

Department of  
Biological Sciences

# Department of Biological Sciences

The Department of Biological Sciences, Graduate School of Science, offers a variety of graduate programs including lectures on a wide range of current biology, research training and advanced seminars focusing on specific topics. The programs are guided by researchers at the Department of Biological Sciences, Institute for Protein Research, Institute of Scientific and Industrial Research, Research Institute of Microbial Diseases, Genome Information Research Center, Frontier Biosciences, and three affiliated institutes outside the university.

The Department of Biological Sciences, Graduate School of Science, was reorganized in 1996 by combining two departments, Physiology and Biochemistry, both of which had been founded in 1953. As a result of reorganization and together with the cooperation of three institutes outside the university, the research conducted at the department covers a wide range of the research fields of current biology and life sciences, which have been rapidly expanding.

When the Department of Biology for undergraduate studies started with three laboratories in 1949, two of them were protein chemistry (Professors Akabori and Okunuki) and one for biophysical cell biology (Professor Kamiya). The department was different from other biology, zoology and/or botany departments at that time. We follow this unique tradition in a modernized way and are always aiming at developing new research fields in biology, especially in "supramolecular biology" which might surpass ordinary molecular biology and ultimately elucidate the life and living organisms at the atomic and supramolecular levels. To pursue this task, we welcome students who have backgrounds other than biology, such as chemistry and physics. Of course, we also welcome students with a solid background in biology. New research fields will be established in this kind of amalgamating atmosphere.

Postgraduate students enrolled in the Master and/or Doctoral programs are requested to conduct their own researches in the laboratories to be conferred with their degrees. The research is supervised by one of the supervisors of the Graduate School. In the doctor course, two advisors in addition to the supervisor will guide your research.

For detailed information of research topics, see the following pages and <http://www.bio.sci.osaka-u.ac.jp/en>



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## Laboratory of Cellular & Structural Biology

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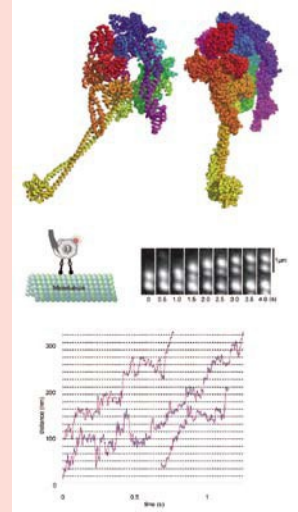
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### [Research interests]

In the cells that make up our bodies, a wide variety of macromolecules including proteins move quickly at the velocity of several meters per second using thermal energy. However, that is not useful for the long-distance transportation to the specific direction in the cells because the direction of the thermal motion is random. For example, in an elongated neuron with the length of 1 m, it will take more than 100 years to transport an average-sized protein from the cell body to the nerve terminal by the thermal motion. Eukaryotic cells manage this problem by establishing intracellular transport systems that powers a wide variety of fundamental biological processes including ciliary beating, cell division, cell migration and active transport of numerous cargoes. The partial loss of the function has been implicated in neurodegenerative disease, infertility and developmental abnormality. Our laboratory aims to elucidate the molecular mechanism underlying the intracellular transport system by means of atomic-level structural analysis and single-molecule functional

analysis. Recently, we have focused on a huge motor protein complex, dynein, which is the heart of the transport system toward the center of the cells, and determined its atomic structures. We have also started research projects to achieve a comprehensive understanding of mRNA transport systems in neurons.



Upper panel: Atomic structure of "Dynein", the heart of the transport system.  
Lower panel: Single-molecule observation of dynein moving along a microtubule track.

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## Laboratory of Single Molecule Biology

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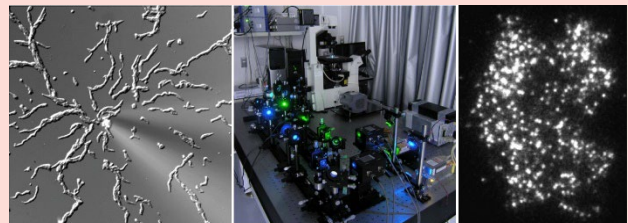
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### [Research interests]

Living cells are complex but well-organized systems comprising various kinds of biomolecules. Because biomolecules operate stochastically under the strong influence of thermal fluctuations, living cells can be referred to as stochastically-operating biomolecular computation systems. Through the dynamic processes in reaction networks of biomolecules, cells can respond flexibly and adaptively to environmental changes. Recent progress in single molecule imaging techniques has made it possible to monitor directly the stochastic behaviors of biomolecules in living cells, in which the locations, movements, turnovers, and complex formations of biomolecules can be detected quantitatively at the single molecule level, providing powerful tools to elucidate molecular mechanisms of intracellular signaling processes. Our laboratory develops quantitative single-molecule imaging methods, computational modeling methods and biochemical synthetic methods to reveal the molecular mechanisms of cellular chemotaxis with single-molecule resolution.

### [Research projects]

- 1) Development of automated in-cell single-molecule imaging system (AISIS)
- 2) Single-molecule biology of chemotactic signaling system
- 3) Synthetic biology of chemotactic signaling system



Left: Chemotaxis of *Dictyostelium discoideum* amoebae to cyclic AMP gradients.

Middle: Total internal reflection fluorescence microscopy (TIRFM) for single molecule imaging.

Right: Single molecule imaging of PTEN molecules on the membrane of living cells. Individual white spots represent single molecules of PTEN.

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# Laboratory of Genome Structure and Function

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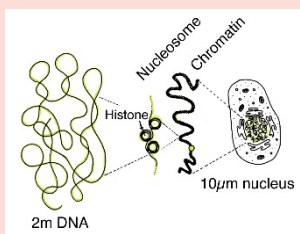
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[Research Interest]

## Molecular mechanism for genetic and epigenetic inheritances in mammalian cells

The ability of cells to store, retrieve, and translate the genetic information is essential for making and maintaining living organisms. The genetic information of mammalian cells is preserved in the nucleus, in which DNA together with proteins and RNA form a complex called chromatin. Different types of cells in our body are originated from a one cell embryo. Thus, such different types of cells still possess same genetic information, but their cellular identities are determined by each cell-type



specific gene expression. This cell-type specific gene expression is controlled by epigenetic information including DNA methylation, histone post-translational modifications and chromatin structure. These epigenetic information or epigenomes

can be changed during differentiation or by environmental factors, but are also maintained and inherited by the next generation if cellular identity is fixed. We are interested in genetic and epigenetic mechanisms to inherit the genetic information and utilize it properly. In addition, we want to understand how cell-type specific epigenome can be switched or maintained through cell division at molecular level. We employ omics approaches using mass spectrometry and next generation sequencer, as well as molecular biological and genetical, biochemical, and cell biological approaches, to elucidate these issues.



Mass spectrometer for proteomic analysis



Next generation sequencer for genomics

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# Laboratory of Plant Development

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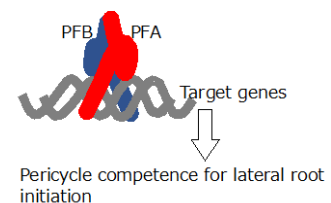
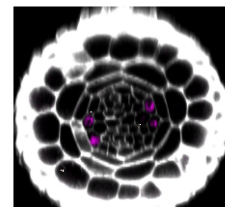
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[Research interests]

Plant development relies on coordinated division, differentiation and expansion of cells. In order to understand the underlying mechanisms, we study both inter-cellular communication and cellular events. Plant hormones play pivotal roles in almost all processes of plant development. We have identified biosynthetic enzymes and receptors of cytokinins, and clarified the role of cytokinins in plant development. We are also working on the roles of secretory signaling peptides. We identified several peptides that regulate plant development, including EPF1, which regulate spacing of stomata; EPF2 and stomagen, which regulate epidermal cell number, CLE9/10 peptide that regulates stomatal number and vascular cell pattern; and CLE25,26,45, which regulate phloem formation. We are also working on transcription factors that regulate the development of epidermis, vascular cells, and pericycle. We would like to understand regulatory networks, consisting of transcription factors and intercellular signaling molecules, that regulate plant development.

We are also trying to understand how plants modulate regulatory systems for development depending on environmental cues.



Left, cross section of a lateral root showing expression of PFA (magenta) in the xylem-pole pericycle. PFA/PFB transcription factor complex confer the competence of pericycle to undergo auxin-induced cell division and lateral root primordial formation. Right, PFA/PFB regulates target genes conferring the pericycle identity.

