the followings (the foreign language exam type E3 in the Guidelines): (1) Take TOEFL-ITP, (2) Submit a TOEFL score report, and/or (3) Submit a TOEIC score report. Applicants to the Medical Sciences Group or to the Biomedical Innovation Course are not allowed to take option 3, “Submit a TOEIC score report” (Type E4 in the Guidelines).
Schedule B: Submit a TOEFL score report (the foreign language exam type E8 in the Guidelines).

Please indicate your choice(s) in the Foreign Language section of the Inquiry Sheet (Doctoral Course). Please make sure that TOEFL/TOEIC score reports are submitted by the deadline described in the Guidelines. See the Guidelines for how to submit score reports. Late submissions will not be considered.

Specialty Subjects
Depending on your status, you have to take either of (1) Specialty Type A, or (2) Specialty Type B, unless specifically exempted. Please choose on Inquiry Sheet (Doctoral Course) your preferred language for problem descriptions. Note that you have to choose either language, not both. You can answer in English and/or in Japanese regardless of your choice for the problem descriptions.

▷ Specialty Type A:
There are two types of applicants who must take Specialty Type A.

Applicant Type A-1: Applicants to the Medical Sciences Group or the Computational Biology Group who graduated or are expected to graduate from a six-year undergraduate course in medicine, dentistry, veterinary, or pharmacy, or those who passed the individual screening.

Applicant Type A-2: Applicants to the Computational Biology Group who graduated or are expected to graduate from a different department from the Department of Computational Biology and Medical Sciences in the University of Tokyo.

Applicants of type A-1 and A-2 must answer four questions out of twelve in biology, information science, and the related fields. Applicants to the Biomedical Innovation Course must answer two questions out of six in intellectual property, bioethics, medical statistics, and related fields. The problem descriptions are provided either in Japanese or in English.

▷ Specialty Type B:
Applicants to the Biomedical Innovation Course who have graduated or are expected to graduate from a six-year undergraduate course in medicine, dentistry, veterinary, or pharmacy, or applicants who passed the individual screening must answer two questions out of six in intellectual property, bioethics, medical statistics, or related fields.

Oral Examination
Applicants who passed screening based on the written examinations take an oral examination. Academic achievements as well as your motivation for research will be evaluated.

Examination Schedule
The following is the examination schedule. All the examinations will be held in the Kashiwa campus. The detailed information including venues will be provided when examination admission tickets are sent to applicants in late July.
[Schedule A]
August 6, 2019  Tue.  9:30-11:30  Specialty Subjects (Type A, B)
12:30-14:50  Foreign Language (TOEFL-ITP)†
August 7, 2019  Wed.  13:00-  Oral exam (the Biomedical Innovation Course)‡
August 8, 2019  Thu.  13:00-  Oral exam (only for *1, *2, and *3)‡
Early February, 2020 (TBA)  Oral exam (only for *4)
† Only for those who choose to take TOEFL-ITP.
‡ Only for those who pass the screening based on the written examinations.

*1 Applicants who meet all of the following conditions: (1) Applicants to the Medical Sciences Group or to the Biomedical Innovation Course who have graduated or are expected to graduate from a college or university by September 2019; (2) Applicants who wish to take the examinations in Schedule A; (3) Applicants who wish to enroll in September 2019, or applicants who have graduated from a college or university at the time of application. Applicants who wish to enroll in September must indicate so on the Inquiry Sheet (Doctoral Course).

*2 Applicants to the Computational Biology Group, except for those who are expected to graduate from our department in September 2019. Applicants who wish to enroll in September must indicate so on the Inquiry Sheet (Doctoral Course).

*3 Applicants who are specifically asked by our department to take the oral examination on this day.

*4 Applicants who meet either of the following conditions: (1) Applicants to the Medical Sciences Group who are expected to graduate from a college or university by March 2020, (2) Applicants to the Computational Biology Group who are expected to graduate from our department in March 2020.

[Schedule B]
Early February, 2020 (TBA)  Oral exam (*5, *6)

*5 The schedule will be sent to you along with an examination admission ticket.

