

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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Entrance Examination Guide was revised in the following sections

Applying for the Master course Ver.2

Check Sheet (Master) Ver. 2

Inquiry Sheet (Master) Ver. 2

Applying for the Doctoral course Ver.2

Check Sheet (Doctor) Ver. 2

Inquiry Sheet (Doctor) Ver. 2

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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.

Laboratory of Biomolecules

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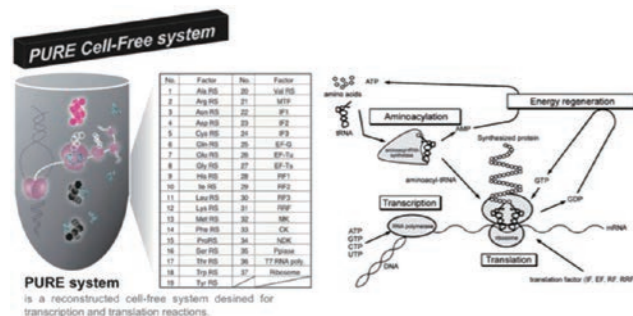
[Key Words] translation system, ribosome, tRNA, yeast, mitochondria

※ Prof. Takuya Ueda has been transferred to Waseda University from April 2019. Please also look at the laboratory HP for research content (<https://sites.google.com/view/molbio>).

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

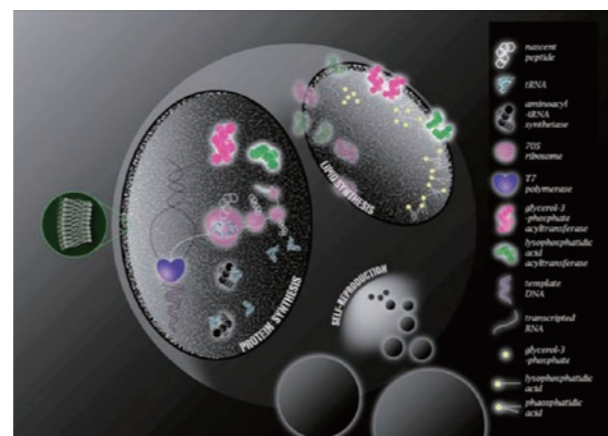


PURE system

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

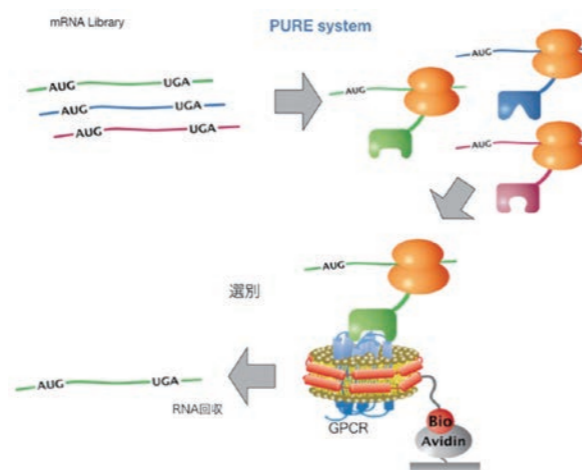


Artificial cell

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.



PURE ribosome display method

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Laboratory of Molecular Genetics

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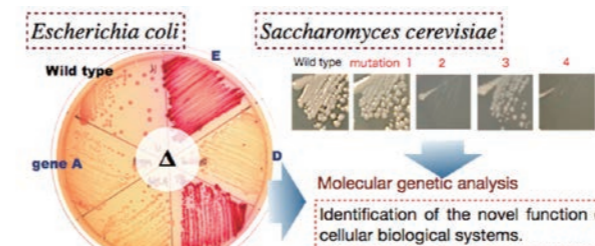
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[Key Words] tRNA mimicry protein, mRNA quality control, genetic switch, yeast prion, genetic decoding

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.



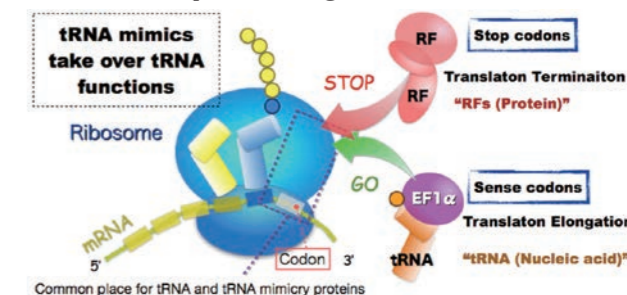
Decoding mechanism of the stop codons and its versatile functions.

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 step of translation. In eukaryotes translation termination is catalyzed by two class of proteins, eRF1 and eRF3. eRF1 recognizes stop codons and hydrolyzes peptidyl-tRNA as a tRNA mimic, while eRF3, an elongation factor 1 α (EF-1 α) 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 (Selenocysteine) insertion, translational frameshifting and so on. Such mechanisms are called translational RECODING (=Reprogrammed

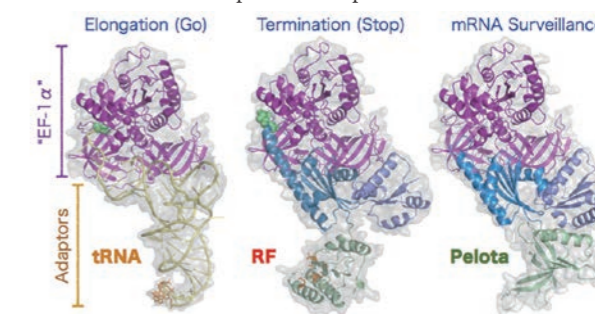
genetic decoding). Moreover, in eukaryotes, the premature stop codons in aberrant mRNAs are recognized differently from normal stop codons and trigger the NMD (=Nonsense mediated mRNA decay) system to avoid harmful protein synthesis.

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



The ribosome function and the tRNA mimicry protein complexes

Two homologs of EF1 α in eukaryotes form complexes with protein factors mimicking the structure and function of tRNA, rather than with genuine tRNAs. One of the homologs, the class 2 eukaryotic release factor (eRF3) forms a complex with the class 1 eukaryotic release factor (eRF1), which mimics tRNA's functional as well as structural aspects to catalyze the decoding of stop codons in a way similar to tRNAs. The other homolog, HBS1 forms a complex with Dom34 (Pelota), which is partly homologous to eRF1. The HBS1-Dom34 complex resembles the EF1 α -tRNA complex in appearance, and this complex is thought to function in mRNA surveillance or mRNA quality control. However, precise molecular mechanism underlying this putative function is not well understood. Our recent studies have revealed that archaeal EF1 α functions as a versatile carrier protein for tRNA and tRNA-like protein adaptors.



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Laboratory of Genome Technology

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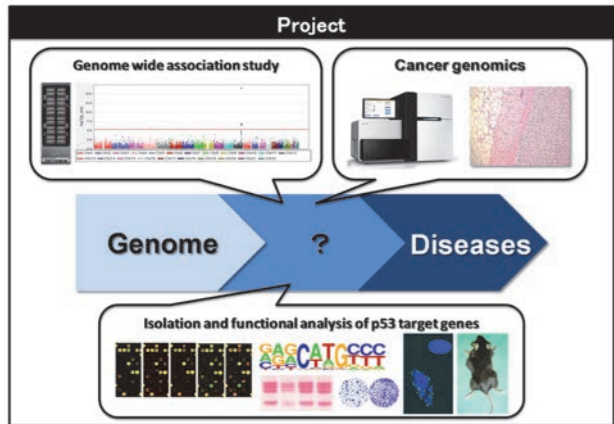
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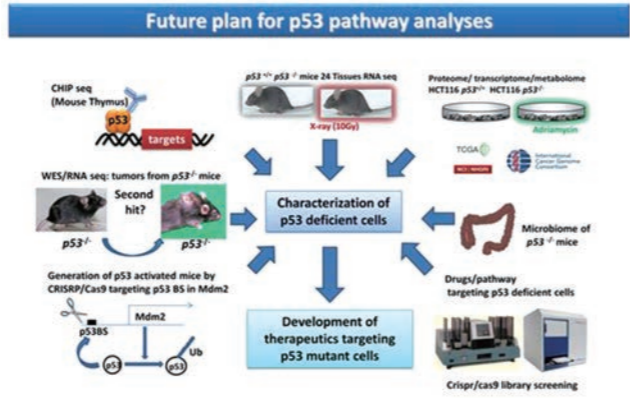
[Key Words] genome, cancer, p53, Large scale cohort, SNP

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



(<http://www.ims.u-tokyo.ac.jp/nakamura/matsuda/index.html>).



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Laboratory of RNA Biology

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[Key Words] RNA processing, function, structure, regulation

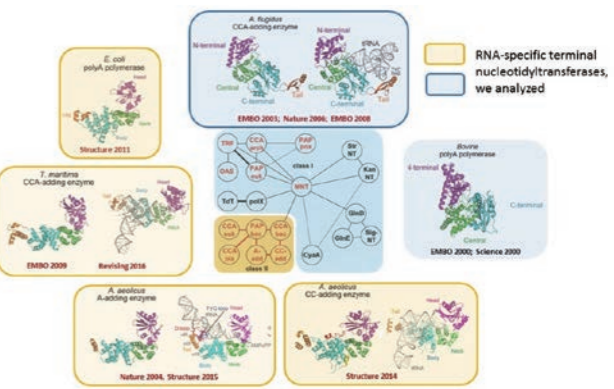
RNA processing, which includes maturation process of functional RNAs and biogenesis and metabolism of RNAs, is important step for the regulation of gene expression in cells. RNA processing dysregulations are often associated with the human diseases.

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/>

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Laboratory of Complex Trait Genomics

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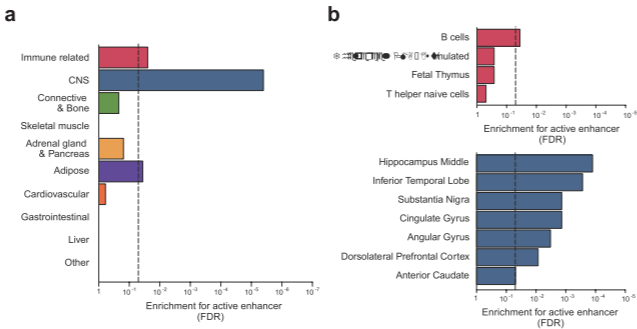
[Key Words] genome, statistical genetics, cellular network

Our laboratory aims to reveal complex trait genomics by applying statistical genetics approach with statistical learning to human genome and -omics data set.

A “trait” is a characteristic of an organism and characterizes an individual. It includes appearance, personality, laboratory tests, and diseases. A trait which cannot be defined by a few genes is called complex trait. Most of the complex trait exhibits heritability, and such traits are composed by multiple genetic factors and also environmental factors. We and several researchers employed genome-wide association study (GWAS) approach for complex trait analysis and identified more than tens or hundreds of susceptibility variants, and they are mostly located in the active gene regulatory region. Furthermore, we found that some of the complex traits are genetically closely correlated with each other. We suppose this might mean that differences in genomic sequence lead to individual complex trait as a result of the diversity of the general cellular response to various environmental factors. We think that this cellular response might be described as a non-linear network on the basis of genome.

Now we move to the next phase of complex trait genomics, and will perform integrative analysis for rare variants and -omics data. To detect genetic effects of common variants, GWAS, a linear model, worked very well. However, for these latest biological data sets we think non-linear model is required, and our aim is to apply statistical learning on the basis of statistical genetics, to create a novel analysis of complex traits.

Figure 1



Also, students will learn how to make use of complex trait genomics at clinical medicine or the society in the future.

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Laboratory of Molecular Oncology

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[Key Words] Hematopoietic neoplasms, Cancer stem cells, Molecular targeted therapy, Tumor immunity, Clonal hematopoiesis

“Curing cancer” was a dream. Today, advances in technology make it no longer a dream: A cure for cancer has become possible, even probable. Our laboratory is interested in the molecular, cellular, and genetic basis of cancers, with a specific focus on hematopoietic neoplasms. Our ultimate goal is developing curative therapies for cancer patients.

(1) Targeting transcription and epigenetic factors through PPI modulation

Transcription factors and epigenetic regulators play pivotal roles in various types of diseases. However, most of these molecules have been considered “undruggable”. We are trying to develop therapies targeting these “undruggable” molecules using the cutting-edge technology to modulate protein-protein interaction (PPI). For example, we found several compounds to inhibit the interaction between transcription factor RUNX1 and its cofactor CBFB using the AlphaScreen assay (Fig.1, left). We also identified STUB1 as an E3 ubiquitin ligase to induce RUNX1 ubiquitination and degradation (Publication 7). Based on the data, we are currently developing “PROTACs” to promote STUB1-induced RUNX1 degradation (Fig.1, right).

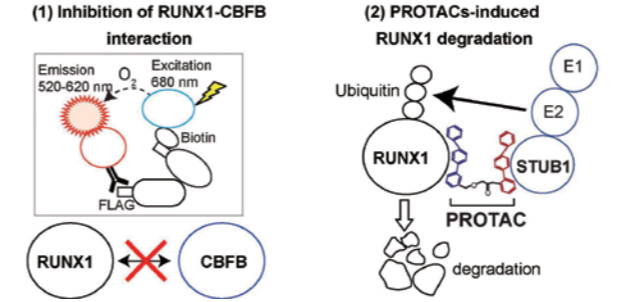


Fig.1. Two strategies to target transcription factor RUNX1

(2) Cancer Stem Cells and Tumor Immunity

To develop curative cancer therapies, we need to eradicate cancer stem cells, the key drivers of tumor progression, therapy resistance and relapse. Recently, we identified “immune

escape” as an important mechanism of leukemia stem cells to survive under the treatment of the p53-activating drug (Fig.2,

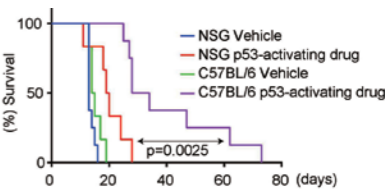


Fig.2. Leukemic mice were treated with the p53-active drug. The therapeutic effect was markedly attenuated in immunodeficient (NSG) mice compared to that in normal (C57BL/6) mice.

Publication 1). We are interested in how cancer stem cells resist and survive during chemotherapy, and how cancer stem cells evade from antitumor immunity.