## Plant Cell Biology Group

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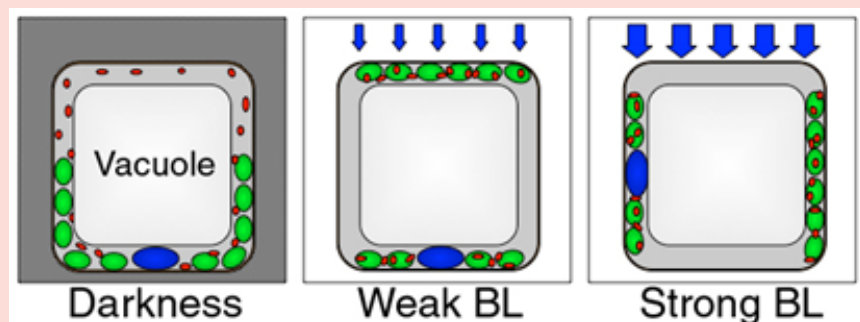
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### [Research Topics]

We are dissecting cellular processes from the sensing of environmental fluctuations, for example, in light condition, CO<sub>2</sub> concentration, metal ions distribution, to the final physiological responses in plants. Ongoing subjects include intracellular positioning and movement of organelles (we found that chloroplasts, mitochondria, and nuclei in *Arabidopsis* mesophyll cells change their distribution patterns under different light conditions: see Figure), dynamic behavior of cytoskeleton and nucleoskeleton, and circumnutation of stems. Our goal is to disclose the sensing mechanisms, roles of cytoskeletons, and signaling factors, together with biological significance of these intriguing responses.

Furthermore, we recently identified long unrevealed candidate genes for plant nuclear lamina components. The mode of action of these candidates in regulating gene expression via intranuclear chromosome rearrangement is under investigation.



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## Laboratory of Developmental Biology

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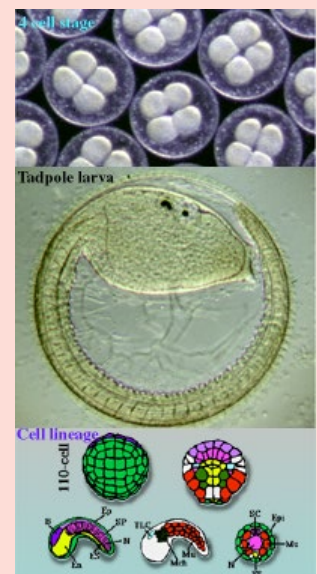
### [Research: Mechanisms of animal embryogenesis]

We all have developed from fertilized eggs of 100 µm in diameter. Have you thought about how it can be possible? Our laboratory is working on mechanisms how eggs develop into a well organized adult body using micromanipulative and molecular approaches.

In animal development, embryonic cells not only proliferate, but also generate various types of cells such as epidermis, muscle, neuron, and blood cells. All of these cells are originally derived from a fertilized egg. What kinds of mechanisms are involved in these processes in which some cells are fated to become muscle and other cells to become neuron? Namely, cellular and molecular mechanisms of cell fate determination during embryogenesis are the theme of our laboratory.

We use embryos of ascidian (sea squirt, *Halocynthia roretzi*) as an experimental material. Ascidian has been regarded as a primitive chordate that evolved to basic vertebrates. Fertilized eggs develop into tadpole larvae within 35 hours of development (Figure). Its embryogenesis has been intensively described in details so that we can predict which cells of the early embryo give rise to which cells of the tadpole larva (Figure, bottom).

Ascidian embryos provide us the unique possibility of understanding various mechanisms of fate determination in every cell type, because the tadpole consists of a small number of cells, and of a few types of tissue. Understanding fate determination mechanisms using this simple model organism with the basic body plan of Chordates would contribute to our knowledge in Developmental Biology.



# Laboratory of Cell Biology

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[Research Area]

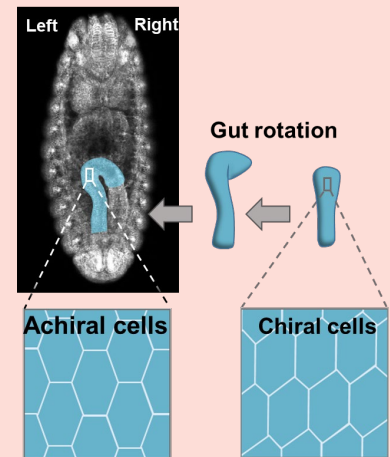
## 1. Left-right asymmetric development in *Drosophila*

The internal organs of many animals show directional left-right (LR) asymmetry. However, mechanisms of LR asymmetric development remain largely unknown in most animals. *Drosophila*, a fruit fly, is a good model organism for studying developmental biology. We aim to understand the mechanisms of LR asymmetric development, such as chirality of cells, using combinations of genetics, computer simulation, and bioimaging.

## 2. Mechanisms of Notch signaling

Development and homeostasis require cell-cell interactions in multicellular organisms. Notch is a receptor and transduces cell-signal through a direct cell-cell interaction. We are studying cell-signaling through the Notch receptor using *Drosophila* as a model system. We aim to understand the mechanisms of Notch signal transduction and find ways to control the Notch signaling.

Cell chirality induce LR asymmetry



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# Laboratory of Comparative Neurobiology

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[Research Interests]

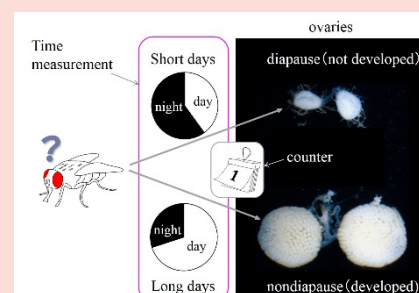
Animals and plants are organized on a daily and seasonal schedule. By using endogeneous clock system organisms anticipate and prepare for environmental harsh period to change their physiological conditions. We study neuronal mechanisms underlying biological timing system.

### 1) Photoperiodism and diapause

For seasonal adaptation animals and plants read day length to change their morphs or development. This is called photoperiodism. We study photoperiodic mechanisms using insects (flies, true bugs, a silkworm) and a mollusk. The blowfly *Protophormia terraenovae* develop the ovaries under long days but suppress their development to enter diapause under short days (Figure). We have identified circadian clock neurons involved in photoperiodic response and different types of brain neurosecretory neurons controlling diapause in *P. terraenovae*. However, it remains unknown how the photoperiodic clock system discriminates between short and long days (time measurement) and counts number of days required for switching diapause and nondiapause states (day counting). We investigate into time-measurement and day-counting system in the brain.

### 2) Circa'bi'dian rhythm

The large black chafer *Holotrichia parallela* have a unique two-day periodicity called circa'bi'dian rhythm. In the field they appear on the ground to forage and mate every two nights. In the laboratory the rhythm continues under constant darkness with a period about 48h. Phase responses of the rhythm to light pulses suggest the circadian clock (ca 24 h) produces circa'bi'dian rhythm (ca 48 h). We propose a novel function of the circadian clock characterized by the release of an output signal every two cycles to produce the 2-day rhythm. We are interested in proximate and ultimate causation of the circadian rhythm.



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# Laboratory of Cellular Life Science

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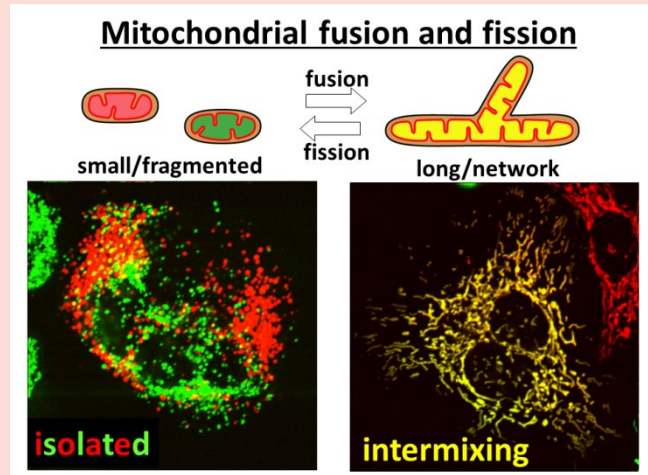
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## [Research Area]

Mitochondria, double membrane-bound organelles with tubular network structures, are essential for oxidative ATP production and play pivotal roles in regulating calcium homeostasis, ROS production and apoptosis. Mitochondria dynamically change their morphology by frequent fusion and fission, and three types of high molecular-weight GTPase proteins have been identified as core components of the fusion and fission machineries. We are analyzing their molecular mechanism and the physiological roles in mammals, and found that the regulation of mitochondrial dynamics coupled with a quality control system is essential for cellular homeostasis, mtDNA regulation, and tissue differentiation. To analyze mitochondrial dynamics, we characterize purified proteins, observe live imaging, and analyze *in vivo* phenotypes in mitochondrial-dynamics defective cells/animals.