*6 Applicants to the Medical Sciences Group or the Biomedical Innovation Course who wish to take the entrance examinations in Schedule B, and who wish to enroll in September 2020 must indicate so on the Inquiry Sheet (Doctoral Course).

Announcement of Results and Admission Procedures

[Schedule A]
Written exams: The announcement of the screening results (pass or fail) based on the written examinations will be made at noon on August 7 (Wed) both at the bulletin board in the entrance hall of Transdisciplinary Sciences Building on the Kashiwa campus, and on the web page of our department.
Oral exam: Please refer to Section 10 (Announcement of Results and Admission Procedures) and Table 2 (A−12, A−13, A−14, A−15) of the Guidelines.

[Schedule B]
Please refer to the Section 10 (Announcement of Results and Admission Procedures) and Table 2 (B−8, B−9, B−12, B−13) of the Guidelines.

Miscellaneous

Enrollment in September (Schedule A): If you wish to enroll in September 2019, please indicate so on the Inquiry Sheet (Doctoral Course). You must have already graduated or are expected to graduate from a college or university by September 2019. Please be aware that you cannot change the time of enrollment from September 2019 to April 2020 even if you fail in graduating from a college or university by September 2019. Please contact the Student Affairs if you will graduate from a college or university between
September 20 and September 30 in 2019.

Enrollment in September (Schedule B): If you wish to enroll in September 2020, please indicate so on the Inquiry Sheet (Doctoral Course). You must have already graduated or are expected to graduate from a college or university by September 2020. Please be aware that you cannot change the time of enrollment from September 2020 to April 2021 even if you fail in graduating from a college or university by September 2020.

Past Examinations: Past written examinations for Specialty Subjects are available on our department website (http://www.cbms.k.u-tokyo.ac.jp/).

General Note: Please make sure that you read the Guidelines carefully. It can be downloaded from our department website (http://www.cbms.k.u-tokyo.ac.jp/).

Personal Information Statement
The school shall use personal information of applicants such as names and addresses only for the purpose of selecting successful applicants (e.g., processing applications, conducting screening), announcing accepted applicants, and conducting admission procedures. The personal information of admitted students shall be used for the purpose of student affairs (school registration, schooling, grading and other administrative matters), student assistance (healthcare, career support, tuition exemption, scholarship applications, the use of libraries, etc.), and tuition payments. The examination results may be used in future studies for improving both the entrance examination system and the education at the University of Tokyo.

Table 1: Examination Types. The abbreviations are shown below.

<table>
<thead>
<tr>
<th>Exam Type</th>
<th>CBMS Master</th>
<th>UTokyo Master</th>
<th>Other Univ Master</th>
<th>6−year Undergrad</th>
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<tbody>
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<td>Aug/Feb †</td>
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<td>Aug</td>
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† Applicants who have graduated or are expected to graduate from a college or university by September 2019 take the oral examination in August 2019, otherwise in February 2020.

Medical Sciences Group

[Schedule A]

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[Schedule B]

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Computational Biology Group

[Schedule A]

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† Applicants who have graduated or are expected to graduate from a college or university by September 2019 take the oral examination in August 2019, otherwise in February 2020.

[Schedule B]

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Biomedical Innovation Course

[Schedule A]

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† Applicants who have graduated or are expected to graduate from a college or university by September 2019 take the oral examination in August 2019, otherwise in February 2020.

[Schedule B]

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Contact

Student Affairs,
Graduate School of Frontier Sciences, the University of Tokyo
5-1-5 Kashiwanoha, Kashiwa, Chiba pref., JAPAN 277-8561
Phone: +81-4-7136-4092
Attending Entrance Examinations

Examination Date and Time
The examination schedule is shown in the selection procedure section in this book.

Venues
The written examinations are held in Kashiwa Research Complex. The oral examinations are held in Biosciences Building. Both buildings are on the Kashiwa campus, where Graduate School of Frontier Sciences, The University of Tokyo is. The address of the Kashiwa campus is 5-1-5 Kashiwanoha, Kashiwa, Chiba, JAPAN. Also see the map in this book.