(3) Cross talk between clonal hematopoiesis and solid tumors

Aging is associated with an accumulation of somatic mutations in hematopoietic stem cells, which results in clonal expansions of mutant blood cells (clonal hematopoiesis: CH). We are interested in the role of CH in the development of cancers and other age-related diseases. Our preliminary results suggest that the abnormal blood cells expressing CH-related mutations in fact supports the development of melanoma (an aggressive type of solid tumor) (Fi.3).

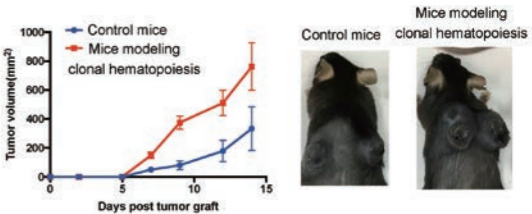


Fig.3. Melanoma cells were injected into control mice and the mice modeling clonal hematopoiesis (CH). Abnormal blood cells in the CH mice accelerated tumor progression.

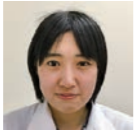
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(Underlined names indicate that they are students in CBMS.)

Laboratory of Multi-Omics Data Analysis

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Laboratory of AIDS Vaccine Development

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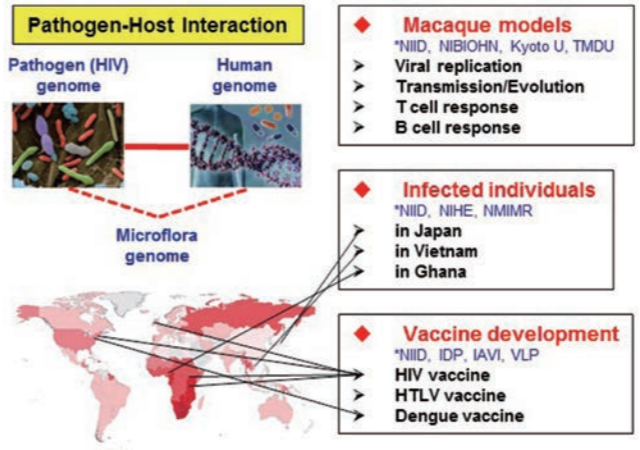


[Key Words] Pathogen-host interaction, Antibody & T cell responses, Vaccine development, HIV

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

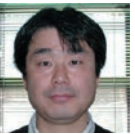


progression.

Laboratory of Innate Immunity

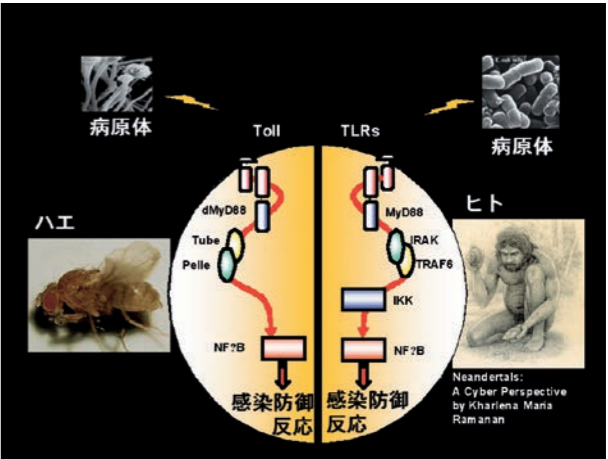
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[Key Words] immunology, innate immunity, toll-like receptor, autoimmune disease, disease model

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.



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 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

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 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)

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 Advanced Genome Medicine

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[Key Words] gastroenterology, inflammation, cancer, stem cell, microbe, animal model

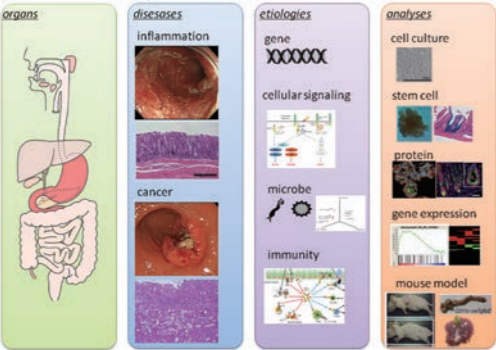
Our laboratory focus on the total pathogenic processes initiated at genome and extended to the whole body. The main object of our research is the inflammatory and malignant diseases developed in digestive systems.

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 world-wide 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>

Our research objects



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.

Laboratory of Molecular Pathology

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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 Medical Proteomics

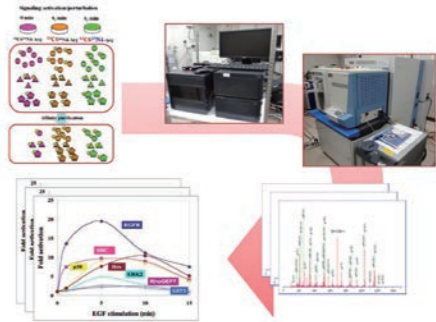
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Proteomics and systems biology of signal transduction networks
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[Key Words] proteomics, network analysis, cancer, signal transduction, translation control

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.



Large-scale network analysis of cellular signaling based on high-resolution proteomics technology

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>

Laboratory of Cell Signaling and Molecular Medicine

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

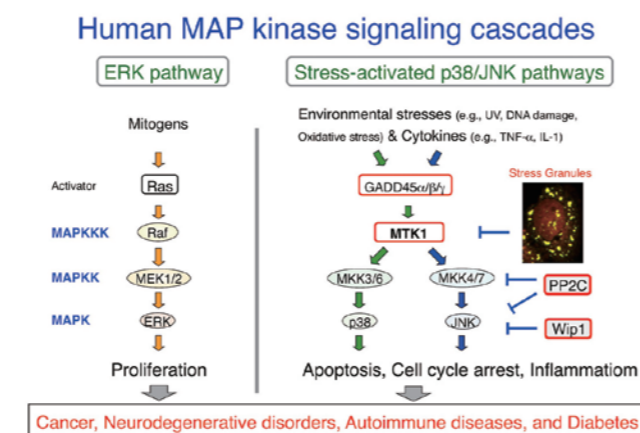
The aims and ongoing research projects in our laboratory are to elucidate molecular mechanisms that underlie the regulation of signal transduction systems, such as “MAP

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., TNF α), and are associated with inflammation, 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/>

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.

Laboratory of Cancer Cell Biology

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[Key Words] DNA methylation, epigenome, histone modification, DNA replication, senescence

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>)

Laboratory of Vaccine Science

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[Key Words] Vaccine, Adjuvant, Innate immunity, Clinical trial, Human immunity

Primary goal of our laboratory is to understand the immunological mechanisms of the intra- and inter-cellular signaling pathways that mediate the immunogenicity of successful vaccines, as well as biological responses to adjuvants. Such knowledge will enable us to develop novel concepts, modalities and next generation immuno-preventive and/or therapeutic agents against infectious diseases, cancer and allergy as well as other non-communicable diseases.

Future prospect;

Vaccine target diseases are now not only restricted to a framework of infectious diseases but include a broad range of diseases such as cancer, allergy, Alzheimer's disease, and many other lifestyle-related diseases. We will continue 'innovative' research and development vaccines against these diseases together closely with National Institute of Biomedical Innovation, Health and Nutrition (NIBIOHN) accompanying active exchanges of researchers.

Selected publications:

- 1: Masuta Y, et al. An Antigen-Free, Plasmacytoid Dendritic Cell-Targeting Immunotherapy To Bolster Memory CD8(+) T Cells in Nonhuman Primates. *J Immunol.* 2018 200(6):2067-2075.
- 2: Kuroda E, et al. Inhaled Fine Particles Induce Alveolar Macrophage Death and Interleukin-1 α Release to Promote Inducible Bronchus-Associated Lymphoid Tissue Formation. *Immunity.* 2016 45(6):1299-1310.
- 3: Kobiyama K, et al. Nonagonistic Dectin-1 ligand transforms CpG into a multitask nanoparticulate TLR9 agonist. *PNAS* 2014 111(8):3086-91.
- 4: Desmet CJ, Ishii KJ. Nucleic acid sensing at the interface between innate and adaptive immunity in vaccination. *Nat Rev Immunol.* 2012 12(7):479-91.
- 5: Koyama S, et al. Plasmacytoid dendritic cells delineate immunogenicity of influenza vaccine subtypes. *Science Transl*

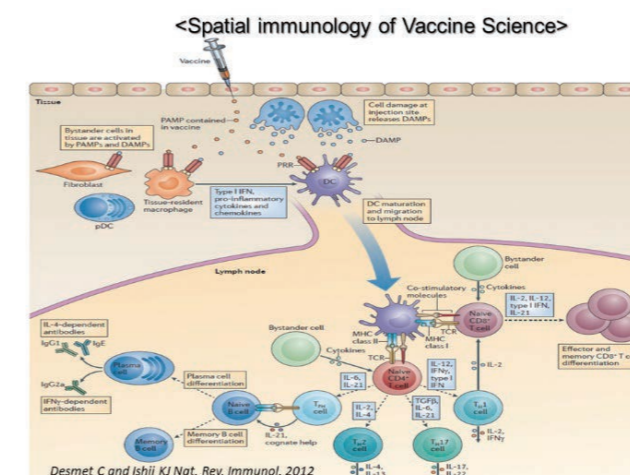
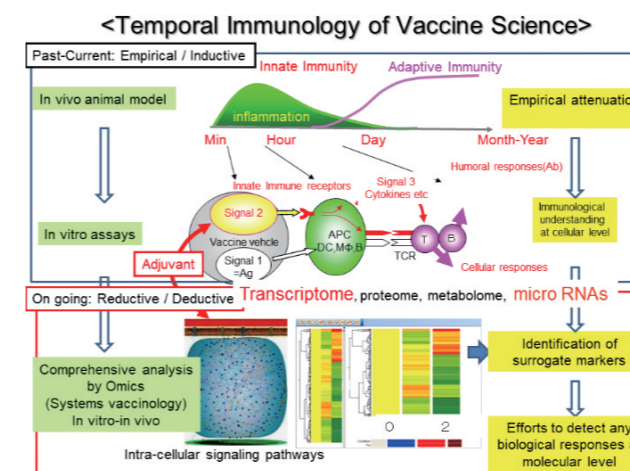
Med. 2010 31;2(25):25ra24.

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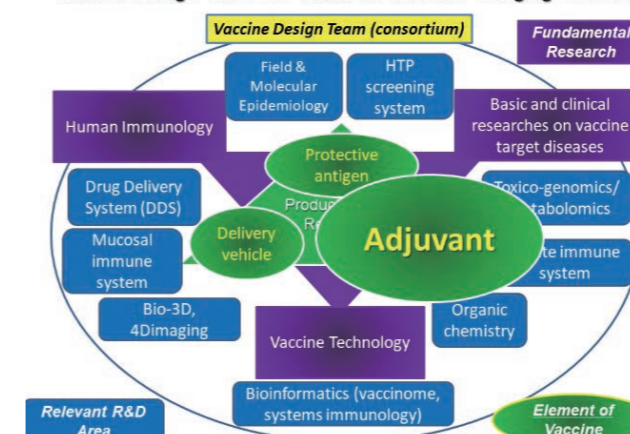
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Vaccine Design Team will create an ultimate 'merging' science



Laboratory of Animal Genetics

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[Keyword] Genome editing, Laboratory animal science, Humanized animal, Developmental engineering, Regenerative Medicine, Immunodeficient rat, Gene therapy, Immunotherapy, CRISPR/Cas3

Prof. Mashimo came to the University of Tokyo and set up this new laboratory in June, 2019. The genome editing technology (ZFN, TALEN, CRISPR/Cas, etc.) brought a revolution in the development of medical science and life science. By using this technology, we can easily operate genomes in different human cell lines or laboratory animals, which is widely applied in investigation of genes' function, generating animal models for human diseases, gene therapy and so on.

The main subjects in our laboratory including: (1) development of novel genome editing system, CRISPR/Cas3, and related application in the cell therapy and gene therapy for human diseases; (2) generation of new animal models by conducting genome editing in animal zygotes, especially the humanized animals which are modified by human genome. Furthermore, we are also working on developing humanized animals with human organs by transplanting human somatic cells or iPS cells into immunodeficient animals. Following is the detail research interests in our laboratory:

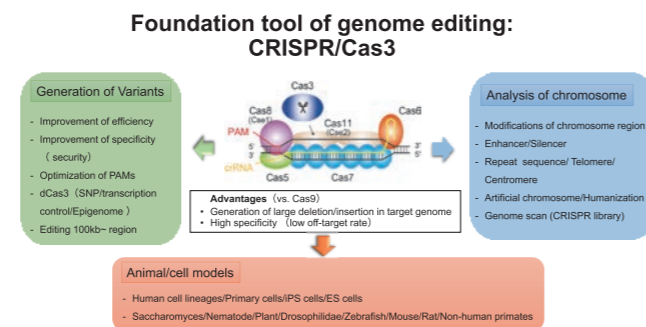
1. Development of CRISPR/Cas3 system.

- (1) Development of highly Efficient immunotherapeutic strategies by genome editing in human somatic cells, iPS cells, T cells, etc;
- (2) Virus vectors (AAV), Liposome drug delivery system, Genome editing in vivo;
- (3) Library of CRISPR/Cas3, Genome scan.

2. Generation of humanized animals which carry human genome or tissues

- (1) Humanized animal (genome): modify the genome of laboratory animals with human genes by genome editing tools.
- (2) Humanized animal (tissue): transplant human cells or tissues into the immunodeficient animals.