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# Laboratory of RNA Biofunction

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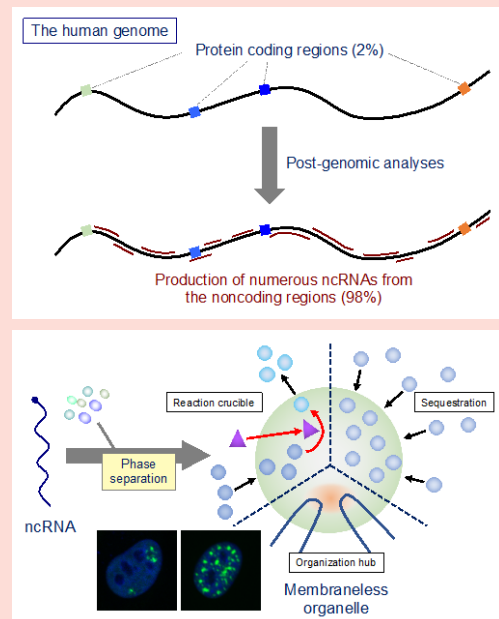
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## [Research Interests]

Transcriptome analyses in the beginning of the 21st century have revealed that large portions of the eukaryotic genomes produce numerous numbers of non-coding RNAs (ncRNAs), which expectedly play important regulatory roles in various biological events. Our laboratory aims to elucidate the functions and the underlying new genetic code, thereby reconstructs the basic concept of genome function. Among thousands of ncRNAs in mammalian cells, we particularly focus on "architectural ncRNAs (arcRNAs)" that play architectural roles to build membraneless organelle through induction of intracellular phase separation. We attempt to elucidate the specific biological functions of the arcRNAs that require to form the massive phase separated structures.



# Laboratory of Animal Morphology

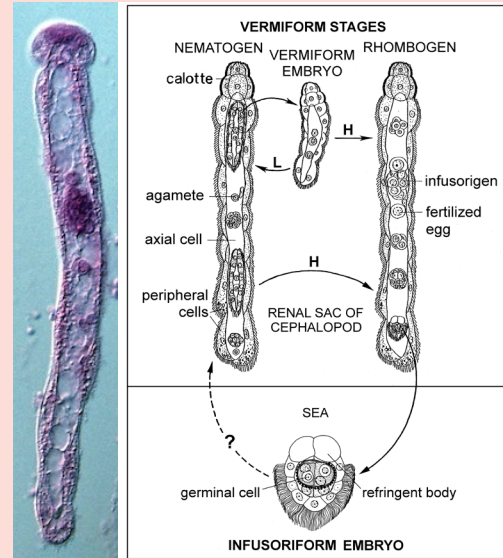
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## [Research Area]

Organisms are quite small, but the most complicated creations in nature. My lab is interested in reading the meaning of animal forms and uses comparative anatomical approaches to understand the morphological evolution and adaptation. We are studying how the animal form had evolved in the life history using the dicyemid mesozoans (Phylum Dicyemida), a unique group of animals that inhabit the renal organ of cephalopod mollusks. The dicyemid body consists of only 20 to 40 cells and represents the smallest number of cells in the animal kingdom. Dicyemids have neither body cavities nor differentiated organs, and were named "Mesozoa" for the dicyemids as an intermediate between Protozoa and Metazoa in body organization. However, some zoologists regard the simple organization of dicyemids to be the result of specialization of parasitism. Recently we have revealed that dicyemids are not truly primitive animals, that deserve the name of "mesozoans", but that they belong to the metazoans. It still remains to be explored how such a simple body organization has evolved. Dicyemids are subjected to a number of selecting pressures due to their unique habitat with the renal organs of cephalopod hosts. In terms of morphological and ecological adaptation, this microenvironment could afford a space for a simple natural experiment.



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# Laboratory of Photosynthetic Biology

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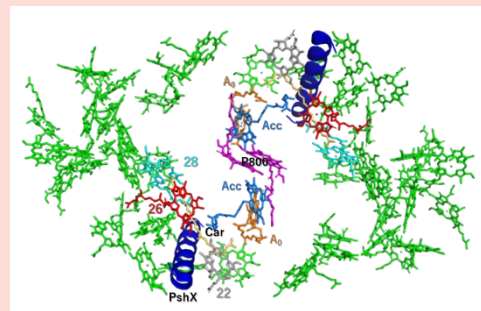
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## [Research Area]

All life activities on the earth are supported by the sun's inexhaustible light energy. Photosynthesis is an important biological reaction system that is indispensable for maintaining the current global environment, efficiently converting light energy into chemical energy that can be used by living organisms. Our research seeks to understand this light-energy conversion mechanism at the molecular level and to explain it using terms of physics and chemistry. The photosynthetic reaction center complexes, which are membrane proteins, are responsible for the process of light energy conversion by plants and photosynthetic microorganisms. In the complexes, absorbed light energy is transferred to the dimeric chlorophyll pigments (special pair of P), which is then excited to  $P^*$  and forms a charge-separated state of  $P^+A^-$  between the special pair and the primary electron acceptor (A). The energetic electrons are then transferred through various electron-transfer

components in a bucket relay-like fashion, eventually producing the reducing power (NADPH) necessary for the anabolic reaction. We are using biochemical, spectroscopic, and molecular biological techniques to elucidate the reaction mechanisms of light-energy conversion.



Arrangement of photosynthetic pigments in heliobacterial reaction center. The P800 consisted of a dimeric (BChl  $g_2$ )<sub>2</sub>.

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## Laboratory of Interdisciplinary Biology 1

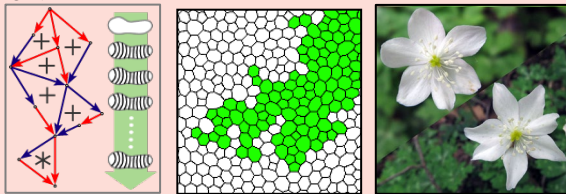
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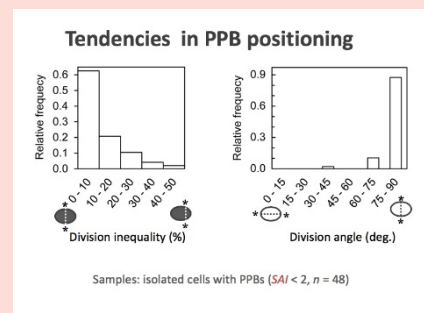
### Theoretical Biology – Koichi FUJIMOTO –

Using physics and mathematics, our laboratory tries to understand the underlying mechanisms of biological processes in a wide spectrum ranging from microbes to animals and plants. We study how gene networks regulate animal and plant morphogenesis, and chemical and mechanical communications of cell populations. By combining theoretical prediction derived from computer simulations with quantitative analysis of experimental data, our missions are to uncover the principles for the evolution of gene regulatory network (left figure), the cell patterning (center), and the organ number and symmetry determination (right).



### Mechanisms of cell's division-plane selection and tissue formation in plants – Tetsuhiro ASADA –

Cell arrangement in plant bodies largely depends on the selection of the plane of cell division. As an effort to understand the mechanisms of controlling the plane of cell division for plant tissue formation, we analyze the tendencies of division plane selection in isolated cells and developing tissues from plants.



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## Laboratory of Interdisciplinary Biology 2

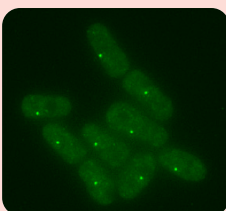
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### Molecular Mechanisms of Chromosome Rearrangements – Takuro NAKAGAWA –

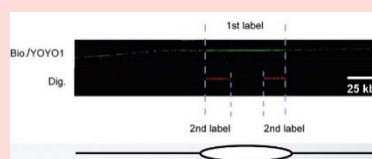
An extremely large number of repetitive sequences are present in a eukaryote genome. Intriguingly, repetitive sequences occupy around half of the human genome. Gross chromosomal rearrangement (GCR) such as translocation occasionally occurs using the repetitive sequences as "DNA glue". GCR can cause genetic diseases including cancer and cell death. From the evolutionary point of view, on the other hand, GCR can be one of the driving forces of evolution. Therefore, GCR appears to be the integral phenomenon of living organisms. Using fission yeast as a model organism, we are trying to identify the genes that suppress or promote GCR and elucidate the molecular mechanism of GCR.