Directions to the Kashiwa campus
- From Kashiwa station of JR Joban Line (25 minutes): Go to the west exit, take Tobu bus bound for National Cancer Center (via Kashiwanoha Park), and get off at Todai-mae bus stop.
- From Kashiwanoha Campus station of Tsukuba Express Line (13 minutes): Go to the west exit, take Tobu bus bound either for Nagareyama Ootaka-no-Mori station (east exit) or for Edogawadai station, and get off at Todai-mae bus stop.
- From Edogawadai station of Tobu Urbanpark Line (5 minutes): Call a taxi.

The exam seating arrangement is shown at each exam room. If you arrive late, contact the proctor.

Items to Bring
1. Examination Admission Ticket
2. Black pencils (or black mechanical pencils), erasers, a portable pencil sharpener (a desktop type is not allowed), and a watch (with a time measurement function only).

Notes (during the Examinations)
1. Applicants are not allowed to leave the exam room in the first one hour of the exam (Specialty Subject).
2. Applicants are not allowed to leave the exam room during the foreign language exam (TOEFL-ITP).
3. Applicants are basically not allowed to temporarily leave the exam room during the exam.
4. Please put the examination admission ticket on the desk during the exam.
5. Please make sure that mobile phones are turned off during the exam. You are not allowed to use a mobile phone during the exam for any purpose.
6. Please write your examinee number on each answer sheet. You are not allowed to write your name on answer sheets.
7. Please write answers only on designated answer sheets.
8. Please write your examinee number to all answer sheets, including answer sheets on which you wrote no answers.
9. You are not allowed to ask questions on the exam problems during the exam.
10. You are not allowed to take answer sheets and/or problem booklets out of the exam room.
Checklist for Master Course Applicants

Place a check (✓) in every appropriate box (□) below as you confirm each item, and enclose this check sheet with your application.

(All applicants)

☐ Application Sheet (included in the Guidelines for Applicants to the 2020 Master Course)
☐ Photo ID Tickets A and B, Examination Admission Ticket
☐ Application screening fee: JPY 30,000.
   See Guidelines for Applicants to the 2020 Master Course for payment methods.
   The fee is not required for international applicants who receive a Japanese Government (Monbukagakusho) Scholarship. Those not enrolled in the University of Tokyo as a regular or research student needs to submit a certificate attesting to their status as Monbukagakusho Scholarship recipients.
☐ Return envelope
   Write your name and address with ¥420 in postal stamps (for addresses in Japan only). If you wish to have the return envelope mailed to an address outside Japan, please contact the following section.
   Student Affairs Section
   Graduate School of Frontier Sciences
   The University of Tokyo
   Phone: +81−4−7136−4092
   Email: k-kyomu@adm.k.u-tokyo.ac.jp
☐ Address label
☐ Inquiry Sheet (included in this book)
☐ Diploma or certificate of graduation/completion
   Required for those who have already graduated from an undergraduate program at the time of application. Not required for those who have not yet graduated from an undergraduate program.
   In addition to the above, applicants who have graduated or are expected to graduate from a university in China are required to submit a credential, report of your degree (认证报告) issued by China Academic Degree & Graduate Education Development Center (CDGDC; 教育部学位与研究生教育发展中心; http://www.cdgdc.edu.cn/). You can submit the CDGDC credential report later but no later than the time of the admission procedure.
☐ Academic Record/Transcript of an undergraduate course
   Required for applicants to the Computational Biology Group and for foreign applicants. When the record/transcript is not described in English/Japanese, please also attach the translation certified by a public institution such as the university you graduated from, an embassy/consulate, a government.
☐ Research/Work Balance Plan
   If you wish to attend school while staying in service of a company, a government, or an organization.
☐ Residence certificate
   Required for foreign nationals currently residing in Japan, except for regular and research students currently enrolled in our department.
Checklist for Doctoral Course Applicants

Place a check (✓) in every appropriate box (□) below as you confirm each item, and enclose this check sheet with your application.