Location: 2nd Floor of General research building, The Institute of Medical Science



Laboratory of Malaria Immunology

Professor Cevayir COBAN

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[Key Words] Immunopathology, Malaria, Vaccine, Imaging

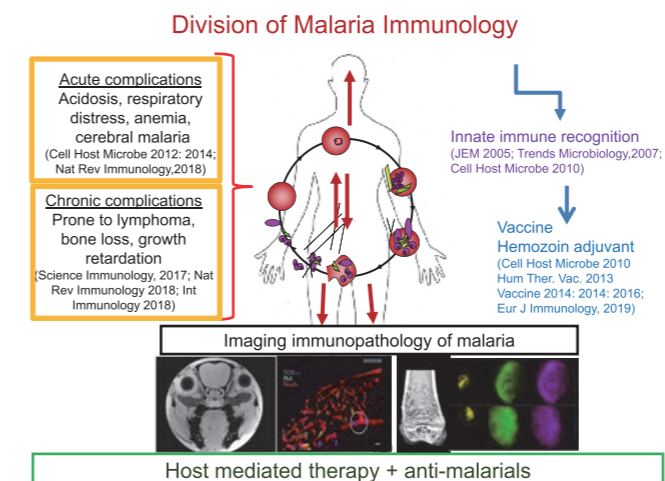
Although it is eradicated in most countries, malaria, however, is still the disease for poor affecting about 100 countries in the world. There is no successful vaccine available against malaria yet. Why years of scientific research cannot beat *Plasmodium* parasites (a causative agent of malaria) and eliminate them by vaccines is an important question in my lab. Moreover, while acute malaria kills mostly children, chronic malaria causes unforeseen complications which are not fully understood. We have focused on the host-*Plasmodium* interactions aiming at understanding how these parasites manipulate the immune system particularly in the context of specific tissue/organs and their specific cell environment (i.e. brain, bone). To achieve our goals we use cutting edge information and technologies. Our overall aim is to use the knowledge derived from state-of-the-art modalities to develop host-mediated therapies to heal acute and chronic complications of malaria and develop new vaccination strategies.

We support our students to access knowledge and provide international environment to enjoy scientific endeavors driven by a scientific curiosity. We believe *Plasmodium* parasites are challenging tool to study scientific questions related to immunology, parasitology and biology.

<https://www.ims.u-tokyo.ac.jp/malimmun/>

Selected publications from the Malaria Immunology Laboratory:

International Immunology, **2020**; Cytometry A, **2019**; European J Immunology, **2019**; Nature Review Immunology, **2018**; Science Immunology, **2017**; Cell Host Microbe, **2014**; Cell Host Microbe, **2012**; Cell Host Microbe, **2010**; Trend. Microbiology, **2007**; J Exp. Medicine, **2005**



Laboratory of RNA Function

Professor Yukihide TOMARI

Mechanism and function of non-coding RNAs

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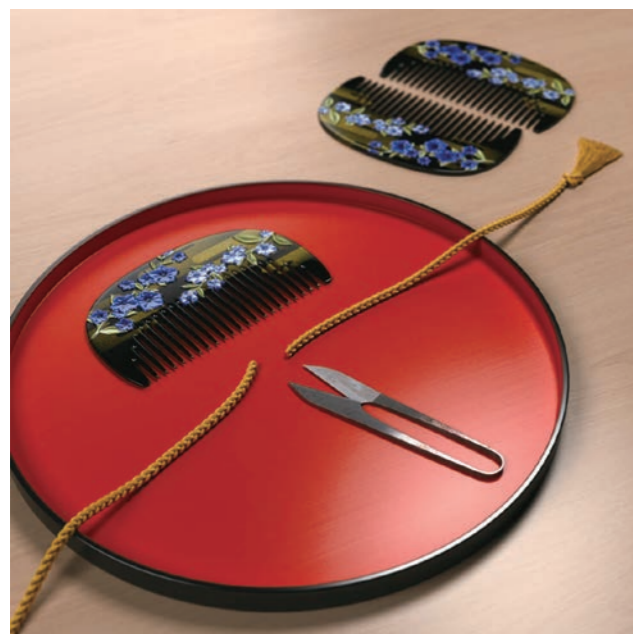
[Key Words] RNA, silencing, biochemistry, biophysics

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>



siRNAs (combs), a major class of small RNAs, silence their target mRNAs (cords) by cleaving (scissors) the complementary sequences via the effector complex, termed RISC (tray).

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

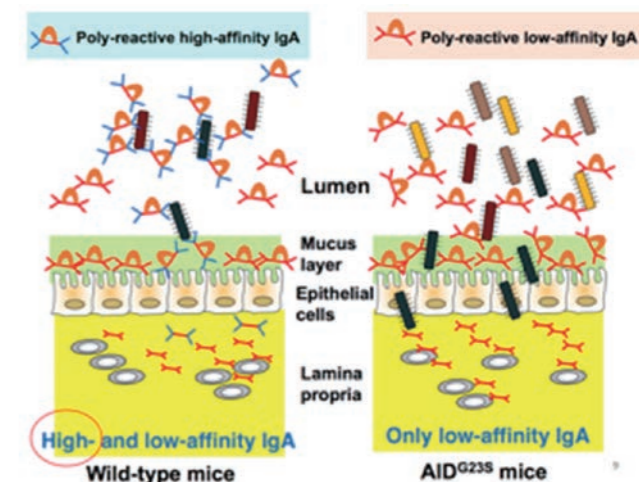
We have found that a N-terminal mutant AID (G23S; glycine to serine mutation at the 23rd AA) showed defective SHM but relatively intact CSR both *in vitro* and *in vivo*, suggesting the N-terminus of AID may be the domain responsible for SHM-specific co-factor binding. Through the search of SHM-specific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

Laboratory of Biomedical Sciences

(Tokyo Metropolitan Institute of Medical Science)

Professor Keiji TANAKA

Protein Recycling System — Science of Protein Turnover—

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【Key Words】 Protein Degradation, Proteasome, Ubiquitin, Autophagy, Mitophagy

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- κ B 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 RABGEF1, 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.

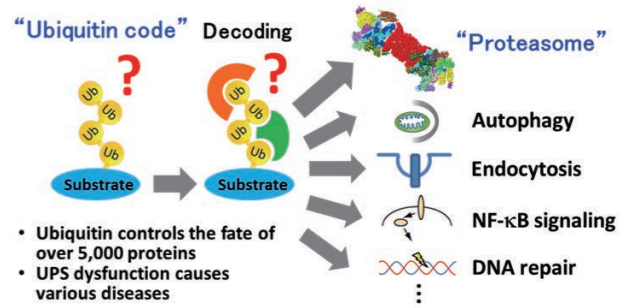


Figure 1. The Ubiquitin proteasome system

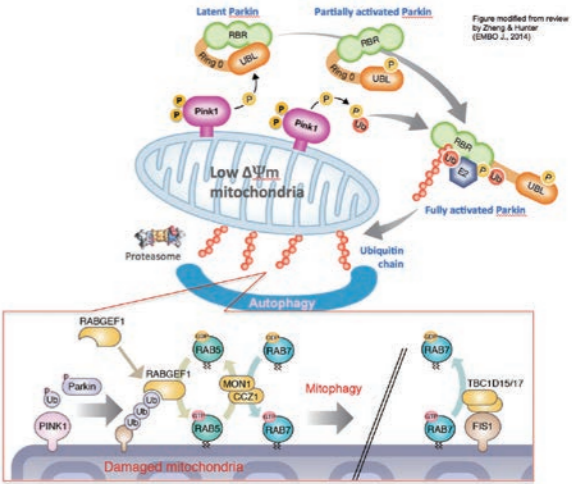


Figure 2. Ubiquitin-mediated mitochondria quality control by Pink1 and Parkin

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[Key Words] DNA replication, genome stability, cell cycle, chromatin architecture, DNA replication stress checkpoint, G-quadruplex, RNA-DNA hybrids, cancer cells

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 (15,18).

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**; 11). Recent reports indicate crucial roles of these non-canonical DNA/ RNA structures in diverse biological reactions as well as in pathogenesis of diseases (**Fig. 1**). 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

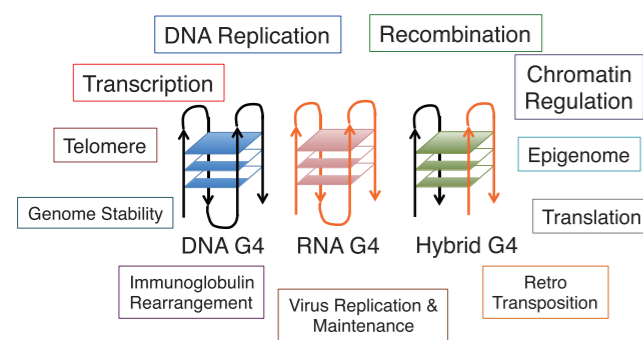


Figure 1. Various G-quadruplex (G4) are generated on DNA, RNA and DNA-RNA hybrid with varied shapes, and are involved in a number of chromatin regulations.

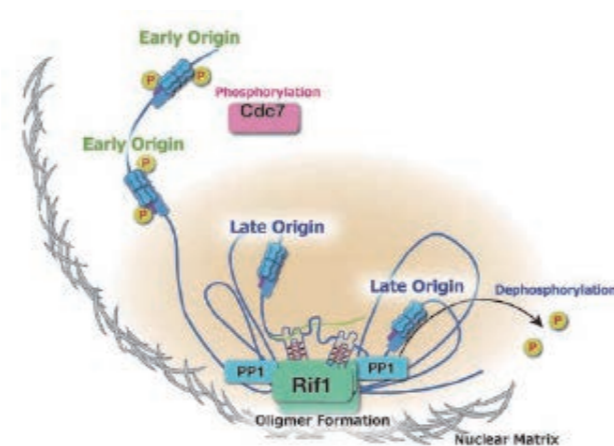


Fig. 2 Rif1 regulates chromatin architecture near nuclear periphery by binding to G4 structures on the genome.

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 (1,9,10,13). 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 (1,3,4,6,11,12,14,16,17). 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 and blood cells. 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 (2).

To achieve these goals, we are using *E. coli*, fission yeast,

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, Hong Kong, Vietnam, 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. Interview by Skype is also welcome.

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

Why is homo sapiens 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 time's 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/>

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Laboratory of Functional Biomolecules Engineering

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Protein engineering, evolutionary molecular engineering, synthetic biology, biologics, pharmaceutical proteins

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[Key Words] protein engineering, evolutionary 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 evolutionary 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] evolutionary 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.

Refs) *Curr Opin Biotechnol* 20: 616–22 (2009); *ISME J* 3: 1335–48 (2009); *Environ Microbiol* 9: 2289–97 (2007)

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.

Ref) *J Biol Chem* 281: 10236–42 (2006); *Trends Biochem Sci* 26: 100–6 (2001); *J Mol Biol* 297: 1015–26 (2000)

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 to the question on the robustness of life (or ribosome) and to use thus engineered organisms for industrial applications.

Ref) *Nat Commun* 2: 549 (2011); *PNAS* 109: 19220–5 (2012)

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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 technology, necleic 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

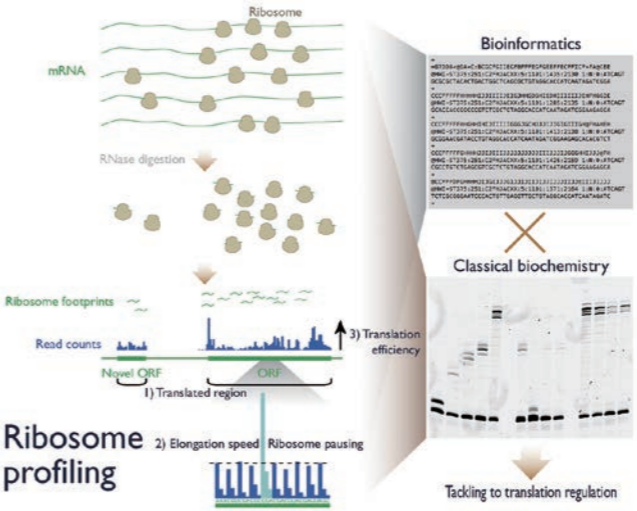
this technology, we are using “ribosome profiling”, which allows one to survey which RNAs are translated and which codons are decoded by ribosome, among transcriptome comprehensively. Indeed, this technique is revolutionizing our understanding of translation dynamics in cells.

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!



Laboratory of Molecular Target Therapy of Cancer

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

Now in Japan, we are facing the era when one in two people will experience cancer. While more than 370 thousand people die of cancer every year, its age-adjusted mortality rate is decreasing. One reason for this trend is that molecular targeting drugs have significantly improved the treatment outcomes for cancer patients. However, we still have many unsolved problems, including cancer without obvious Achilles’ heel, undruggable target molecules and drug resistance, which hinders complete eradication of the disease. This Laboratory consists of three independent labs, which are investigating mechanisms for telomere maintenance and cancer stemness (Seimiya lab), cellular adaptation to tumor microenvironment (Tomida lab), anticancer drug resistance and cancer metastasis (Katayama lab), respectively. Based on these basic researches, we are also conducting applied and translational researches for new drug development.



Professor Hiroyuki SEIMIYA

Telomere biology, cancer stemness, and drug discovery.

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[Key Words] Molecular Target, Cancer 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 innovative druggable seeds. First, we are developing telomere-targeting drugs, such as G-quadruplex (G4) ligands, which stabilize G4s, unusual higher-order nucleic acid structures

in the genome, and preferentially attack glioma stem cells and other intractable cancer. Second, we are developing chemical inhibitors for the poly (ADP-ribose) polymerase called tankyrase. This enzyme promotes telomere elongation by telomerase and Wnt/ β -catenin signaling in cancer. Third, employing functional genomics and comprehensive gene expression and single-cell analyses, we are pursuing therapeutic molecular targets of cancer stem cells. (http://www.jfcr.or.jp/english/chemotherapy/department/molecular_biotherapy/index.html)

Professor Akihiro TOMIDA

Cell biology and chemotherapy in tumor microenvironment.

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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. (<http://www.jfcr.or.jp/english/chemotherapy/department/genome/index.html>)

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Drug resistance and cancer metastasis

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[Key Words] Drug resistance, kinase inhibitor, immune checkpoint inhibitor, cancer metastasis, platelets

One of the goals of our research is to identify the molecular mechanisms of the drug resistance against molecular targeted therapy and immune checkpoint inhibitor in cancer, and find the therapeutic strategies to overcome the resistance. To achieve the goal, we examine the resistant mechanisms using the clinical specimens from the cancer patients relapsed on those drug treatments by collaborating with the physicians in our cancer institute hospital in JFCR, under approved IRB.

We also focusing on the mechanisms of cancer metastasis (the spread of cancer cells from the primary tumor organ to surrounding tissues or distant organs), which is the primary cause of cancer morbidity and mortality. We previously identified that Aggrus/Podoplanin overexpression in cancer cells induce platelet aggregation thar resulting in the formation of pulmonary metastasis. Thus, we are now developing anti-Podoplanin targeted monoclonal antibody and inhibitors. (<https://www.jfcr.or.jp/chemotherapy/department/fundamental/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 biblio-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 biblio-metrics 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.