Fluorescent image of fission yeast:  
The centromere region of chromosomes  
that contain DNA repeats.

### Initiation of DNA Replication in Eukaryotic Cells – Yumiko KUBOTA –

One of most fundamental feature of life is reproduction. All living organisms are made up of a cell or cells and DNA in cell nuclei carries the genetic information of the organisms to construct and maintain them. Therefore, the precise duplication and distribution of DNA to daughter cells during cell division cycle is the basis of keeping an organism alive. The failure of these processes would cause the severe defect in the organisms, such as cell death or serious diseases like cancer. To understand the faithful duplication of DNA, we investigate the basic mechanisms and the regulations of initiation of DNA replication using the cell-free DNA replication system of *Xenopus* egg extracts, which contain plentiful proteins for DNA replication to support the rapid early cell division cycle of embryo.



Replicated DNA visualized  
by incorporation of labeled  
nucleotides.



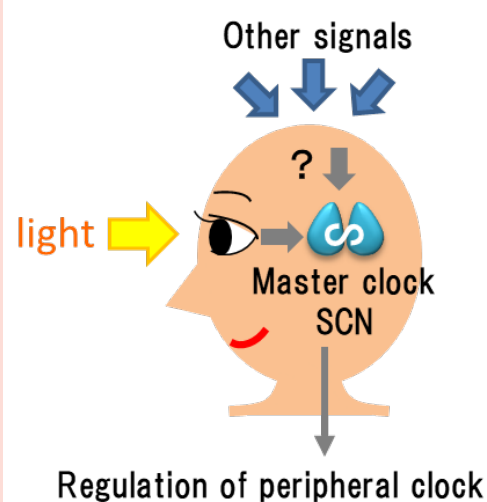
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## Laboratory of Synaptic Plasticity

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## [Research Theme]

Most living things on the earth have the circadian clock (biological clock) to adapt to the daily environmental changes. In mammals, the master circadian clock is located in the suprachiasmatic nucleus (SCN) in the hypothalamus. The master clock synchronizes its autonomous oscillation with the environmental changes corresponding with the day-night cycle, and adjusts the internal environment with the external environment regulating the peripheral clocks in other brain regions and the body (right figure). We aim to elucidate how various environmental factors including light affect the biological clock at the molecular level. In addition, we are studying the aftereffects of those factors, that is, plasticity of the biological clock.



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## Laboratory of Organic Biochemistry

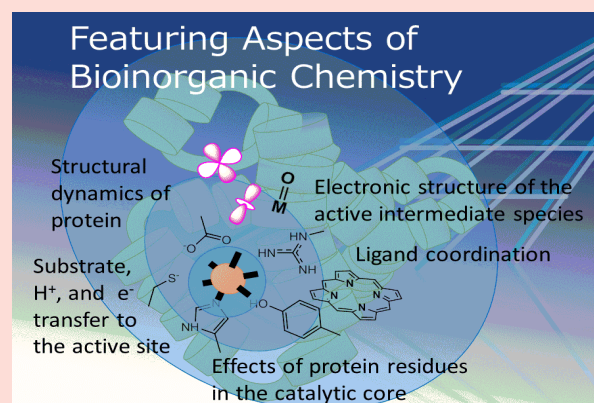
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## [Research Interests]

- 1) Synthesis of dinuclear and multinuclear metal complexes activating molecules
- 2) Synthesis of heterometallic multinuclear complexes activating molecules
- 3) Synthesis of novel metal complexes as a photosensitizer
- 4) Development of artificial metalloenzymes activating molecules
- 5) Investigation of relationships between structures and functions of metalloprotein
- 6) Synthetic and mechanistic study on metal complexes with anticancer activity

The photosynthetic energy transduction and metabolism involve photo-excitation coupled with electron transfer process, and activation of substrates including small

molecules such as  $O_2$  and  $N_2$ . The 1<sup>st</sup> transition metals are frequently essential trace elements for organisms, working at the active sites in the proteins. The metal complexes sometimes show pharmaceutical activity. We study on metals in biology, and we newly develop relevant metal complexes and metalloenzymes.





# Biomolecular Machine Design Group

**Members** Ken'ya FURUTA (Guest Associate Professor)

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## [Research Area]

### - Design principles of biomolecular motors

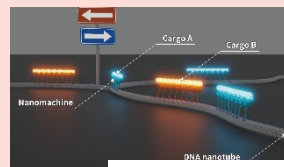
In an environment governed by thermal fluctuations, it seems difficult for a protein to move uni-directionally. In addition to analyzing existing biomolecular motors, we are trying to establish a constructive approach by combining simple domains into a new biomolecular motor prototype and observing how it behaves.

### - Design and control of collective dynamics

Individual molecular motors cannot explain many biological phenomena. To address this, we are creating experimentally accessible model systems using DNA nanostructures and other biological materials to explore the collective dynamics.

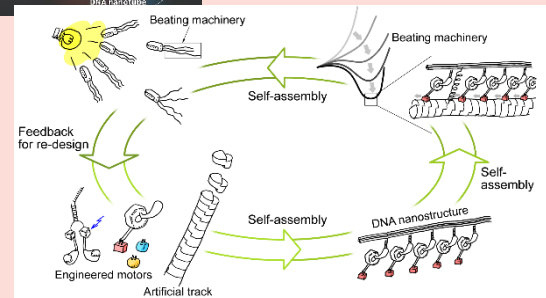
### - Design of autonomous micro-robots

The 3 key elements of a robot are sensors, processors, and actuators. Cells are equipped with these elements



Top: Sorting with nanomachines (Ibusuki et al., *Science* 2022).

Bottom: Autonomous micro-robots (Furuta et al., *Curr Opin Biotechnol* 2017).



and can be viewed as micro-robots that move autonomously. We aim to understand the mechanisms by which cells remember information and make decisions based on that memory, through a synthetic biology approach—the creation of such micro-robots by assembling structures using biological materials and self-assembling techniques.

# Laboratory for Molecular and Developmental Biology (Institute for Protein Research)

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## [Research Interests]

Our laboratory studies molecular mechanisms underlying the development and function of the vertebrate central nervous system (CNS) using various research methods of molecular biology, mouse genetics, biochemistry, cell biology and neural physiology. We use the retina as a model system to understand how DNA encodes programs to generate various neurons and glial cells, form precise neuronal circuits, and enable complicated neuronal function. We also focus on how abnormality of biological processes in development and maturation leads to human diseases. We are eager to contribute to development of diagnosis and cure of human diseases. Together, our lab aims to elucidate mechanisms and principles underlying the CNS development from DNA programs to physiological function and human diseases.

## [Research Project]

1) Molecular analysis of synapse formation in the CNS.

2) Elucidation of functional roles of microRNAs (miRNAs) in CNS development.

3) Analysis of molecular mechanisms underlying transcription and chromatin regulation in neuronal differentiation.

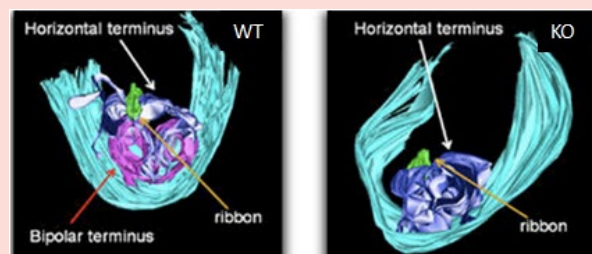


Figure. We previously identified Pikachurin, an extracellular matrix-like retinal protein, and observed that it localized to the synaptic cleft in the photoreceptor ribbon synapse. Pikachurin KO mice showed improper apposition of the bipolar cell dendritic tips to the photoreceptor ribbon synapses, resulting in alterations in synaptic signal transmission and visual function. WT (left), Pikachurin KO (right)

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# Group of Homeostatic Integration

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## [Research Programs]

- (1) Metabolism and function of dipeptides in mammals
- (2) Proteomic analysis of protein and peptide breakdown

In living cells, there are numerous short peptides such as dipeptides and tripeptides, some of which are produced by protein degradation, while the others synthesized from amino acids by specific enzymatic reactions. Regardless of their route of production, short peptides are essential to protein metabolism and its homeostasis. We have been studying the function and metabolism of short peptides, especially focusing on dipeptide-hydrolyzing enzymes or dipeptidases, CN1 and CN2.