(All applicants)

□ Application Sheet (included in the Guidelines for Applicants to the 2020 Doctoral Course)
□ Photo ID Tickets A and B, Examination Admission Ticket
□ Application screening fee: JPY 30,000
   See Guidelines for Applicants to GSFS Doctoral Course for payment methods.
   The fee is not required for:
   1) those who are expected to complete a master program at the University of Tokyo by March, 2020 (September, 2019 for enrollment in September, 2019), or
   2) international applicants who receive a Japanese Government (Monbukagakusho) Scholarship.
   Those not enrolled in the University of Tokyo as a regular or research student needs to submit a certificate attesting to their status as Monbukagakusho Scholarship recipients.
□ Return envelope
   Write your name and address with ¥420 in postal stamps (for addresses in Japan only). If you wish to have the return envelope mailed to an address outside Japan, please contact the following section.
   Student Affairs Section
   Graduate School of Frontier Sciences
   The University of Tokyo
   Phone: +81−4−7136−4092
   Email: k-kyomu@adm.k.u-tokyo.ac.jp
□ Address label
□ Inquiry Sheet (included in this book)
□ TOEFL/TOEIC score report (if applicable)
□ Diploma or certificate of graduation/completion for a graduate program
   Required for those who have already completed a graduate program at the time of application. Not required for those who have not yet completed a graduate program. Not necessary for those who are expected to graduate or have graduated from Graduate School of Frontier Sciences, The University of Tokyo.
   In addition to the above, applicants who have graduated or are expected to graduate from a university in China are required to submit a credentials report of your degree (认证报告) issued by China Academic Degree & Graduate Education Development Center (CDGDC; 教育部学位与研究生教育发展中心; http://www.cdgdc.edu.cn/). You can submit the CDGDC credential report later but no later than the time of the admission procedure.
□ Diploma or certificate of graduation/completion for an undergraduate program (foreign applicants only)
   In addition to the above, applicants who have graduated from a university in China are required to submit a credentials report of your degree issued by CDGDC.
□ Academic Record/Transcript of an undergraduate course and a graduate course
   Required for applicants to the Computational Biology Group and for all foreign applicants.
   Not necessary if you have graduated from Graduate School of Frontier Sciences, The University of Tokyo. When the record/transcript is not described in English/Japanese, please also attach the translation certified by a public institution such as the university you graduated from, an embassy/consulate, a government.
□ Research/Work Balance Plan
   If you wish to attend school while staying in service of a company, a government, or an organization.
□ Residence Certificate
   Required for foreign nationals currently residing in Japan, except for regular and research students currently enrolled in our department.
**INQUIRY SHEET (Master Course)**

Applicants must submit this form with your application documents

Department of Computational Biology and Medical Sciences, GSFS, The University of Tokyo

<table>
<thead>
<tr>
<th>Full Name (incl. furigana)</th>
<th>Examinee number (Do not write)</th>
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<tr>
<th>Last Educational Experience</th>
<th>I graduated/completed or will graduate/complete (circle which applies)</th>
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<td>University:</td>
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<td>Department:</td>
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<td>Year:</td>
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Address & phone number of your home/lodging

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<th>Address:</th>
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Current laboratory and its phone number

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Do you wish to enroll in September, 2019? [Schedule A] (Respond only if eligible)

a. YES  

b. NO (I prefer April, 2020)

Language Preference for Specialty Subjects

(Please choose the language of the problem descriptions. You can answer in either language regardless of the choice here.)

a. English  
b. Japanese

State your reasons for applying

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LABORATORY YOU WISH TO JOIN

* Choose one of the Medical Sciences Group, the Computational Biology Group, and the Biomedical Innovation Course. Write the order of your preference in the Group or the Course you choose.

* Applicants are not allowed to specify labs in multiple groups/course.

* An applicant to the Medical Sciences Group specifies at least two, at most three labs. An applicant to the Computational Biology Group specifies at least two, at most five labs. An applicant to the Biomedical Innovation Course specifies exactly one lab.

* Labs not listed here do not accept students.