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 micriRNA 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”.

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 cuttingedge 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.

Laboratory of Omics

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[Key Words] DNA, Omics, Single cell analysis, algorithm, parallel computation, Machine Learning

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;

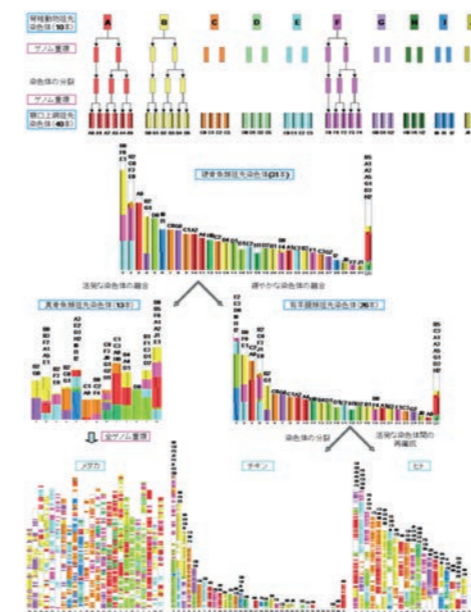


Fig. 1 : Chromosomal evolution in vertebrates
(Source in: *Nature*, 447 : 714–719, 2007, *Genome Research*, 17(9) : 1254–1265, 2007)

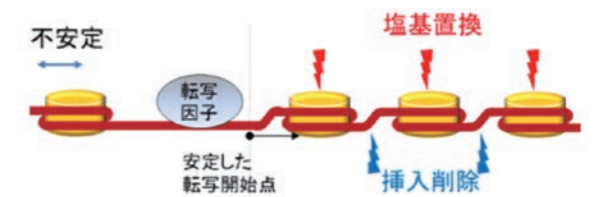


Fig. 2 : Chromatin-correlated genetic variation
(Source: *Science*, 323(5912) : 401–404, 2009)

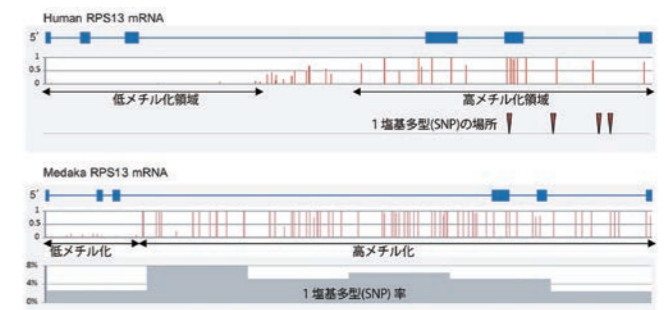


Fig. 3 : More mutations are seen around methylated CpGs
(Source: *Genome Research*, 22 (8) : 1419–1425, 2012)

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 $10\mu\text{m}$ 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 $\sim 200\text{bp}$ 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).

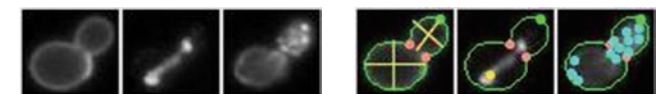


Fig. 4 : Raw images of budding yeast (left) and processed images (right)
(Source: *PNAS*, 102 (52) : 19015–20, 2005)

Laboratory 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 mRNAs.

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”
KAKANHI 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.

Laboratory of Systems Genomics

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[Key Words] genome, transcriptome, epigenome, cancer genome, genomic drug discovery

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, biding 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 a 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 filed 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.

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Laboratory of Large-scale Knowledge Discovery

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[Key Words] Machine learning, Artificial Intelligence, Bioinformatics

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.

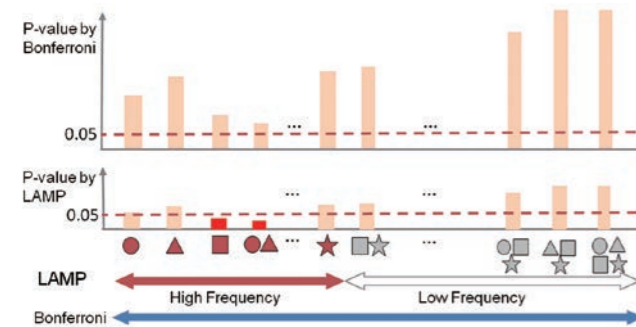


Fig. 1 Combinatorial effect discovery by LAMP

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

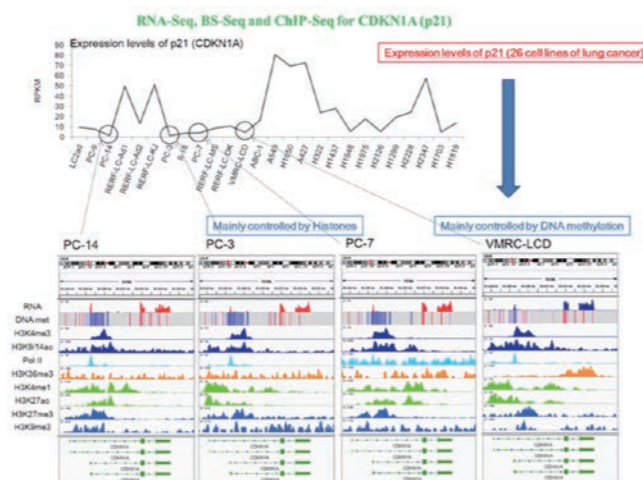


Fig3. Subgraph features discovered from chemical data by gBoost

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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.

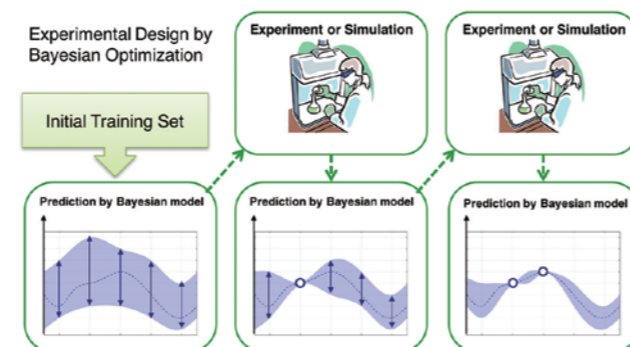


Fig. 2 Automatic design of molecules and materials.

Machine learning and data mining

We are also committed in developing fundamental theories and algorithms for machine learning and data mining. It requires expertise in statistical theories, discrete algorithms and optimization. For example, we have developed the gBoost algorithm that accurately predicts properties of graph-structured data such as chemical compounds [2]. In addition, fast methods to discover similar pairs from a large dataset are in focus. These methods are expected to contribute in multi-omics data analysis including genomic, epigenomic and metabolite data.

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.

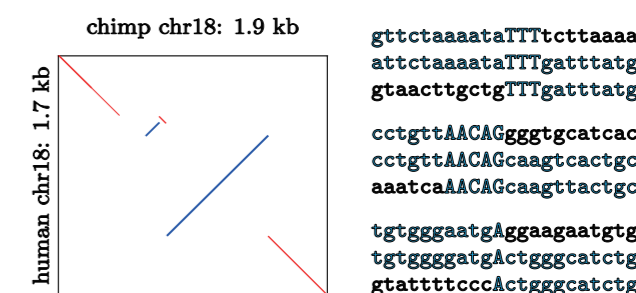


Fig.1 A complex rearrangement in the human genome, with microhomologies at the breakpoints

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].

tatatacatatgtgtgtgtgtatataatatacacacacaca
aaataaaataaaaaaattaggtattaaattataactgtaaaaat

Fig.2 Two types of “complex” simple sequence.

Another long-term interest is promoter sequences and DNA motifs that regulate gene expression. The aim is to understand the function and evolution of features such as CpG islands, and ultimately the DNA “code” that controls

gene expression.

Further interests are everything “weird”: malaria genomes (80% A+T), frameshifts (especially in microbial metagenomes), unexplained evolutionary conservation, trans-splicing, etc.

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.

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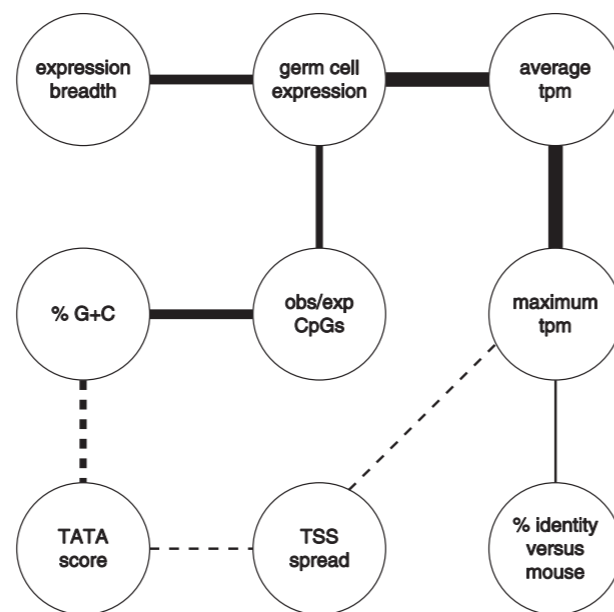


Fig.3 Direct correlations (solid) and anticorrelations(dashed) among properties of promoters [3] .

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.

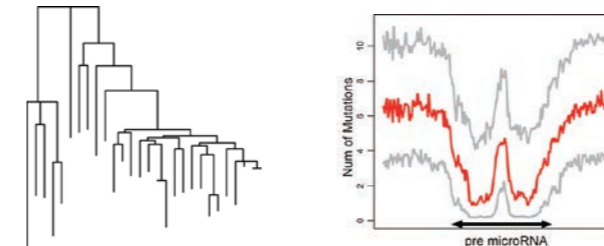


Fig. 2: (Left) Phylogenetic tree analysis of local evolution in 28 vertebrate species, including human, calculated using Fdur, a program that we developed. (Right) Base substitution patterns in micro-RNA regions calculated by Fdur.

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

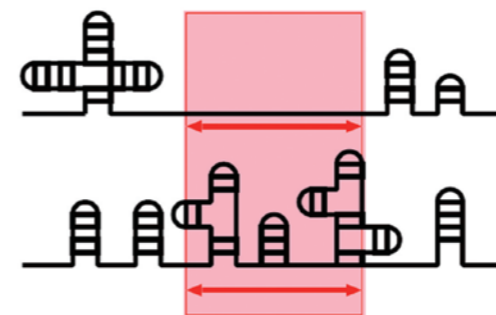


Fig. 1: Genomic-scale sequence analysis using the software tool Raccess to calculate RNA accessibility. Raccess is useful for determining which region forms exposed secondary structures in all regions of RNA transcription.

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.

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. What do you use the DNA sequence for in 2025? Most functional elements on genomes will be identified. The cause of most common heritable diseases will be identified. Probably we will have learned how cancers happen and evolve. Common cold will be classified into more specific diseases according to pathogens, which are easy to identify by DNA/RNA sequencing. We will not need broad-spectrum antibiotics anymore, being less worried about multidrug-resistant

pathogens. We may even identify species in a sushi restaurant to reveal fish are illegally taken.

However, such futures would not be realized without developing computational analysis methods for new and big data. A big reduction in DNA sequencing cost requires a big reduction in analysis cost by nature. We aim for developing analysis software for new measurement devices including emerging DNA sequencers.

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.

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).

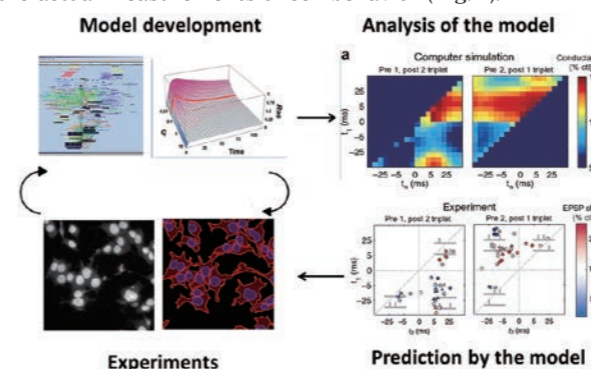


Fig. 1 Strategy of Systems Biology

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 shown 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.

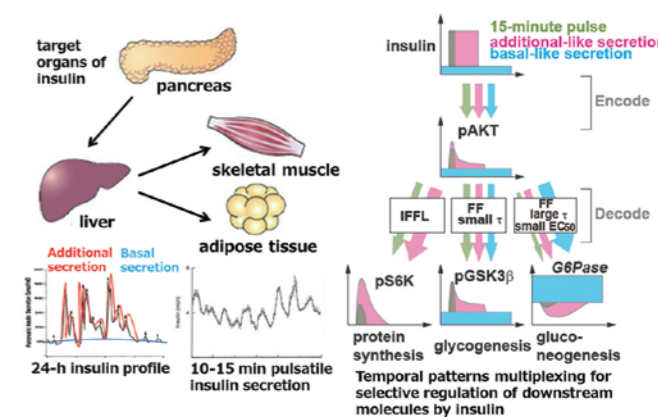


Fig. 2 Temporal coding of insulin action

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.

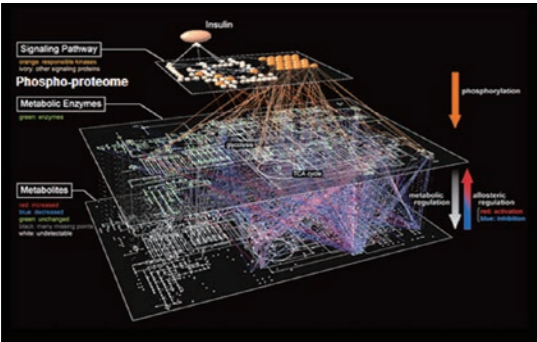


Fig. 3 The large-scale trans-omic networks

Laboratory of Bioinformatics and Systems Biology

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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.