We have also been trying to develop proteomic procedures to analyze protein degradation, and apply them to study disease-induced changes in protein degradation products

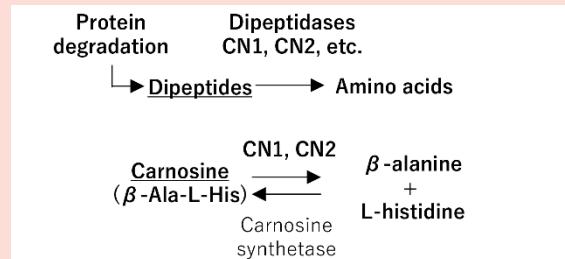


Fig. 1 Dipeptide breakdown and carnosine metabolism

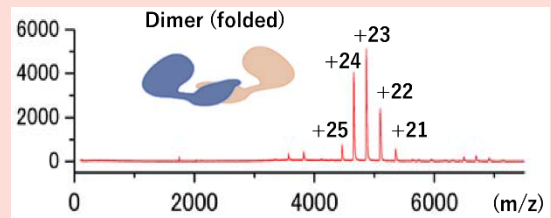


Fig. 2 ESI-MS analysis of CN2 dimer (106 kDa)

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# Laboratory for Molecular Biophysics (Institute for Protein Research)

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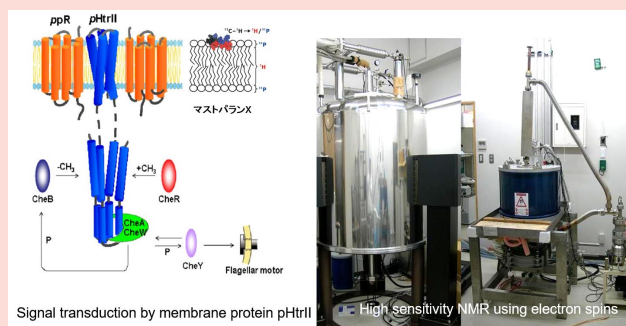
**Home Page** <http://www.protein.osaka-u.ac.jp/biophys/>

## [Research Interests]

Signal transduction and energy conversion play very important roles in the human body. Many these functions are performed by supramolecular systems across biomembranes. These systems are also responsible for forming networks of integrated biological activities. We are elucidating these essential functions of proteins on the basis of structures and the interactions revealed mainly by nuclear magnetic resonance spectroscopy (NMR).

NMR reveals structure and function of biologically important molecular complexes that not amenable to X-ray crystallography and electron microscopy. These systems include proteins bound to lipid bilayers and noncrystalline large molecular complexes, such as membrane protein pHtrII for the transmission of light signal, halorhodopsin for light-driven ion pumping, amyloid protein fibers, and model G-protein-receptor complexes.

We are also developing NMR methods by using advanced technologies for NMR experiments, bioinformatics and molecular biology. Two NMR spectrometers features high-power terahertz wave sources, gyrotron for enhancing the sensitivity by using electron spin polarization.



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# Laboratory of Organelle Biology

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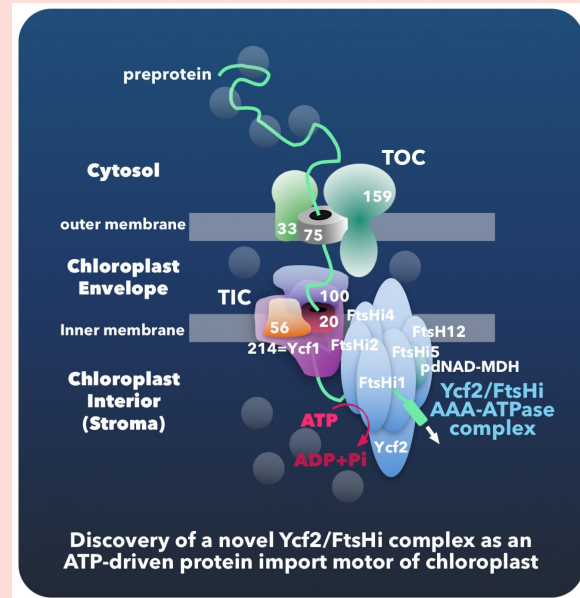
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## [Research Interests]

In plants and algae, the eukaryotes, photosynthesis is carried out in a specialized organelle called chloroplast. It is now widely accepted that virtually all chloroplasts in today's photosynthetic eukaryotes derive from one fairly rare primary endosymbiotic event with a cyanobacterium-like ancestor thought to have occurred more than a billion years ago. Extant higher plants can synthesize only ~100 proteins inside the chloroplast but must import such 2000-3000 different cytosolically-synthesized nuclear-encoded proteins, across the double envelope membranes surrounding this organelle, to fulfill their complex physiological roles including photosynthetic functions. Two successive protein translocators at the outer and inner envelope membranes, termed TOC and TIC, respectively, are responsible for the task of protein import into chloroplasts. Our recent discoveries of the genuine TIC translocon (*SCIENCE* 2013) and associated import motor (*PLANT CELL* 2018) both of which are well conserved among most land plants as well as green algae could provide us an entirely revised view on the molecular mechanisms of protein translocation across the inner envelope membrane of chloroplasts and also novel insights on the evolution of the chloroplast protein import system.



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# Laboratory of Protein Synthesis and Expression (Institute for Protein Research)

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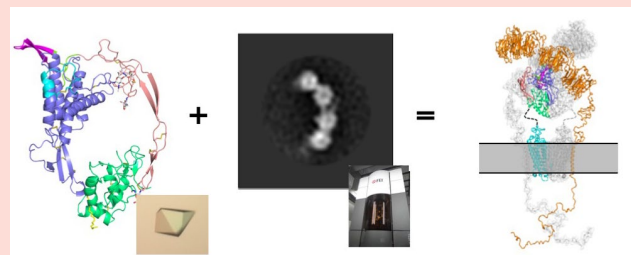
**Home Page** <http://www.protein.osaka-u.ac.jp/rcsfp/synthesis/index.html>

## [Research Interests]

- 1) Elucidation of mammalian signal transduction mechanism via structural study of ligand-receptor complexes
- 2) Structure-based design of "novel therapeutic proteins" through state-of-the-art protein/antibody engineering
- 3) Near-atomic resolution structural analysis of biologically important macromolecules by using cryoelectron microscopy (cryo-EM)

Cellular response to the extracellular environment depends on the "sensing" the extracellular cues by use of the receptor-ligand system. Binding of ligands to the extracellular domain of the receptors transduce signals into cells that initiates various cellular events, ultimately changing the cell fate. Most of the "signal transduction researches" deal with cytoplasmic events such as phosphorylation/dephosphorylation of signaling molecules and subsequent recruitment of adapter molecules, but mechanism for the "signal transmission across the membrane", the very first step in the signaling pathway is poorly understood.

Our study focuses on questions such as how receptors recognize their specific ligands, how this recognition leads to structural change in the receptor complex, and how the information cross the plasma membrane without transporting chemical entity. Using structural as well as chemical approach, we would tackle on this difficult problem to obtain insights into the mechanism of transmembrane signaling. Such information would eventually be used for drug development and benefit medical as well as biological research in general.



Crystal structure of human Wnt3 (left) and cryo-EM structure of LRP6 (center), combined to give hypothetical structure of the entire signaling machinery on cell surface (right).

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# Laboratory for Computational Biology (Institute for Protein Research)

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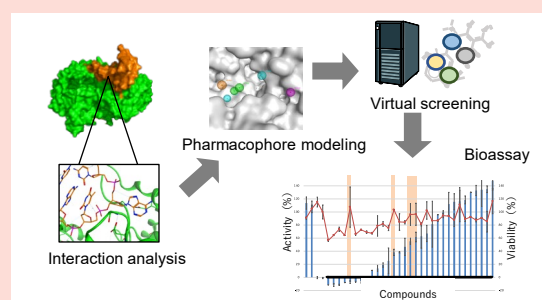
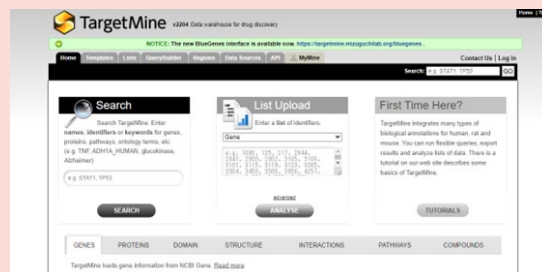
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## [Research Area]

- 1) Data integration for relating molecular-level events to higher-order biological systems.
- 2) Understanding and predicting molecular interactions involving proteins, modelling biological responses.
- 3) Transcriptome analysis of early human embryos.
- 4) In silico prediction of pharmacokinetic parameters.