### Medical Sciences Group

**Core laboratories**

- Laboratory of Biomolecules (Tomita N.)
- Laboratory of RNA Biology (Tomita K.)
- Laboratory of Tumor Cell Biology/Viral Oncogenesis (Uchimaru, Nakano)
- Laboratory of Complex Trait Genomics (TBA)

**Intra-university cooperative laboratories**

- Laboratory of AIDS Vaccine Development (Matano)
- Laboratory of Molecular Virology (Kawaguchi)
- Laboratory of RNA Function (Tomari)
- Laboratory of Infectious Diseases (Yotsuyanagi)
- Laboratory of Medical Proteomics (Oyama)
- Laboratory of Stem Cell Pathology (Yamada)
- Laboratory of Stem Cell Regulation (Tanaka M.)
- Laboratory of Stem Cell and Molecular Medicine (Iwata)
- Laboratory of Canter Call Biology (Nishiyama)

**Inter-institute cooperative laboratories**

- Laboratory of Biomedical Sciences (Tanaka K.)
- Laboratory of Molecular Target Therapy of Cancer (Fujita)
- Laboratory of Molecular Target Therapy of Cancer (Tomida)

### Computational Biology Group

**Core laboratories**

- Laboratory of Omics (Morishita)
- Laboratory of Systems Genomics (Suzuki Y.)
- Laboratory of High-Performance Analysis System (Kasahara)
- Laboratory of Large-Scale Bioinformatics (Martin)

**Intra-university cooperative laboratories**

- Laboratory of Bioinformatics and Systems Biology (Tsunoda)
- Laboratory of Bioinformatics and Systems Biology (Iwasa W.)
- Laboratory of Informatics of Molecular Functions (TBA)

**Inter-institute cooperative laboratories**

- Laboratory of Informatics of Molecular Functions (Tomiil)
- Laboratory of Informatics of Molecular Functions (TBA)
- Laboratory of Cancer Medical Information (Yamasahita)

### Biomedical Innovation Course

**Core laboratory**

- Laboratory of Bio Innovation Policy (Kano)

**Intra-university cooperative laboratories**

- Laboratory of Public Policy (Muto, Inoue)
- Laboratory of Advanced Medicine Promotion (Nojima)
DOCTORAL

INQUIRY SHEET (Doctoral Course)

Applicants must submit this form with your application documents

Department of Computational Biology and Medical Sciences, GSFS, The University of Tokyo

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If you have graduated or are expected to graduate from a six-year undergraduate course, circle the letter that corresponds to the course.

a. MEDICINE b. DENTISTRY c. VETERINARY MEDICINE d. PHARMACY

Do you wish to enroll in September, 2019? [Schedule A] (Respond only if eligible)

a. YES b. NO (I prefer April, 2020)

Do you wish to enroll in September, 2020? [Schedule B]

a. YES b. NO (I prefer April, 2020)

Language Preference for Specialty Subjects

(Please choose the language of the problem descriptions. You can answer in either language regardless of the choice here.)

a. English b. Japanese

Foreign Language Exam [Applicants to Schedule A]

(Multiple choice; “c. submit a TOEIC score report” is only for applicants to the Computational Biology Group.)

a. take TOEFL-ITP b. submit a TOEFL score report c. submit a TOEIC score report

State your reasons for applying
**LABORATORY YOU WISH TO JOIN**

*Choose exactly one lab you wish to join.*

*We recommend that you contact your potential supervisor in advance to the application, but you can still apply even if you do not do so.*

*Labs not listed here do not accept students.*

### Medical Sciences Group

**Core laboratories**

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<tr>
<td>Laboratory of Biomolecules (Tomita N.)</td>
<td>Laboratory of Molecular Genetics (Ito K.)</td>
</tr>
<tr>
<td>Laboratory of RNA Biology (Tomita K.)</td>
<td>Laboratory of Genome Technology (Matsuda)</td>
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<tr>
<td>Laboratory of Tumor Cell Biology/Viral Oncogenesis (Uchimaru, Nakano)</td>
<td>Laboratory of Complex Trait Genomics (TBA)</td>
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**Intra-university cooperative laboratories**