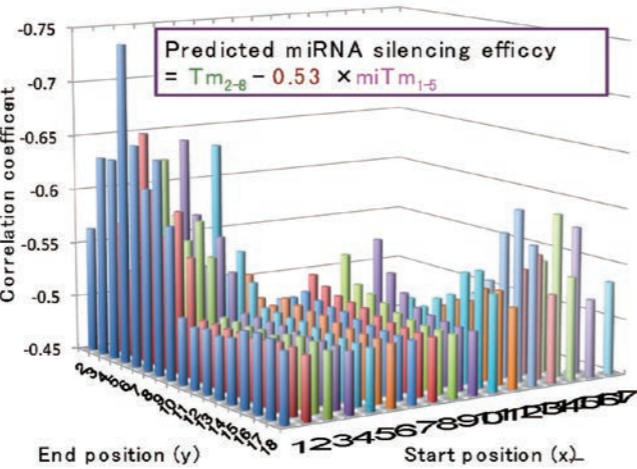


Fig. 1 :Optimization of the factors to estimate possible miRNA-mediated gene silencing efficacy.

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

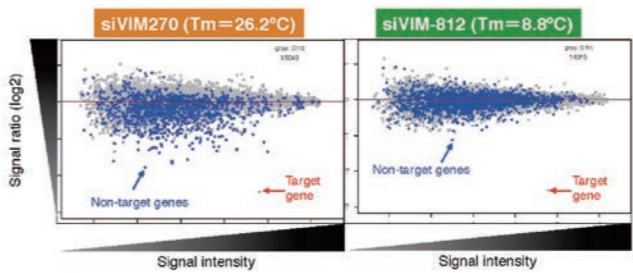


Fig. 2: Confirmation of target gene-specific RNA interference by microarray. The siRNA with strong base-pairing in the seed-target region (left), siRNA with weak base-pairing in the seed-target region (right).

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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[Keywords] Evolutionary and ecological bioinformatics, Genome and life system evolution, Metagenomics, Microbial dark matter, Environmental DNA

Evolutionary and ecological bioinformatics

The field of biology has expanded from the traditional approaches of focusing on specific organisms and phenomena to utilizing data science approaches in the pursuit of obtaining a comprehensive understanding of life. Under this context, our laboratory employs interdisciplinary approaches, including but not limited to: bioinformatics, laboratory experiments, mathematics, and field samplings to study evolution and ecology of diverse life forms, and to develop novel biotechnological methods.

Bioinformatics

Mathematics
$$N_{cut} = W_{AB} \left(\frac{1}{d_A} + \frac{1}{d_B} \right) \\ = \frac{p^T (D - W) p}{(a + b)^2} \cdot (a + b)^2 \\ = \frac{p^T (D - W) p}{p^T D p}.$$

Lab Experiment

Field Sampling

Fig. Four approaches adopted in our laboratory

Research Topics

1. Evolutionary and ecological bioinformatics
2. Evolution of genomes and life systems
3. Microbial dark matter, non-model organisms
4. Microbial ecology, metagenomics
5. Environmental DNA

In particular, we are aiming at the following objectives:

- (1) Finding new principles behind the evolution of genomes and life systems
- (2) Finding new principles behind the development of complex ecosystems
- (3) Revealing and utilizing functions of uncultured microbes and non-model organisms
- (4) Identifying novel biological concepts based on meta-analysis and multi-level analysis of large-scale datasets
- (5) Developing new experimental methods for expanding metagenomic and environmental DNA technologies
- (6) Developing new bioinformatic methods for accelerating these researches

Joining our laboratory as a graduate student

We welcome students 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. If you are interested in joining our lab, please examine our publication list on our laboratory website and email the Principal Investigator.

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 additional information on our laboratory website.

Address

Our laboratory is located on Hongo Campus of the University of Tokyo, which is near the center of Tokyo.
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[Key Words] Genomic Medicine, Trans-omics, Precision Medicine, Cancer Immunology

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.

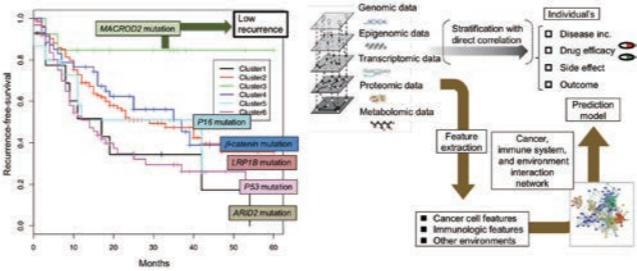


Figure 1. Classification and prognosis with genomic mutations of liver cancer (left), treatment prediction by cancer immunology (right).

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 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.

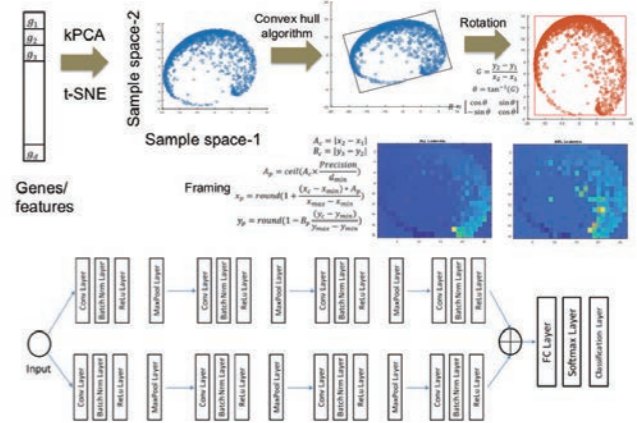


Figure 2. A methodology to transform a non-image data to an image for convolution neural network architecture.

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 [3].

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.

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Informatics of Biological Functions

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[Keywords] Genomics, Next generation sequencer, data-driven analysis, multi-NGS omics

Genome-wide analyses with Next Generation Sequencer (NGS) is a mainstream method in computational genomics and has led to important discoveries for dynamic regulation of the genome related to diseases, cell differentiation and evolutionary conservation. Our group has been trying to develop new tools and analyze various NGS data including ChIP-seq, ATAC-seq, RNA-seq, Exome-seq, Hi-C, ChIA-PET, and Single-cell analysis, to extract important biological information from large-scale datasets (~ hundreds of samples), namely “data-driven analysis.” Our aim is to develop a pipeline for multi-NGS omics that integratively analyzes large-scale datasets from multiple NGS assays and achieve an epoch-making discovery, e.g., higher-order coordination of multiple DNA-binding factors. Currently we mainly focus on the ChIP-seq (epigenome), Hi-C (3D genome folding) and single-cell analysis (cellular heterogeneity in tissue samples). We accept students both of biology and of informatics who are interested in bioinformatics.

Research themes:

- Develop a tool for integrative NGS analysis (e.g., ChIP-seq and Hi-C)
- Quality assessment, normalization and visualization of NGS data
- Whole-genome annotation using multiple NGS data
- Machine-learning method for imputation and noise reduction to refine NGS data
- Fast and memory-efficient computation for large-scale NGS analysis
- Collaboration with biology labs: obtain new biological insights from new NGS data
- Other collaborative themes also available: in-silico simulation of 3D genome (polymer simulation), time-course modeling of single-cell RNA-seq data (systems biology)

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Laboratory of Informatics of Molecular Functions

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[Key Words] Protein structure prediction, Structure comparison, Protein function prediction, Drug discovery, Sequence 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].

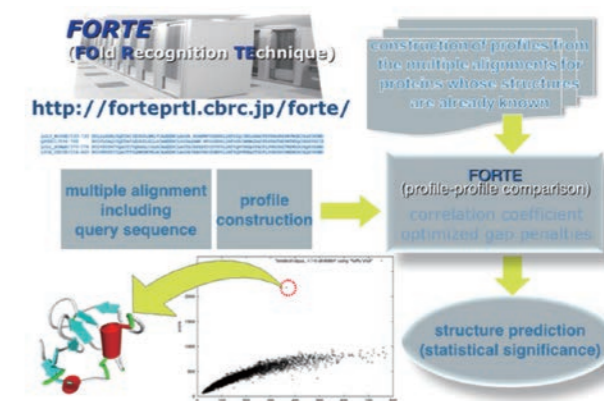


Fig. 1: Protein structure prediction using FORTE

We have also succeeded in comparing protein profiles related to sequence (evolution) and structure to discover common sequential and conformational characteristics between unrelated proteins [7].

Research at our lab

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

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Laboratory of Informatics of Molecular Functions

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[Key Words] Protein 3D-structure modeling, Protein-ligand docking, Pharmacoinformatics, Molecular Dynamics

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

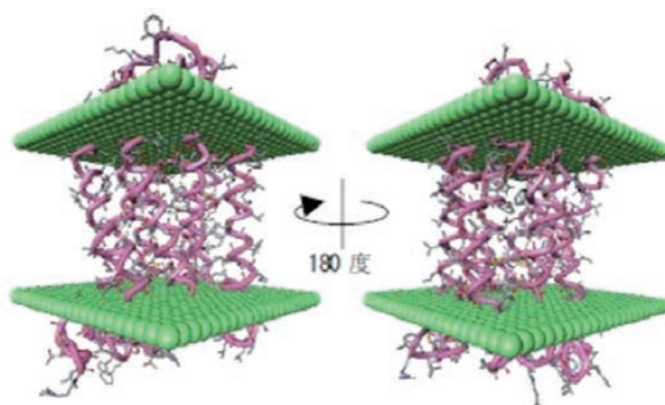


Fig. 1: Molecular modeling of a human H2 histamine receptor. Projection is in the horizontal direction from the membrane (green).

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).

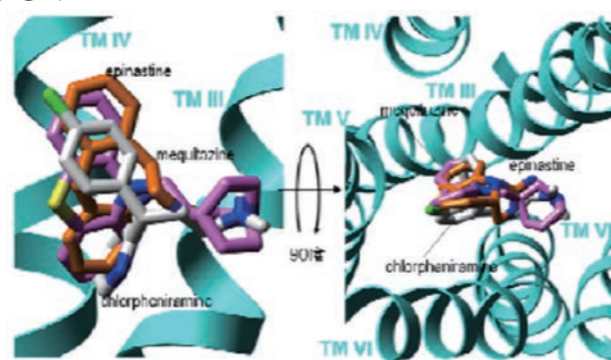


Fig. 2: A binding model for three types of inhibitor for a histamine H1 receptor, selected by CoLBA.

Virtual screening

Virtual screening is performed based on molecular modeling of a target protein and a binding model between the target protein and a compound, as obtained from a

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 Informatics of Molecular Functions

(AIST)

Associate Professor Yutaka Saito

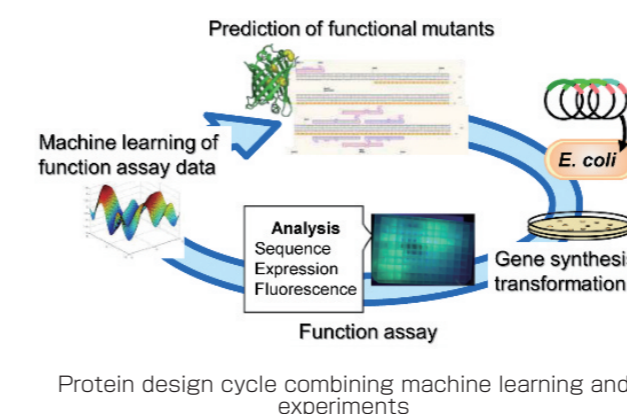
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[Key Words] Machine learning, Bioinformatics, Protein engineering, Epigenome, RNA, Robotic biology

Information technology accelerates life science research

Even with the recent advances in experimental technologies, life science research still involves numerous trials-and-errors and reproducibility issues. We tackle these problems using machine learning and bioinformatics approaches. We also develop informatics methods for enhancing the applicability of experiment robots, aiming to establish “laboratory automation by experiment robots” as a future direction of life science research.



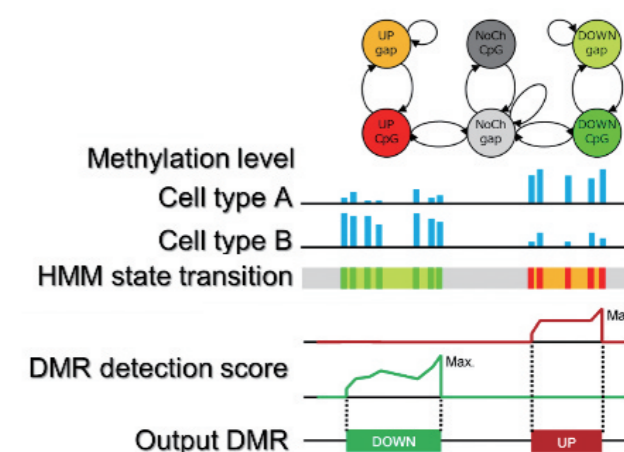
Machine-learning-guided design of biomolecules: proteins, mRNAs, promoters

The development of functional proteins such as antibod-

ies and enzymes involves trials-and-errors where a lowly-functional wild-type protein is to be improved by random mutations. To accelerate this process, we proposed a machine-learning method based on Bayesian optimization that predicts mutations for improving the protein function to the desired direction. In the collaborative work with experimental biologists, we demonstrated that our method successfully altered the green fluorescent protein (GFP) into the yellow fluorescent protein (YFP). Recently, we also develop methods to design mRNA codon sequences for improved translational efficiency, and to design promoter sequences for improved transcriptional activity.

Omics data analysis: from DNA methylation to 3D genome structure

We develop bioinformatics methods for omics data analysis. Examples are: BPLA Kernel that predicts noncoding RNAs from sequence data, ComMet that detects differentially methylated regions from DNA methylation data (bisulfite-seq), and Cosearge that detects spatial co-localization of genomic elements from 3D genome structure data (HiC-seq). We also apply these methods in the collaborative work with experimental biologists: BPLA Kernel was used to find snoRNAs in the worm genome, and ComMet was used to analyze epigenomic changes in fat differentiation. Recently, we also study DNA methylation in industrially-important microorganisms.



ComMet detects differentially methylated regions with hidden Markov models

Robotic biology: towards laboratory automation by experiment robots

Experimental technologies in life science often involve reproducibility issues depending on persons who conduct experiments and/or laboratories where experiments are conducted. These problems could be resolved by experiment ro-

bots that can conduct exactly the same procedure repeatedly based on an electronically-described experimental protocol. However, current experiment robots have limitations e.g. they only support a limited set of pre-defined movements, hindering their applications. We are developing informatics methods for enhancing the applicability of experiment robots using “Maholo” installed in AIST as a model case. For example, we plan to develop “human-robot protocol translation” method that enables to transform a human experimental protocol to the equivalent robot protocol using a pre-defined set of movements.