We aim to increase our understanding of biological systems and diseases by combining computer science and computational chemistry approaches, with applications to drug discovery and other research areas. Artificial Intelligence (AI) is expected to play major roles in many domains. Recognizing that the availability of a large amount of data in a computer-friendly format is key to the successful development of AI models, our research is focused on integrating a wide array of data, including genes, proteins, chemical compounds and diseases. We also develop methods for predicting protein structure, function and interaction, and apply them to specific biological problems.



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# Laboratory of Supramolecular Crystallography (Institute for Protein Research)

**Members** Atsushi NAKAGAWA (Professor), Eiki YAMASHITA (Associate Professor), Mamoru SUZUKI (Associate Professor)

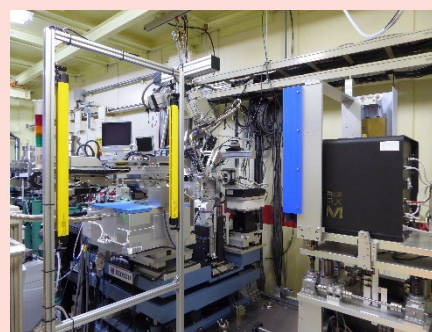
**Home Page** <http://www.protein.osaka-u.ac.jp/rcsf/supracryst/>

## [Current Research Projects]

- 1) X-ray structure determination of biological macromolecular assemblies and proteins.
- 2) Development methodologies for X-ray structure determination of biological macromolecular assemblies using synchrotron radiation.
- 3) Development of data processing algorithm of diffraction data from large unit cell crystals and micro-crystals.

Our laboratory aims to elucidate the molecular interactions and molecular recognition mechanisms that are important for understanding biological functions based on precise atomic structures. For this purpose, X-ray crystallography and cryo-electron microscopy are used.

Major research targets include drug efflux complexes that play an important role in drug resistance in *Pseudomonas aeruginosa*, one of the bacteria causing hospital-acquired infections, Rice dwarf virus with a molecular weight of 75 million, PIV, a virus-like particle that forms stable spherical particles even under high temperature conditions of over 90 °C.



SPring-8 BL44XU

## Laboratory of Protein Profiling and Functional Proteomics (Institute for Protein Research)

**Members** Toshifumi TAKAO (Professor), Toshiki TAKEI (Assistant Professor), Qiuyi WANG (Assistant Professor)

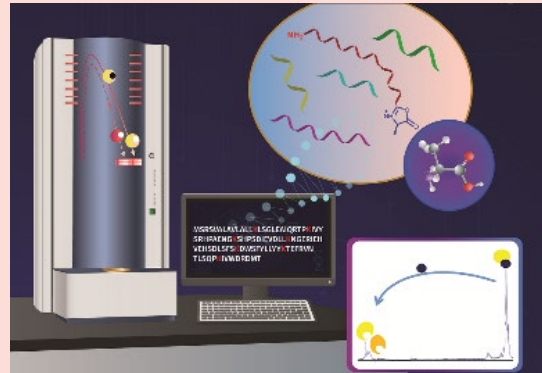
**Home Page** <http://www.protein.osaka-u.ac.jp/rcsfp/profiling/>

### [Research Programs]

- 1) Development of chemical/analytical methods and software for analysis of protein primary structure by mass spectrometry
- 2) Mass spectrometric analysis of post-translational modifications
- 3) Development of chemical and analytical methods for proteomics
- 4) Study on fragmentation of peptides and carbohydrates in mass spectrometry
- 5) Hardware development for high-sensitivity and high-accuracy mass spectrometry

Mass spectrometry (MS) is a well-accepted technique for the analysis of chemical structures of biological compounds. For the last four decades, we have been working to develop methods for determining primary structures and post-translational modifications of proteins using MS. In conjunction with accumulating protein and gene sequence databases, we are using state-of-the-art MS for large-scale protein identification, which is indispensable for understanding

biological events. We apply the following developed methods to the structural analysis of micro quantities of peptides, proteins, and their related substances.



MALDI-TOFMS can reveal the peptide C-terminus.

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## Laboratory of Genome and Chromosome Functions (Institute for Protein Research)

**Members** Akira SHINOHARA (Professor), Asako FURUKOHRI (Associate Professor), Masaru ITO (Assistant professor), Yurika FUJITA (Assistant professor)

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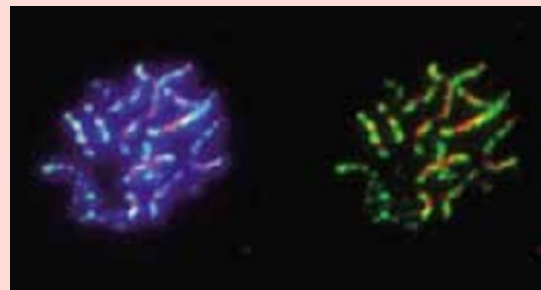
### [Research Area]

#### [Research Subjects]

- 1) In vivo and in vitro analysis of recombination reactions
- 2) Analysis of proteins working with RecA homologues in recombination
- 3) Analysis of the roles of chromatin modification in meiotic recombination
- 4) Mechanisms of choice of DSB repair pathways
- 5) Analysis of recombination in human cells
- 6) Mechanism of chromosome dynamics in mouse meiosis

Homologous recombination, an exchange between DNA strands, plays a role in the maintenance of genome stability and the production of genome diversity. While, in mitosis, it is required for the repair of DNA damage, it is for the segregation of homologous chromosome at meiotic division I. Meiotic recombination is coupled with chromosome of the recombination leads cancer and infertility in human. To reveal molecular mechanism of the recombination,

we have been analyzing genes/proteins involved in the process using molecular, genetical, biochemical, and structural methods.



Synaptonemal complex (SC) formation. Immuno-staining analysis of the SC components, Zip1 (red) and Red1 (green) in the budding yeast. In SCs, paternal and maternal chromosomes are fully paired along chromosomes. Blue shows DNA, thus chromosomes.

# Laboratory of Protein Crystallography

(Institute for Protein Research)

## Members

Genji KURISU (Professor), Hideaki TANAKA (Associate Professor),  
Akihiro Kawamoto (Assistant Professor), Naoko NORIOKA (Technical Assistant)

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<http://www.protein.osaka-u.ac.jp/crystallography/EngHP/>

## [Research Interests]

- 1) Structural studies of photosynthetic energy-transducing membrane protein complex and related redox enzymes
- 2) Crystal structure analyses of dynein motor
- 3) Damage-free crystal structure analysis of metalloproteins at high resolution

Three-dimensional protein structure brings us a deeper insight into the biological function. X-ray crystallography combined with Cryo-TEM is the best method to determine atomic coordinates of protein molecules. The main aim of our group is the structure determination of the biological macromolecular assemblies including membrane protein complexes, in order to elucidate the molecular mechanism of the highly organized biological process at atomic level.



Crystal Structure of the dynein motor domain

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# Laboratory of Protein Organic Chemistry

(Institute for Protein Research)

## Members

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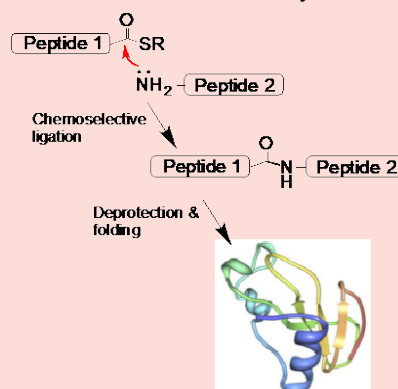
<https://sites.google.com/site/takatoshihikidalaboratory/home>

## [Research interests]

- 1) Establishment of a method for protein synthesis
- 2) Chemical synthesis of glycoprotein, modified histone, and membrane protein

Chemical methods enable the synthesis of proteins, which can not be prepared by the recombinant method, such as site-specifically labeled, glycosylated and phosphorylated proteins. Our laboratory is aiming to promote new protein researches using these synthetic proteins. Thus, our laboratory is developing facile methods for protein synthesis based on ligation chemistries. In addition, the synthetic method is applied for the preparation of membrane proteins and their partial sequence

to elucidate the signal transduction mechanism by solid state NMR and IR. Modified histones and their partial sequences, glycosylated proteins are also synthesized for the functional analyses.



General procedure for the chemical protein synthesis.