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<td>Laboratory of Cellular Therapy (Goyama)</td>
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<td>Laboratory of Molecular Pathology (Murakami Y.)</td>
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<td>Laboratory of Clinical Genome Research (Furukawa)</td>
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<td>Laboratory of Advanced Genome Medicine (Hirata)</td>
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<td>Laboratory of Genetics (Yamanashi)</td>
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<td>Laboratory of Cell Signaling and Molecular Medicine (Takekawa)</td>
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<td>Laboratory of Regenerative Medicine (Taniguchi)</td>
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<td>Laboratory of Canine Cell Biology (Nishiyama)</td>
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### Intra-university cooperative laboratories

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### Inter-institute cooperative laboratories

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<td>Laboratory of Biomedical Sciences (Itoh)</td>
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<td>Laboratory of Functional Biomolecules Engineering (Noda)</td>
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<td>Laboratory of Molecular Target Therapy of Cancer (Tomida)</td>
<td>Laboratory of RNA System Biology (Iwasaki S.)</td>
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<td>Laboratory of Molecular Target Therapy of Cancer (Seimiya)</td>
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### Computational Biology Group

**Core laboratories**

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<td>Laboratory of Omics (Morishita)</td>
<td>Laboratory of Genome Informatics (Asa)</td>
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<td>Laboratory of Systems Genomics (Suzuki Y.)</td>
<td>Laboratory of Large-scale Knowledge Discovery (Tsuda)</td>
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<td>Laboratory of High-Performance Analysis System (Kasahara)</td>
<td>Laboratory of Biological Network Analysis (Kiryu)</td>
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<td>Laboratory of Large-Scale Bioinformatics (Mtin)</td>
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**Intra-university cooperative laboratories**

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<td>Laboratory of Bioinformatics and Systems Biology (Kuroda)</td>
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**Inter-institute cooperative laboratories**

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<td>Laboratory of Computational Systems Biology (Zhang)</td>
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<tr>
<td>Laboratory of Cancer Medical Information (Yamasahita)</td>
<td>Laboratory of Life Science Databases (Goto)</td>
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### Biomedical Innovation Course

**Core laboratory**

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<td>Laboratory of Bio Innovation Policy (Kano)</td>
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**Intra-university cooperative laboratories**

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<tr>
<td>Laboratory of Public Policy (Muto, Inoue)</td>
<td>Laboratory of Advanced Medicine Promotion (Nojima)</td>
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Venues for Examinations

Directions to Kashiwa Campus

◆ Address
5-1-5 Kashiwanoha, Kashiwa-shi, Chiba

◆ To Kashiwa Campus
Nearest Sta.
- Kashiwa Station (JR Joban Line, Subway Chiyoda Line)
- Edogawadai Station (Tobu Urban-Park Line)
- Kashiwanoha Campus Station (Tsukuba Express)

Directions
- From Kashiwa Station:
  Regular bus lines (Tobu Bus stop no. 2 outside west exit)
  Nishi-Kashiwa 01, bound for National Cancer Center (via Kashiwanoha Park) [Approx. 25 minute]
  Get off at the Todai-nishi or Todai-mae stop. 3 minutes' walk.
- From Edogawadai Station:
  Approx. 5-minute ride by taxi.
- From Kashiwanoha Campus Station:
  Approx. 20-minute walk.
  Nishi-Kashiwa 03, bound for East Exit of Nagareyama-OUTakanomori Station
  Nishi-Kashiwa 04, bound for East Exit of Edogawadai Station [Approx. 13-minute]
  Get off at the Todai-mae stop. 3 minute's walk.

A complimentary shuttle service will be provided from Kashiwanoha Campus Station.
The details will be sent along with an Examination Admission Ticket enclosed in the packet.

Map of the Kashiwa Campus

Transdisciplinary Sciences Laboratory, GSFS
TXCC (Total-JAXA Center for Complexes)

Computational Biology Laboratory, GSFS
Center for Omics and Bioinformatics

Biosciences, GSFS
Biomaging Center

Environmental Studies, GSFS Functional Proteomics Center

Atmosphere and Ocean Research Institute

Plaza (health Care Center)

Food Shop & Caf., Cafeteria

Administrative Office, GSFS 1st Floor

Kashiwa Library

Kashiwa Research Complex

Institute for Cosmic Ray Research

Todai-mae