Experiment robot “Maholo”

Research environment: Students can select different research styles including (1) develop new machine learning and/or bioinformatics methods, (2) analyze publicly available data for new biological findings, and (3) analyze data in a collaborative work with experimental biologists. The laboratory location is Artificial Intelligence Research Center, AIST (Tokyo, Odaiba).

Laboratory of Computational Systems Biology

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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

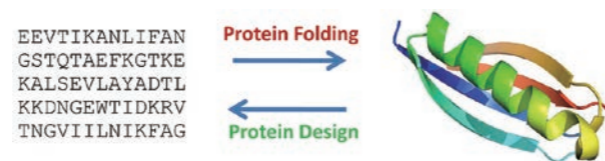
correctly folded native structure is critical for the proper function of a protein in a cell. Small deviations from its native structure can often lead to malfunction of the protein and cause diseases. We are interested in understanding the protein functions through computational studies of their structures. 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.

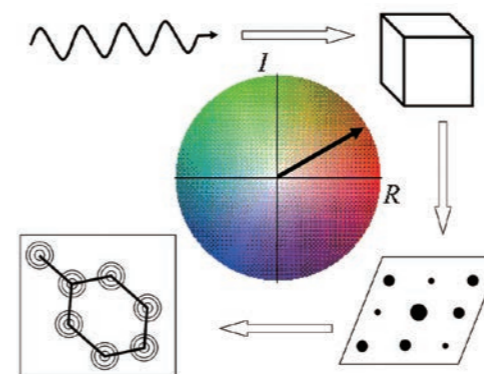
Protein design allows us to explore large regions of the protein universe not yet observed in nature. Recently, we have developed a very efficient method and have used it to design the first perfectly symmetric β -propeller proteins that self-assemble according to simple arithmetic rules. We are interested 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

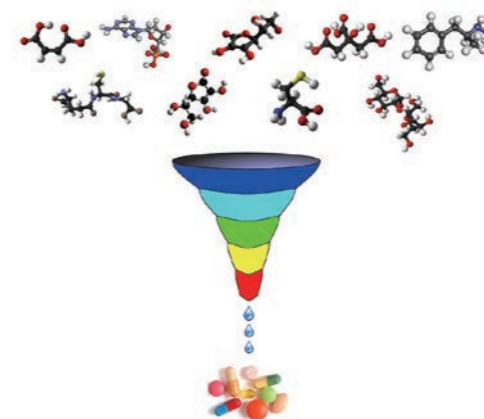
We are developing new computational methods to solve the X-ray crystallographic phase problem for protein structure determination. Our efforts are focused on improving de novo models predicted computationally so that they can be used as templates for structure determination by molecular replacement. 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.



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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.

Laboratory of Life Science Database Integration

Professor Susumu GOTO

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<https://dbcls.rois.ac.jp>



[Keywords] Database integration, Semantic web, Genome analysis, Functional analysis, Text mining

In the life science research field, a huge amount of data is produced by the omics and other projects for various species and it is becoming more and more important to build databases for dealing with such data that has led to a large number and various types of databases. Our laboratory, Database Center for Life Science in Research Organization of Information and Systems, focuses on the research and development of technologies for the integrative use of databases in the life science research field. We mainly apply semantic web technologies to the database integration, specifically linked open data and resource description framework (RDF). We are developing tools and methods for creating RDF-based data sets, middleware for efficient and effective access to the data sets, and application programs to search various information such as genomes and their functions, genome variations and their medical implications, etc. using the middleware. We are also developing tools and methods for extraction knowledge from literature that can augment the current database contents.

DEPARTMENT MEMBERS (COMPUTATIONAL BIOLOGY AND MEDICAL SCIENCES)

		LABORATORY	PROFESSOR	ASSOCIATE PROFESSOR/ LECTURER
MEDICAL SCIENCES GLOUP	CORE LABORATORIES	BIOMOLECULES		Nono TOMITA
		MOLECULAR GENETICS	Koichi ITO	
		FUNCTIONAL GENOMICS		Manabu WATANABE
		TUMOR CELL BIOLOGY	Kaoru UCHIMARU	Hitoshi SATOH
		/VIRAL ONCOGENESIS		Kazumi NAKANO
		GENOME TECHNOLOGY	Koichi MATSUDA	
		RNA BIOLOGY	Kozo TOMITA	
		COMPLEX TRAIT GENOMICS	(TBA)	
	SOCIAL COOPERATION LABORATORY	MULTI-OMICS DATA ANALYSIS		Ayako SUZUKI
	INTRA- UNIVERSITY COOPERATIVE LABORATORIES	INFECTIOUS CONTROL SCIENCE		Misako YONEDA
		AIDS VACCINE DEVELOPMENT	Tetsuro MATANO	
		INNATE IMMUNITY	Kensuke MIYAKE	
		CELLULAR AND MOLECULAR BIOLOGY	Jun-ichiro INOUE	
		FUNCTIONAL ANALYSIS <i>IN SILICO</i>	Kenta NAKAI	
		CELLULAR THERAPY		Susumu GOYAMA
		MOLECULAR VIROLOGY	Yasushi KAWAGUCHI	
		VIROLOGY	Yoshihiro KAWAOKA	Masaki IMAI
		INFECTIOUS DISEASES	Hiroshi YOTSUYANAGI	
		CLINICAL GENOME RESEARCH	Yoichi FURUKAWA	
		ADVANCED GENOME MEDICINE		Yoshihiro HIRATA
		STEM CELL PATHOLOGY	Yasuhiro YAMADA	
		MOLECULAR PATHOLOGY	Yoshinori MURAKAMI	
		RHEUMATOLOGY	Hirotoishi TANAKA	
		MEDICAL PROTEOMICS		Masaaki OYAMA
		GENETICS	Yuji YAMANASHI	
		CELL SIGNALING AND MOLECULAR MEDICINE	Mutsuhiro TAKEKAWA	
		BIOENGINEERING	Hideaki TAHARA	Hiroaki UCHIDA
		STEM CELL AND MOLECULAR MEDICINE	Atsushi IWAMA	
		REGENERATIVE MEDICINE	Hideki TANIGUCHI	
		CANCER CELL BIOLOGY		Atsuya NISHIYAMA
		VACCINE SCIENCE	(TBA)	
		RNA FUNCTION	Yukihide TOMARI	
		IMMUNOLOGY AND INFECTION CONTROL	Reiko SHINKURA	
		STRUCTURAL BIOLOGY OF MACROMOLECULAR COMPLEXES		Shuya FUKAI
		STEM CELL REGULATION		Minoru TANAKA
	INTER- INSTITUTE COOPERATIVE LABORATORIES	BIOMEDICAL SCIENCES (TOKYO METROPOLITAN INSTITUTE OF MEDICAL SCIENCE)	Keiji TANAKA	
			Hisao MASAI	
			Masanari ITOKAWA	
		FUNCTIONAL BIOMOLECULES ENGINEERING (NATIONAL INSTITUTE OF ADVANCED INDUSTRIAL- SCIENCE AND TECHNOLOGY;AIST)	Shinya HONDA	
			Kentaro MIYAZAKI	
			Katsutaka OISHI	
				Naohiro NODA
		VIRAL INFECTIOUS DISEASES (RIKEN)	Yoko AIDA	
		RNA SYSTEM BIOLOGY (RIKEN)		Shintaro IWASAKI
		MOLECULAR TARGET THERAPY OF CANCER (THE CANCER CHEMOTHERAPY CENTER OF JAPANESE FOUNDATION FOR CANCER RESEARCH)	Naoya FUJITA	
			Akihiro TOMIDA	
				Hiroyuki SEIMIYA

		LABORATORY	PROFESSOR	ASSOCIATE PROFESSOR/ LECTURER
BIOMEDICAL INNOVATION COURSE	CORE LABORATORIES	BIO INNOVATION POLICY		Shingo KANO
	INTRA- UNIVERSITY COOPERATIVE LABORATORIES	PUBLIC POLICY (IMS)	Kaori MUTO	Yusuke INOUE
		ADVANCED MEDICINE PROMOTION (IMS)		Masanori NOJIMA
COMPUTATIONAL BIOLOGY GLOUP	CORE LABORATORIES	OMICS	Shinichi MORISHITA	
		GENOME INFORMATICS	Kiyoshi ASAI	
		SYSTEMS GENOMICS	Yutaka SUZUKI	
		LARGE-SCALE KNOWLEDGE DISCOVERY	Koji TSUDA	
		HIGH-PERFORMANCE ANALYSIS SYSTEM		Masahiro KASAHARA
		BIOLOGICAL NETWORK ANALYSIS		Hisanori KIRYU
		LARGE-SCALE BIOINFORMATICS	Martin FRITH	
	INTRA- UNIVERSITY COOPERATIVE LABORATORIES	BIOINFORMATICS AND SYSTEMS BIOLOGY (DE- PARTMENT OF BIOLOGICAL SCIENCES, GRADU- ATE SCHOOL OF SCIENCE)		
			Tatsuhiko TSUNODA	
			Shinya KURODA	
				Kumiko UI-TEI
	INTER- INSTITUTE COOPERATIVE LABORATORIES	INFORMATICS OF BIOLOGICAL FUNCTIONS (INSTITUTE FOR QUANTITATIVE BIOSCIENCE)		Wataru IWASAKI
				(TBA)
		INFORMATICS OF MOLECULAR FUNCTIONS (AIST)	Kentaro TOMII	
			Takatsugu HIROKAWA	
				(TBA)
		COMPUTATIONAL SYSTEMS BIOLOGY (RIKEN)		Kam ZHANG
		CANCER MEDICAL INFORMATICS (NATIONAL CANCER CENTER HOSPITAL EAST)		Riu YAMASHITA
		LIFE SCIENCE DATABASES	Susumu GOTO	

Applying for the Master Course ver 2

Eligibility for Application

Please refer to “the Guidelines for Applicants to the 2021 Master Course ver 2” (the Guidelines v2, hereafter), which is distributed from Graduate School of Frontier Science (GSFS), the University of Tokyo.

Submitting Documents

- Applications will be submitted via the electronic application system, and paper submission of application forms will be abolished
- When applying electronically, we require that you upload PDF versions of the Inquiry Sheet (master's version 2), check sheets (version 2), English score sheets, transcripts, graduation certificates, and other certificates as appendices, as well as post the original copies of the certificates.
- Schedule A: Please check the information on how to submit documents and deadlines (Table 1).
- Please be sure to check the website of the Graduate School (https://www.k.u-tokyo.ac.jp/exam_e/) and follow the instructions for submission.

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〉

[Schedule A]

Applicants are selected by the result of the following examinations: We do not use Written Examination.

Selection will be made by the “Inquiry Sheet (Master Course) ver 2,” the academic transcripts, and the score sheet of foreign language (English), such as TOEFL (*the first-stage selection*) and online Oral examination (*the second-stage selection*). Please use “Inquiry Sheet (Master Course) ver 2”; do not use the previous version of the Inquiry Sheet. Download the MS Word file of the Inquiry Sheet (Master) ver 2 from the web site of our department (<http://www.cbms.k.u-tokyo.ac.jp/english/admission/schedule.html>). Fill it out according to the instructions on this document. After filling out the sheet, please save it as a PDF file and check if it is layout in the same way as the PDF version of Inquiry Sheet (Master Course) ver 2.

[Inquiry Sheet]

All applicants must submit the “Inquiry Sheet (Master Course) ver 2.” Inquiry Sheet (Master Course) ver 2 includes the following columns, (1)–(5), to be filled in. These parts are used for the reference materials for the first-stage selection. Fill in the columns according to the guide in the Inquiry Sheet (Master Course) ver 2 within the limited number of words. Do not use the previous version of the Inquiry Sheet. There are no columns (1)–(5) in the previous version of Inquiry Sheet.

- (1) Reasons for applying to graduate school and for enrolling in our department (CBMS): describe in 250 words
- (2) The current status and challenges, academic and social significance of the research area of the lab you wish to join: describe in 600 words
- (3) The reason that you wish to study in the lab of your choice: describe in 200 words
- (4) Your current research or academic papers you read recently: describe in 400 words
- (5) Your future career path after completing the master's course: describe in 150 words

[Foreign language (English)]

All applicant must submit the score sheet of one or more of TOEFL, TOEIC, or IELTS. TOEFL iBT Special Home Edition is accepted. Official score reports for TOEFL, TOEIC, IELTS, etc. must be received by Tuesday, August 11. Upload a single combined PDF files online by Wednesday, July 29 (17:00 JST). If a delivery delay of the official score reports is anticipated because of postal service conditions, we accept late arrival if you inform the Student Affairs Team so in advance (by July 22). Regarding (1) what types of those English exams are accepted, (2) valid dates of certificates, and (3) how to send certificates to GSFS, please refer to “Section 9: English Language Competency Test Score Reports” in the Guideline v2.

[Online Oral Examination]

Applicants who passed the first-stage selection take an online oral examination. An oral examination will be conducted based on the submitted Inquiry Sheet (Master Course) ver 2. Academic achievements as well as your motivation for research will be evaluated. The details of the online oral examination will be provided in late July and will be announced on the web site of our department <http://www.cbms.k.u-tokyo.ac.jp/english/index.html>.

[Schedule B]

Applicants are selected as described in Schedule A. The details will be announced on the web site of our department.

Examination Schedule

The following is the examination schedule. The detailed information will be provided in late July.

[Schedule A]

August 3, 2020	Mon.	12:00 -	Announcement of successful applicants (the first-stage selection) on the web site of our department
August 4-7			Online connection test (~5 min for each examinee)*
August 11, 2020	Tue.	10:30 -	Online oral examination*
August 12, 2020	Wed.	10:00 -	Online oral examination*
August 13, 2020	Thu.	10:00 -	Online oral examination*
August 14, 2020	Fri.	12:00 -	Announcement of Successful Candidates (the second-stage selection) on the web site of our department

*Only for those who pass the first-stage selection

[Schedule B]

Late January 2021 (TBA)	Announcement of successful applicants (the first-stage selection) and online connection test
Early February 2021 (TBA)	Online oral examination

The detailed information will be announced on the web site of our department.