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# Laboratory of Biomolecular Science and Reaction

(The institute of Scientific and Industrial Research)

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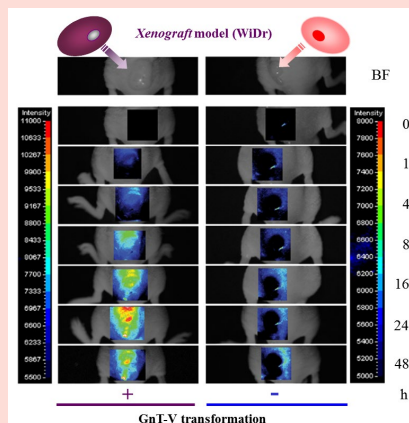
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## [Research Interests]

The aims of this laboratory are the analysis of intermolecular reactions found in various biological phenomena, and the development of bio-industrially useful technologies by utilizing these reactions.

1. *In vivo* pinpoint DDS nanocarriers using virus infection machinery.
2. Single cell analysis by using automated single cell analysis and isolation system.
3. Olfactory receptor repertory analysis by using human OR cell array.
4. Elucidation of biogenesis of novel built-in type cofactors.
5. Structural and functional analysis of bacterial two-component system.



Malignant tumor-specific DDS nanocarrier utilizing sugar-lectin interactions.  
(Left, high malignancy; Right, low malignancy)

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# Laboratory of CryoEM Structural Biology

(Institute for protein research)

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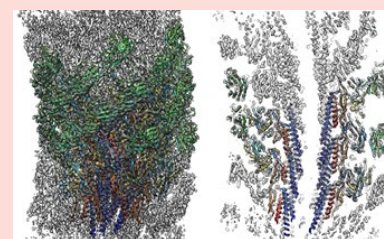
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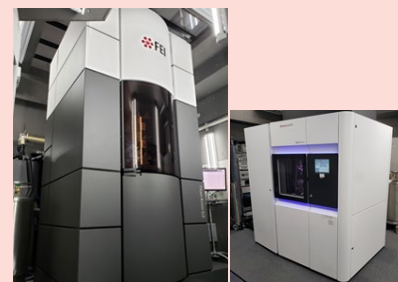
## [Research Interests]

- (1) Study of energy conversion mechanism of molecular motor
- (2) Structural analysis of olfactory receptors
- (3) Study of molecular dynamics by cryo-electron microscope
- (4) Development of high-resolution structural analysis method by cryo-electron microscope

The biomolecules such as protein and nucleotide are responsible for life activity, its function is relative to the structure. In our laboratory, we will clarify the molecular mechanism by structural analysis using a cryo-EM. In particular, we are analyzing the energy conversion mechanism of motor protein such as flagellar motors and ATPase, and the mechanism of olfactory receptors. We are also developing of the method for analysis of molecular dynamics by cryo-EM and for high-resolution and high-resolution structural analysis by cryo-EM.



Structure of Flagella Hook



Cryo-EMs

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# Laboratory for Cell Systems

## (Institute for Protein Research)

Members

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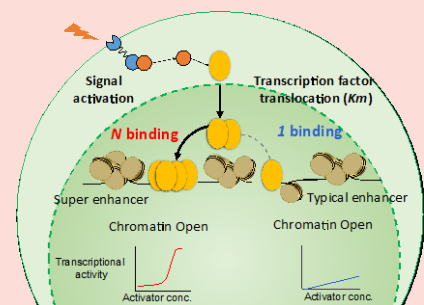
[http://www.protein.osaka-u.ac.jp/cell\\_systems/index.html](http://www.protein.osaka-u.ac.jp/cell_systems/index.html)

### [Research Theme] Understanding the dynamics of cells as time and space network of molecules

Cells carry out various molecular controls, and determine their own fate corresponding to the living environment. Upon the procedure, characteristics of cells occur not only by the property of molecule itself but also by the property of intercellular dynamics. In our laboratory, we quantitatively analyze interaction network of intracellular molecules such as protein, RNA and DNA in order to reveal the mechanism of intracellular process and cell fate control. We particularly focus on the regulation of gene expression dynamics by intracellular signal transduction and transcription factor. We thoroughly analyze the molecular mechanisms by combination of quantitative experimental analysis of molecular activity against input of the cell, mathematical modeling and simulation analysis. We also study data driven cell systems to understand how the original stimulus influences the whole cell and activate self-control by using the comprehensive measurement techniques such as genome, transcriptome, epigenome and proteome.

Studying time development process of cells in proliferation and differentiation, we want to understand the logic structure to induce cellular specificity by focusing on solving the signal transduction and transcription responses. Our laboratory conducts wet experiments along with dry approaches such as computational science, mathematics and bioinformatics.

An integrative approach of wet lab experiments and dry lab computation reveals quantitative mechanisms in cellular information transmission for cell fate control.



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# Laboratory of Nanobiology

## (Institute for Protein Research)

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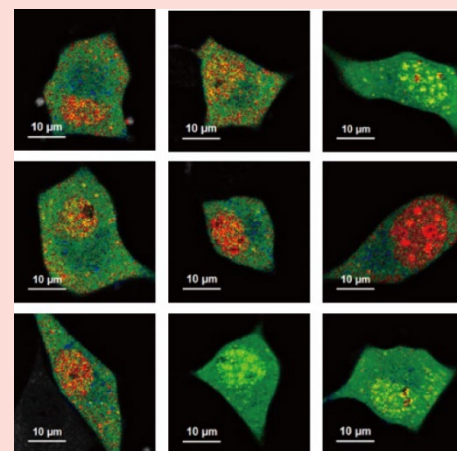
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URL: <http://www.protein.osaka-u.ac.jp/nanobiology/en/>

### [Research Interests]

#### Development of methods for measuring intracellular heat production (temperature)

Temperature that changes with heat is one of the basic parameters expressing the state of matter. However, it is not clear how heat and the resulting temperature change can alter cellular function. To measure the heat production and temperature changes within a single cell, we developed various temperature probes that are based on temperature-sensitive fluorescent polymers, fluorescent dyes, fluorescent nanoparticles, and fluorescent nanodiamonds. We combine various fluorescence imaging techniques such as fluorescence lifetime microscopy and ratiometry. These new measurement methods aim to elucidate the significance and universality of released heat and local temperature changes in cells. We are also conducting joint research on applications of our methods to the biomedical field, such as the evaluation of heat treatment at the cellular level.



#### Intracellular temperature imaging using temperature-sensitive fluorescent polymers and the fluorescence lifetime imaging microscopy.

The distribution of the color suggests the temperature distribution within a cell.

# Laboratory for Advanced Brain Functions (Institute for Protein Research)

**Members** Takatoshi HIKIDA (Professor), Tom MACPHERSON (Assistant Professor),  
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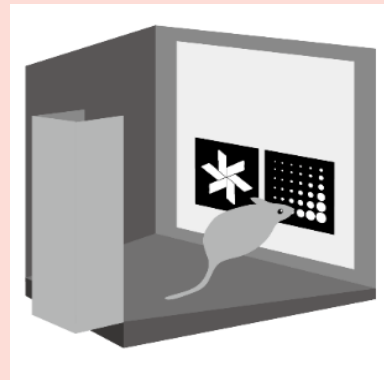
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## [Research Interests]

Our laboratory studies neural circuit mechanisms underlying various advanced brain functions such as cognitive learning and decision making behaviors using molecular techniques for neural circuit specific manipulation. We use several mouse models to reveal molecular pathologies of neuropsychiatric diseases. Especially, we focus on molecular mechanisms of gene-environment interaction in the pathogenesis of mental disorders. We also promote translational research for targeting mental disorders in collaboration with clinical departments and pharmaceutical companies.

## [Research Programs]

1. Analysis of neural circuit mechanisms in advanced brain functions
2. Molecular analysis of neuropsychiatric pathologies
3. Translational research of mental disorders



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# Laboratory of Oncogene Research (Research Institute for Microbial Diseases)

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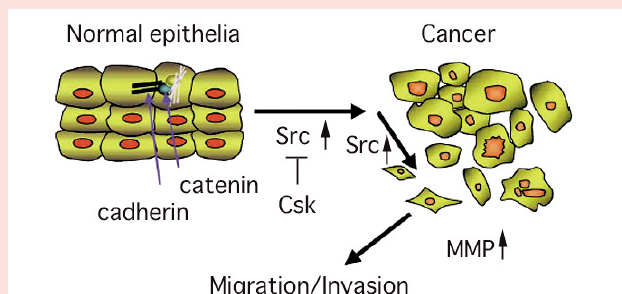
**Home Page** <http://www.biken.osaka-u.ac.jp/biken/oncogene/index.htm>

## [Research Projects]

- 1) Studies on the roles of proto-oncogene products in the development of multicellular animals.
- 2) Studies on the roles of Src family kinases in the metastasis and/or invasion of cancer.

The primary focus of this department is to understand the functions and regulatory mechanisms of proto-oncogene products, which play crucial roles in the cell signaling pathways involved in the development and differentiation of animal cells. Understanding the critical functions of these proto-oncogenes would provide insights into the molecular basis of normal cell development as well as oncogenesis, which can be considered as an aberrant form of differentiation. Presently, we are focusing on the proto-oncogenes encoding protein tyrosine kinases, particularly the Src family of tyrosine kinases (SFK). SFK is known to be involved in regulating cell-cell and cell-substrate adhesion and cell migration. Malignant cancer role of SFK in the progression of cancer metastasis. To elucidate the principal functions of SFK and to search for new molecules that can be targeted by drugs to block

SFK-mediated cancer progression, we are currently engaged in the above projects.



**Potential roles of Src and its regulator Csk in the regulation of metastasis and invasion of cancers.** In various human cancers, it is known that the kinase activity of Src is elevated. The activation of Src leads to disruption of cell-cell interaction, enhancements of substrate adhesion and cell mobility, and increased secretions of MMPs and cytokines. As a consequence of these events, the metastatic and invasive actions of cancer cells are greatly promoted.

Department  
of  
Biological  
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# Laboratory of Cellular Regulation

## (Research Institute for Microbial Diseases)

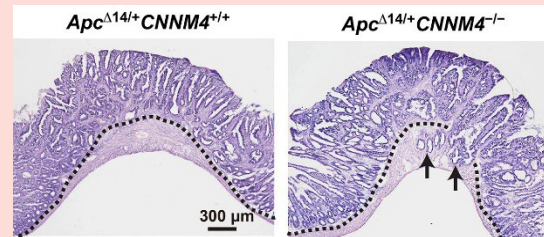
**Members** Hiroaki MIKI (Professor), Yosuke FUNATO (Associate Professor),  
Osamu HASHIZUME (Assistant Professor)

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**Home Page** <http://www.biken.osaka-u.ac.jp/lab/cellreg/>

### [Research Interests]

Most cancers originate from epithelial cells that normally form tight cell-cell adhesion. Accumulating gene mutations in epithelial cells promote their malignant progression, expanding their territory from the original epithelial tissue to the surrounding tissues and finally metastasizing to other organs via blood vessels. While a number of oncogenes and anti-oncogenes that are involved in the regulation of cell proliferation and survival have been identified, the molecular mechanisms governing the phenotypical changes of cancer cells in the three-dimensional space, such as cancer invasion and metastasis that accompany the dynamic change of the tissue architecture, remain to be determined. How do the cancer cells escape from the tightly-connected epithelial tissue where they arise? How do the cancer cells expand their territory by invading into the surrounding tissue? To tackle and solve these important questions in cancer biology, we are investigating the molecular mechanism of cancer progression using mice and mammalian cultured cells.



In the intestine of mice that spontaneously form multiple polyps, gene disruption of CNNM4 stimulates malignant progression of the tumor cells in the epithelial tissue layer to cancers that have invaded into the muscle tissue layer (arrows in the right panel).

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Department  
of  
Biological  
Sciences

# Laboratory of Homeostatic Regulation

## (Research Institute for Microbial Diseases)

**Members** Tohru ISHITANI (Professor), Yuki AKIEDA (Assistant Professor),  
Masayuki OGINUMA (Assistant Professor),

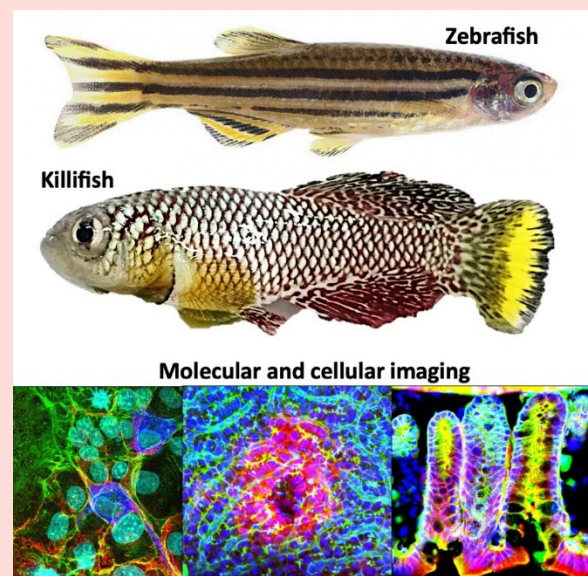
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### [Research Interests]

1. A new concept of tissue homeostasis "Morphostasis"
2. Aging programs and their regulation
3. Robustness supporting signal transduction systems
4. Molecular basis underlying "Diapause", the systems suspending vital activities

In our body, cells recognize their position and role and behave accordingly via cell-cell communication. Such behavior supports tissue morphogenesis and homeostasis, while its dysregulation is involved in congenital malformation, cancer, and aging. We focus especially on the cell-cell communication and behavior supporting tissue homeostasis and explore unknown molecular systems controlling embryonic development, organogenesis, regeneration, aging, and disease, using in vivo imaging, animal model genetics, molecular and cell biology, and biochemistry techniques.



# Laboratory of Biomolecular Informatics

(RIKEN Center for Biosystems Dynamics Research)

**Members** Li-Kun PHNG (Guest Associate Professor), Kyogo Kawaguchi (Guest Associate Professor)

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## [Research Interests]

### 1) Mechanisms of blood vessel formation (Phng).

We investigate molecular and mechanical mechanisms of how endothelial cells shape blood vessels. We employ the zebrafish embryo as a model system, and perform high-resolution fluorescent live imaging, genetic engineering, chemical and optical perturbations with numerical simulations to understand how endothelial cells behave during vessel morphogenesis (Fig. 1) and respond to haemodynamics during development and homeostasis.

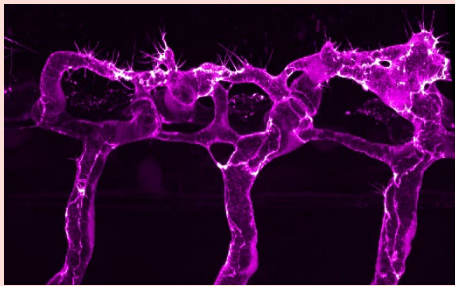


Fig 1: Actin cytoskeleton in a zebrafish vascular network.

### 2) Elucidating of hidden rules in multicellular phenomena and cell differentiation (Kawaguchi)

We are broadly interested in biological phenomena that arise as a result of collective dynamics. We combine theoretical physics, cell culture experiments, and various data analysis methods to elucidate the mechanisms by which tissues undergo rapid turnover during in homeostasis, how cells collectively flow in during development, and the laws that govern the biological condensates that are born and disappear inside cells.

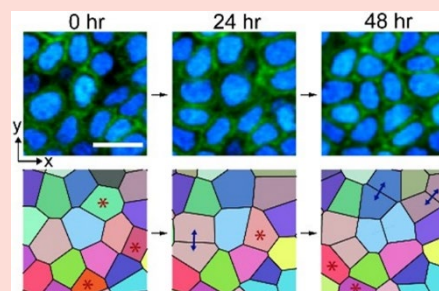


Fig 2: Skin stem cells undergoing rapid turnover in adult tissue

# Laboratory of Biohistory

(JT Biohistory Research Hall [BRH])

**Members** Zhi-Hui SU (Guest Professor), Chikara HASHIMOTO (Guest Professor), Hiroki ODA (Guest Associate Professor)

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**Home Page** <http://www.brh.co.jp>

## [Research Area]

- 1) Insect-plant interactions and evolution
- 2) Degenerative evolution of insect flight function
- 3) Origin and evolution of cell and developmental systems in multicellular animals
- 4) Mechanism of chordata gastrulation
- 5) Relationship between cell cycle and differentiation

By deciphering the historicity, diversity, and commonality of living things written in genomes, we conduct experimental researches on development, evolution, and ecosystems of living things, as well as research on expression of study results. By investigating diverse organisms without focusing on individual genes or species, we believe that the fundamentals of development and speciation in the process of evolution can be revealed. We place the love of living things at the

basis of our researches and also disseminate it. In the Biohistory Group, we are conducting research on the above five topics in evolutionary and developmental biology.