Announcement of Results and Admission Procedures

- [Schedule A] First-stage selection: The screening results (pass or fail) based on the submitted documents will be released at noon on August 3, 2020 (Mon) 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. When the restriction level of the university activity is at level 1 or higher, visitors are not allowed to come to the campus, and therefore we may not use the bulletin board in such situation.
- [Schedule A] Second-stage selection (oral exam): Please refer to Section 10 (Announcement of Results and

- Admission Procedures) and Table 2 (A-15, A-16, A-17, A-18) of the Guidelines v2.
- [Schedule B] Second-stage selection (oral exam): Please refer to Section 10 (Announcement of Results and Admission Procedures) and Table 2 (B-10, B-11, B-12, B-13) of the Guidelines v2.

Miscellaneous

Enrollment in September: If you wish to enroll in September 2020, please indicate so on the Inquiry Sheet (Master Course) ver 2. 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.

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 Team,
Graduate School of Frontier Sciences, the University of Tokyo
5-1-5 Kashiwanoha, Kashiwa, Chiba pref., JAPAN 277-8561
Phone: +81-4-7136-4092, k-kyomu@adm.k.u-tokyo.ac.jp

Table 1: How to Submit Documents and Deadlines †

	Documents to be submitted online (June 11-17) at the time of online application	Late submission of documents after June 17	Original (paper) certificates to be mailed (*2)	Relief measure in case of postal system delays
Application form	Online application June 11-17, Due June 17 24:00 JST	—	—	—
Proof of payment of the screening fee (the application fee)	Upload a PDF file of payment proof affixed to the designated card at the time of your application Due June 17, 24:00 JST	No	Payment proof affixed to the designated card.(*3) (Due June 29)	—
Check sheet	Describe in the file designated by the department and upload it as a PDF file.	No	No need	—
Inquiry sheet	Describe in a file designated by our department and upload it as a single PDF at the same time as your application. Due June 17, 24:00 JST	No	No need	—
English Score Sheet	Upload a single PDF at the time of your application. Combine into one file if you have multiple scores.	Possible (*1) Due June 29 17:00 JST	Official score reports Due Aug 11	If you are unable to send the official score reports by the deadline, please contact the Student Affairs Team, GSFS by July 22.
Academic transcript	Upload a single PDF at the time of your application.	Possible (*1) Due June 22 17:00 JST	Original transcripts Due July 29	If you are unable to send the original by the deadline, please contact the Student Affairs Team, GSFS by July 22.
Graduation certificate / Graduation prospectus	Upload a single PDF at the time of your application.	Possible (*1) Due June 22 17:00 JST	Original certificate: Due July 29 Graduation certificate issued by CDGDC for Chinese university: Due Sept 13 (upload online)	If you are unable to send the original by the deadline, please contact Student Affairs Team, GSFS by July 22.

† If the deadlines shown here differ from the deadlines shown in the Guideline v2 by GSFS, applicants should follow the deadlines shown here.

*1 English score sheets, transcripts, certificates, etc. can be uploaded on the web system until the late submission deadlines shown above.

*2 Failure to submit the original documents by the test date may result in denial of the enrollment (except for certificates issued by the CDGDC that must be submit by the day of the admission procedure).

*3 You may be able to make a payment within the online application system

Master

Checklist for Master Course Applicants ver 2

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

(All applicants)

- ☐ Screening fee (application fee):

Schedule A: JPY 10,000, Schedule B: JPY 30,000. (Pay online or upload the proof of your payment in PDF)
See Guidelines for Applicants to the 2021 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.

- ☐ Check Sheet (Master Course) ver 2 (upload a PDF file online)

- ☐ Inquiry Sheet (Master Course) ver 2 (upload a PDF file online)

Please make sure the laboratories you choose are in a single group/course.

Download the MS Word file from the department's webpage and fill in the Inquiry Sheet and Check Sheet with a word processor, save it as a PDF file, and upload them.

- ☐ One or more of TOEFL (iBT, PBT, Special Home Edition), TOEIC and/or IELTS score reports

(upload a PDF online, and send the official score reports by postal mail)

- ☐ Diploma or certificate of graduation/completion (upload a PDF file online, and send the original certificates by postal mail)

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 pdf file of 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 (upload a PDF online, and send the original records/transcripts by postal mail)

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 (Free format. Should be around 1 page in A4 size.) (upload a PDF online)

If you wish to attend school while staying in service of a company, a government, or an organization.

- ☐ Residence certificate (upload a PDF file online)

Required for foreign nationals currently residing in Japan, except for regular and research students currently enrolled in our department.

INQUIRY SHEET (Master Course) ver 2

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

[illegible]

(2) 【The current status and challenges, academic and social significance of the research area of the lab you wish to join】 *describe in 600 words using 10-11 points font*

Italics can be erased at the time of writing, but must fit within the frame

(3) 【The reason that you wish to study in the lab of your choice】 *describe in 250 words using 10-11 points font*

Italics can be erased at the time of writing, but must fit within the frame

Your name :

Laboratory of your first choice :

(4) 【Your current research or academic papers you read recently】 *describe by citing literatures in 400 words using 10-11 points font. If you have scientific achievements (conference presentation, papers etc), describe them.*

Italics can be erased at the time of writing, but must fit within the frame

(5) 【Your future career path after completing the master's course】 *describe in 150 words using 10-11 points font*

Italics can be erased at the time of writing, but must fit within the frame

Only for office use:

Laboratory List

*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. List the laboratories in the order in which you would like to belong to, using numbers in [] in the list.

*Labs not listed here do not accept students.

Laboratory List

Medical Sciences Group: Master Course	
Core Laboratories	
[] Laboratory of Biomolecules (Tomita N.)	[] Laboratory of Molecular Genetics (Ito K.)
[] Laboratory of RNA Biology (Tomita K.)	[] Laboratory of Genome Technology (Matsuda K.)
[] Laboratory of Tumor Cell Biology (Uchimaru, Nakano)	[] Laboratory of Molecular Oncology (Goyama)
[] Laboratory of Complex Trait Genomics (Kamatani)	
Intra-university cooperative laboratories	
[] Laboratory of AIDS Vaccine Development (Matano)	[] Laboratory of Innate Immunity (Miyake)
[] Laboratory of Functional Analysis in Silico (Nakai)	[] Laboratory of Molecular Virology (Kawaguchi)
[] Laboratory of Molecular Pathology (Murakami Y.)	[] Laboratory of RNA Function (Tomari)
[] Laboratory of Immunology and Infection Control (Shinkura)	[] Laboratory of Infectious Diseases (Yotsuyanagi)
[] Laboratory of Clinical Genome Research (Furukawa)	[] Laboratory of Medical Proteomics (Oyama)
[] Laboratory of Advanced Genome Medicine (Hirata)	[] Laboratory of Stem Cell Pathology (Yamada)
[] Laboratory of Genetics (Yamanashi)	[] Laboratory of Stem Cell Regulation (Tanaka M.)
[] Laboratory of Cell Signaling & Molecular Medicine (Takekawa)	[] Laboratory of Stem Cell and Molecular Medicine (Iwama)
[] Laboratory of Regenerative Medicine (Taniguchi)	[] Laboratory of Cancer Cell Biology (Nakanishi, Nishiyama)
[] Laboratory of Vaccine Science (Ishii)	[] Laboratory of Animal Genetics (Mashimo)
[] Laboratory of Malaria Immunology (Coban)	
Inter-institute cooperative laboratories	
[] Laboratory of Biomedical Sciences (Tanaka K.)	[] Laboratory of Functional Biomolecules Engineering (Honda)
[] Laboratory of Biomedical Sciences (Masai)	[] Laboratory of Functional Biomolecules Engineering (Miyazaki)
[] Laboratory of Biomedical Sciences (Itokawa)	[] Laboratory of Functional Biomolecules Engineering (Oishi)
[] Laboratory of RNA System Biology (Iwasaki S.)	[] Laboratory of Functional Biomolecules Engineering (Noda)
[] Laboratory of Molecular Target Therapy of Cancer (Seimiya)	
[] Laboratory of Molecular Target Therapy of Cancer (Tomida)	
[] Laboratory of Molecular Target Therapy of Cancer (Katayama)	
Computational Biology Group; Master Course	
Core Laboratory	
[] Laboratory of Omics (Morishita)	[] Laboratory of Genome Informatics (Asai)
[] Laboratory of Systems Genomics (Suzuki Y.)	[] Laboratory of Large-scale Knowledge Discovery (Tsuda)
[] Laboratory of High-Performance Analysis System (Kasahara)	[] Laboratory of Large-Scale Bioinformatics (Frith)
[] Laboratory of Biological Network Analysis (Kiryu)	
Intra-university cooperative laboratories	
[] Laboratory of Bioinformatics and Systems Biology (Tsunoda)	[] Laboratory of Bioinformatics and Systems Biology (Tei)
[] Laboratory of Bioinformatics and Systems Biology (Kuroda)	[] Laboratory of Bioinformatics and Systems Biology (Nakato)
[] Laboratory of Bioinformatics and Systems Biology (Iwasaki A.)	
Inter-institute cooperative laboratories	
[] Laboratory of Informatics of Molecular Functions (Tomii)	[] Laboratory of Informatics of Molecular Functions (Saito)
[] Laboratory of Informatics of Molecular Functions (Hirokawa)	
[] Laboratory of Computational Systems Biology (Zhang)	
[] Laboratory of Cancer Medical Information (Yamashita)	[] Laboratory of Life Science Databases (Goto)
Biomedical Innovation Course: Master 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)

Applying for the Doctoral Course ver 2

Eligibility for Application

- Please refer to “the Guidelines for Applicants to the 2020 Doctoral Course ver 2” (the Guidelines v2, 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 v2, are subjected to individual screening. Please contact the Student Affair Team for details.

Submitting Documents

- Applications will be submitted via the electronic application system, and paper submission of application forms will be abolished
- When applying electronically, we require that you upload PDF versions of the Inquiry Sheet (master's version 2), check sheets (version 2), English score sheets, transcripts, graduation certificates, and other certificates as appendices, as well as post the original copies of the certificates.
- Schedule A: Please check the information on how to submit documents and deadlines (Table 2).
- Please be sure to check the website of the Graduate School (https://www.k.u-tokyo.ac.jp/exam_e/) and follow the instructions for submission.

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) ver 2.
- 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.

[Schedule A and Schedule B]

〈Ordinary Examination〉

Applicants are selected by the result of the following examinations: We do not use Written Examination.

Selection will be made by the “Inquiry Sheet (Doctoral Course) ver 2”, the academic transcripts, and the score sheet of foreign language (English), such as TOEFL (*the first-stage selection*), and online Oral examination including presentation of your Master thesis (*the second-stage selection*) (See Table 1). Please use “Inquiry Sheet (Doctoral Course) ver 2”; do not use the the previous version of the Inquiry Sheet.

Those who have completed or are expected to complete a Master course in the University of Tokyo are exempt from Foreign Language (English), 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.

[Inquiry Sheet]: Inquiry sheet (Doctoral Course) ver 2 includes the following columns, (1)-(5), to be filled in. These

parts are used for the reference materials for the first-stage selection. Fill in the columns according to the guide in the Inquiry Sheet (Doctoral Course) ver 2 within the limited number of words. Do not use the previous version of the Inquiry Sheet. There are no columns (1)-(5) in the previous version of Inquiry Sheet. Download the MS Word file of the Inquiry Sheet (Doctoral Course) ver 2 from the web site of our department (<http://www.cbms.k.u-tokyo.ac.jp/english/admission/schedule.html>). Fill it out according to the instructions on this document. After filling out the sheet, please save it as a PDF file and make sure that it is formatted in the same way as the PDF Inquiry Sheet.

- (1) Reasons for applying to graduate school and for enrolling in our department (CBMS): describe in 250 words
- (2) The current status and challenges, academic and social significance of research area of the lab you wish to join: describe in 600 words
- (3) The reason that you wish to study in the lab of your choice: describe in 200 words
- (4) Your research outcomes and activities: describe in 400 words
- (5) Your future career path after completing the doctoral course: describe in 150 words

[Foreign language (English)]

All applicant must submit the score sheet of one or more of TOEFL, TOEIC, or IELTS. TOEFL iBT Special Home Edition is accepted. Official score reports for TOEFL, TOEIC, IELTS, etc. must be received by Tuesday, August 11. Upload a single combined PDF files online by Wednesday, July 29 (17:00 JST). If a delivery delay of the official score reports is anticipated because of postal service conditions, we accept late arrival if you inform the Student Affairs Team so in advance (by July 22). Regarding (1) what types of those English exams are accepted, (2) valid dates of certificates, and (3) how to send certificates to GSFS, please refer to “Section 9: English Language Competency Test Score Reports” in the Guideline v2.

[Online Oral Examination]

Applicants who passed the first-stage selection take an online oral examination. An oral examination will be conducted based on the submitted Inquiry Sheet (Doctoral Course) ver 2. Academic achievements as well as your motivation for research will be evaluated. The details of the online oral examination will be provided in late July and will be announced on the web site of our department <http://www.cbms.k.u-tokyo.ac.jp/english/index.html>

Examination Schedule

The following is the examination schedule. The detailed information will be announced in late July.

[Schedule A]

August 3, 2020	Mon.	12:00 -	Announcement of successful applicants (the first-stage selection) on the web site of our department
August 4-7			Online connection test (~5 min for each examinee)*
August 11, 2020	Tue.	10:30 -	Online oral examination (for *1, *2, and *3)‡
August 12, 2020	Wed.	10:00 -	Online oral examination (for *1, *2, and *3)‡
August 13, 2020	Thu.	10:00 -	Online oral examination (for *1, *2, and *3)‡
August 14, 2020	Fri.	12:00 -	Announcement of Successful Candidates (the second-stage selection) on the web site of our department
Early February 2021 (TBA)			Online oral examination (for *4)

*Only for those who pass the first-stage selection

[Schedule B]

Late January 2021 (TBA) Announcement of successful applicants (the first-stage selection) and online connection test

Early February 2021 (TBA) Online oral examination (*5 and *6)‡

The detailed information will be announced on the web site of our department.

*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 2020; (2) Applicants who wish to take the examinations in Schedule A; (3) Applicants who wish to

enroll in September 2020, 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) ver 2.

- *2 Applicants to the Computational Biology Group, except for those who are expected to graduate from our department in September 2020. Applicants who wish to enroll in September must indicate so on the Inquiry Sheet (Doctoral Course) ver 2.
- *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 2021, (2) Applicants to the Computational Biology Group who are expected to graduate from our department in March 2021.
- *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 2021 must indicate so on the Inquiry Sheet (Doctoral Course) ver 2.

Announcement of Results and Admission Procedures

[Schedule A]

- First-stage selection: The announcement of the selection results (pass or fail) based on the submitted documents will be made at noon on August 3, 2020 (Mon) both at the bulletin board in the entrance hall of Transdisciplinary Sciences Building on the Kashiwa campus (may not be available when the campus is not open to visitors), and on the web page of our department. When the restriction level of the university activity is at level 1 or higher, visitors are not allowed to come to the campus, and therefore we may not use the bulletin board in such situation.
- Second-stage selection (Oral exam): Please refer to Section 10 (Announcement of Results and Admission Procedures) and Table 2 (A-10, A-11, A-14, A-15) of the Guidelines v2.

[Schedule B]

- Please refer to the Section 10 (Announcement of Results and Admission Procedures) and Table 2 (B-11, B-12, B-15, B-16) of the Guidelines v2.

Miscellaneous

- Enrollment in September (Schedule A): If you wish to enroll in September 2020, please indicate so on the Inquiry Sheet (Doctoral Course) ver 2. 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. Please contact the Student Affairs if you will graduate from a college or university between September 24 and September 30 in 2020.
- Enrollment in September (Schedule B): If you wish to enroll in September 2021, please indicate so on the Inquiry Sheet (Doctoral Course) ver 2. You must have already graduated or are expected to graduate from a college or university by September 2021. Please be aware that you cannot change the time of enrollment from September 2021 to April 2022 even if you fail in graduating from a college or university by September 2021.

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 Team,
Graduate School of Frontier Sciences, the University of Tokyo
5-1-5 Kashiwanoha, Kashiwa, Chiba pref., JAPAN 277-8561
Phone: +81-4-7136-4092, E-mail: k-kyomu@adm.k.u-tokyo.ac.jp

Table 1: Examination Types.

The abbreviations are shown below.

Report: Submit the Official Score Report of one or more of TOEFL, TOEIC, IELTS to GSFS; Aug: August 2020; Feb: February 2021

Medical Science Group**Schedule A**

Exam Type	CBMS Master	UTokyo Master	Other Univ Master	6-year Undergrad	Others
English	—	—	Report only	Report only	Report only
Specialty	—	—	—	—	—
Oral	Aug/Feb †	Aug/Feb †	Aug/Feb †	Aug/Feb †	Aug

†Applicants who have graduated or are expected to graduate from a college or university by September 2020 take the oral examination in August 2020, otherwise in February 2021.

Schedule B

Exam Type	CBMS Master	UTokyo Master	Other Univ Master	6-year Undergrad	Others
English	—	—	Report only	Report only	Report only
Specialty	—	—	—	—	—
Oral	Feb	Feb	Feb	Feb	Feb

Computational Biology Group**Schedule A**

Exam Type	CBMS Master	UTokyo Master	Other Univ Master	6-year Undergrad	Others
English	—	Report only	Report only	Report only	Report only
Specialty	—	—	—	—	—
Oral	Aug/Feb †	Aug	Aug	Aug	Aug

†Applicants who have graduated or are expected to graduate from a college or university by September 2020 take the oral examination in August 2020, otherwise in February 2021.

Schedule B

Exam Type	CBMS Master	UTokyo Master	Other Univ Master	6-year Undergrad	Others
English	—	Report only	Report only	Report only	Report only
Specialty	—	—	—	—	—
Oral	Feb	Feb	Feb	Feb	Feb

Biomedical Innovation Course**Schedule A**

Exam Type	CBMS Master	UTokyo Master	Other Univ Master	6-year Undergrad	Others
English	—	—	Report only	Report only	Report only
Specialty	—	—	—	—	—
Oral	Aug/Feb †	Aug/Feb †	Aug/Feb †	Aug/Feb †	Aug

†Applicants who have graduated or are expected to graduate from a college or university by September 2020 take the oral examination in August 2020, otherwise in February 2021.

Schedule B

Exam Type	CBMS Master	UTokyo Master	Other Univ Master	6-year Undergrad	Others
English	—	—	Report only	Report only	Report only
Specialty	—	—	—	—	—
Oral	Feb	Feb	Feb	Feb	Feb

Table 2: How to Submit Documents and Deadlines †

	Documents to be submitted online (June 11-17) at the time of online application	Late submission of documents after June 17	Original (paper) certificates to be mailed (*2)	Relief measure in case of postal system delays
Application form	Online application June 11-17, Due June 17 24:00 JST	—	—	—
Proof of payment of the screening fee (the application fee)	Upload a PDF file of payment proof affixed to the designated card at the time of your application Due June 17, 24:00 JST	No	Payment proof affixed to the designated card. (*3) (Due June 29)	—
Check sheet	Describe in the file designated by the department and upload it as a PDF file.	No	No need	—
Inquiry sheet	Describe in a file designated by our department and upload it as a single PDF at the same time as your application. Due June 17, 24:00 JST	No	No need	—
English Score Sheet	Upload a single PDF at the time of your application. Combine into one file if you have multiple scores.	Possible (*1) Due June 29 17:00 JST	Official score reports Due Aug 11	If you are unable to send the official score reports by the deadline, please contact the Student Affairs Team, GSFS by July 22.
Academic transcript	Upload a single PDF at the time of your application.	Possible (*1) Due June 22 17:00 JST	Original transcripts Due July 29	If you are unable to send the original by the deadline, please contact the Student Affairs Team, GSFS by July 22.
Graduation certificate / Graduation prospectus	Upload a single PDF at the time of your application.	Possible (*1) Due June 22 17:00 JST	Original certificate : Due July 29 Graduation certificate issued by CDGDC for Chinese university: Due Sept 13 (upload online)	If you are unable to send the original by the deadline, please contact the Student Affairs Team, GSFS by July 22.

† If the deadlines shown here differ from the deadlines shown in the Guideline v2 by GSFS, applicants should follow the deadlines shown here.

*1 English score sheets, transcripts, certificates, etc. can be uploaded on the web system until the late submission deadlines shown above.

*2 Failure to submit the original documents by the test date may result in denial of the enrollment (except for certificates issued by the CDGDC that must be submit by the day of the admission procedure).

*3 You may be able to make a payment within the online application system

Doctoral

Checklist for Doctoral Course Applicants ver 2

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

(All applicants)

- ☐ Screening fee (application fee):

Schedule A: JPY 10,000, Schedule B: JPY 30,000. (Pay online or upload the proof of your payment in PDF)
See Guidelines for Applicants to the 2021 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, 2021 (September 2020 for enrollment in September 2020), 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.

- ☐ Check sheet (Doctoral Course) ver 2 (upload a PDF file online)

- ☐ Inquiry Sheet (Doctoral Course) ver 2 (upload a PDF file online)

Download the MS Word file from the department's webpage and fill in the Inquiry Sheet and Check Sheet with a word processor, save it as a PDF file, and upload them.

- ☐ One or more of TOEFL (iBT, PBT, Special Home Edition), TOEIC and/or IELTS score reports
(upload a PDF online, and send the official score reports by postal mail)

- ☐ Diploma or certificate of graduation/completion for a graduate program
(upload a PDF file online, and send the original by postal mail)

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 pdf file of 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 universities only). (upload a PDF online, and send the original certificates by postal mail).

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.
(upload a PDF file online, and send the original records/transcripts by postal mail).

Required for all 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 (Free format. Should be around 1 page in A4 size.) (upload a PDF file online)
If you wish to attend school while staying in service of a company, a government, or an organization.

- ☐ Residence Certificate (upload a PDF file online)

Required for foreign nationals currently residing in Japan, except for regular and research students currently enrolled in our department.

INQUIRY SHEET (Doctoral Course) ver 2

Applicants must submit this form via online application system

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

[illegible]

(2) 【The current status and challenges, academic and social significance of the research area of the lab you wish to join】 *describe in 600 words using 10-11 points font*

Italics can be erased at the time of writing, but must fit within the frame

(3) 【The reason that you wish to study in the lab of your choice】 *describe in 250 words using 10-11 points font*

Italics can be erased at the time of writing, but must fit within the frame

Your name :

Laboratory of your first choice :

(4) **【Your research outcomes and activities】** *describe by citing literatures in 400 words using 10-11 points font. If you have scientific achievements (conference presentation, papers etc), describe them.*

Italics can be erased at the time of writing, but must fit within the frame

(5) **【Your future career path after completing the doctoral course】** *describe in 150 words using 10-11 points font*

Italics can be erased at the time of writing, but must fit within the frame

Only for office

LABORATORY LIST

*Choose exactly one lab you wish to join, check [] in the list.

*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.

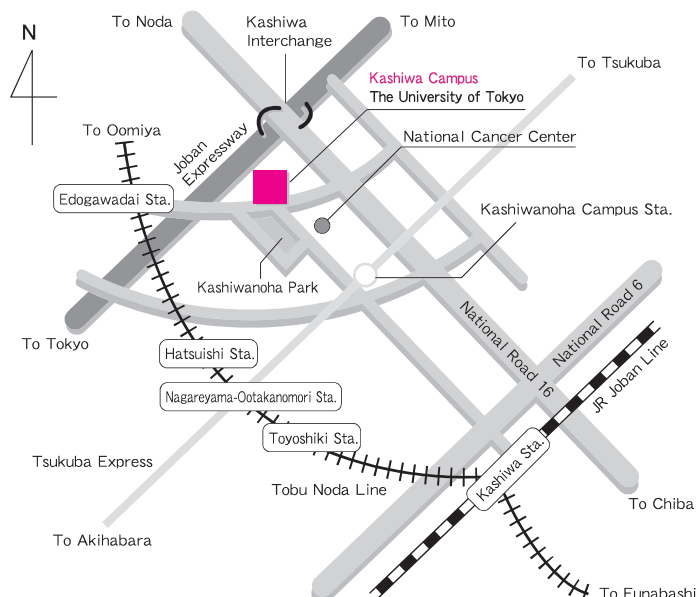
*Labs not listed here do not accept students.

Laboratory List

Medical Sciences Group: Doctor Course	
Core Laboratories	
[] Laboratory of Biomolecules (Tomita N.)	[] Laboratory of Molecular Genetics (Ito K.)
[] Laboratory of RNA Biology (Tomita K.)	[] Laboratory of Genome Technology (Matsuda K.)
[] Laboratory of Tumor Cell Biology (Uchimaru, Nakano)	[] Laboratory of Molecular Oncology (Goyama)
[] Laboratory of Complex Trait Genomics (Kamatani)	
[] Laboratory of Multi-Omics Data Analysis (Suzuki A.)	
Intra-university cooperative laboratories	
[] Laboratory of AIDS Vaccine Development (Matano)	[] Laboratory of Innate Immunity (Miyake)
[] Laboratory of Functional Analysis in Silico (Nakai)	[] Laboratory of Molecular Virology (Kawaguchi)
[] Laboratory of Molecular Pathology (Murakami Y.)	[] Laboratory of RNA Function (Tomari)
[] Laboratory of Immunology and Infection Control (Shinkura)	[] Laboratory of Infectious Diseases (Yotsuyanagi)
[] Laboratory of Clinical Genome Research (Furukawa)	[] Laboratory of Medical Proteomics (Oyama)
[] Laboratory of Advanced Genome Medicine (Hirata)	[] Laboratory of Stem Cell Pathology (Yamada)
[] Laboratory of Genetics (Yamanashi)	[] Laboratory of Stem Cell Regulation (Tanaka M.)
[] Laboratory of Cell Signaling & Molecular Medicine (Takekawa)	[] Laboratory of Stem Cell and Molecular Medicine (Iwama)
[] Laboratory of Regenerative Medicine (Taniguchi)	[] Laboratory of Cancer Cell Biology (Nakanishi, Nishiyama)
[] Laboratory of Vaccine Science (Ishii)	[] Laboratory of Animal Genetics (Mashimo)
[] Laboratory of Malaria Immunology (Coban)	
Inter-institute cooperative laboratories	
[] Laboratory of Biomedical Sciences (Tanaka K.)	[] Laboratory of Functional Biomolecules Engineering (Honda)
[] Laboratory of Biomedical Sciences (Masai)	[] Laboratory of Functional Biomolecules Engineering (Miyazaki)
[] Laboratory of Biomedical Sciences (Itokawa)	[] Laboratory of Functional Biomolecules Engineering (Oishi)
[] Laboratory of RNA System Biology (Iwasaki S.)	[] Laboratory of Functional Biomolecules Engineering (Noda)
[] Laboratory of Molecular Target Therapy of Cancer (Seimiya)	
[] Laboratory of Molecular Target Therapy of Cancer (Tomida)	
[] Laboratory of Molecular Target Therapy of Cancer (Katayama)	
Computational Biology Group; Doctor Course	
Core Laboratory	
[] Laboratory of Omics (Morishita)	[] Laboratory of Genome Informatics (Asai)
[] Laboratory of Systems Genomics (Suzuki Y.)	[] Laboratory of Large-scale Knowledge Discovery (Tsuda)
[] Laboratory of High-Performance Analysis System (Kasahara)	[] Laboratory of Large-Scale Bioinformatics (Frith)
[] Laboratory of Biological Network Analysis (Kiryu)	
Intra-university cooperative laboratories	
[] Laboratory of Bioinformatics and Systems Biology (Tsunoda)	[] Laboratory of Bioinformatics and Systems Biology (Tei)
[] Laboratory of Bioinformatics and Systems Biology (Kuroda)	[] Laboratory of Bioinformatics and Systems Biology (Nakato)
[] Laboratory of Bioinformatics and Systems Biology (Iwasaki A.)	
Inter-institute cooperative laboratories	
[] Laboratory of Informatics of Molecular Functions (Tomii)	[] Laboratory of Informatics of Molecular Functions (Saito)
[] Laboratory of Informatics of Molecular Functions (Hirokawa)	
[] Laboratory of Computational Systems Biology (Zhang)	
[] Laboratory of Cancer Medical Information (Yamashita)	[] Laboratory of Life Science Databases (Goto)
Biomedical Innovation Course: Doctor 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)

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-Ootakanomori 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

