

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>



Home Page

<http://www.bio.sci.osaka-u.ac.jp/en/index.html>

Department
of
Biological
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Laboratory of Cellular & Structural Biology

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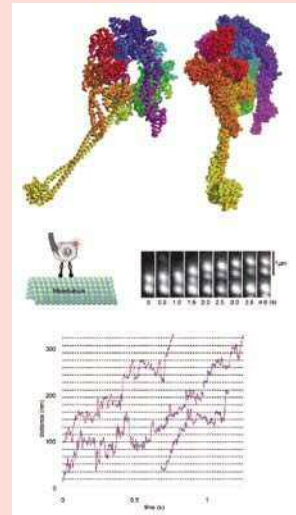
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[Research interests]

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.

Department
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Laboratory of Single Molecule Biology

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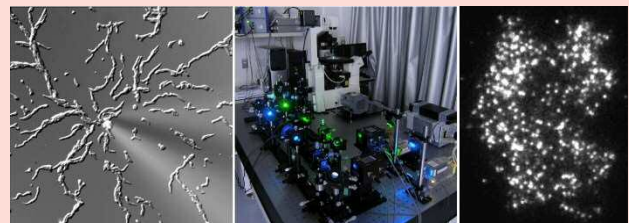
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[Research interests]

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.

Department
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Laboratory of Genome Structure and Function

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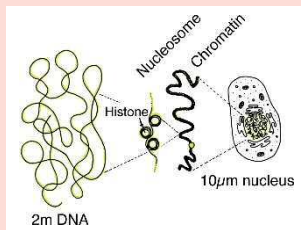
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[Research Interest]

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

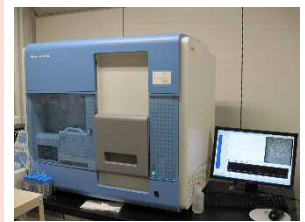


specific gene expression. This cell-type specific gene expression is controlled by epigenetic information including DNA methylation, histone post-translational modifications and chromatin structure. These epigenetic information or epigenomes

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 massspectrometry 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

Department
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Laboratory of Plant Development

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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, and CLE9/10 peptide that regulates stomatal number and vascular cell pattern. 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 environments plants are facing.

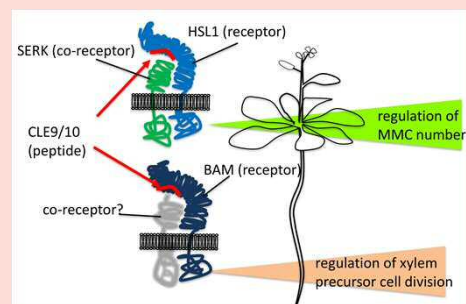


Figure. The signaling molecule CLE9/10 regulates two different developmental processes, depending on which large protein receptor interacts with the peptide. When it interacts with HSL1 receptor in the leaf, it regulates how many leaf pores (stomata) develop. When it binds to BAM receptor in the root, it regulates the development of the cells that form the water-conducting vessels (xylem).

Plant Cell Biology Group

Members Shingo TAKAGI (Professor), Yuki SAKAMOTO (Assistant Professor)

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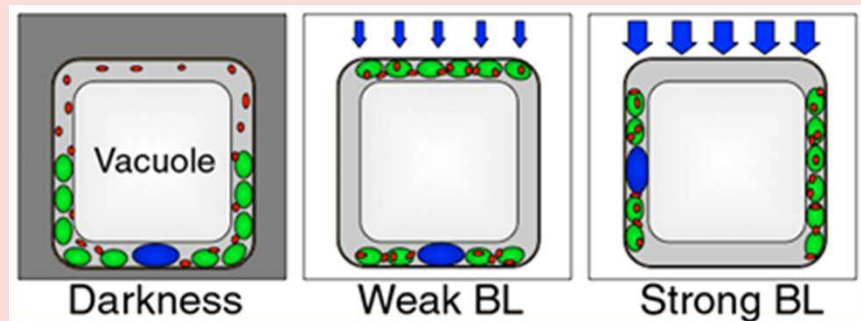
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[Research Topics]

We are dissecting cellular processes from the sensing of environmental fluctuations, for example, in light condition, CO₂ 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.



Laboratory of Developmental Biology

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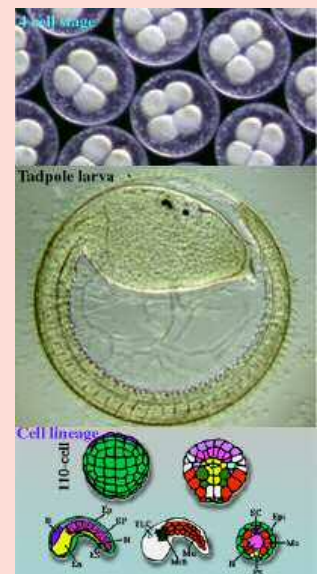
[Research: Mechanisms of animal embryogenesis]

We all have developed from fertilized eggs of 100 μ m 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]

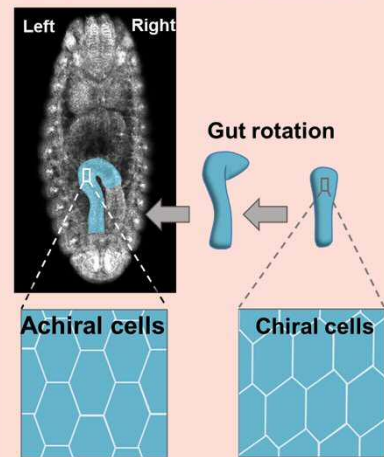
1. Left-right asymmetric development in *Drosophila*

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



Laboratory of Comparative Neurobiology

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[Research Interests]

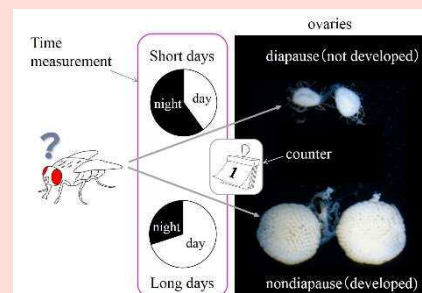
Animals and plants are organized on a daily and seasonal schedule. By using endogenous clock system organisms anticipate and prepare for environmental harsh period to change their physiological conditions. We study neuronal mechanisms underlying biological timing system.

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.



Laboratory of Cellular Life Science

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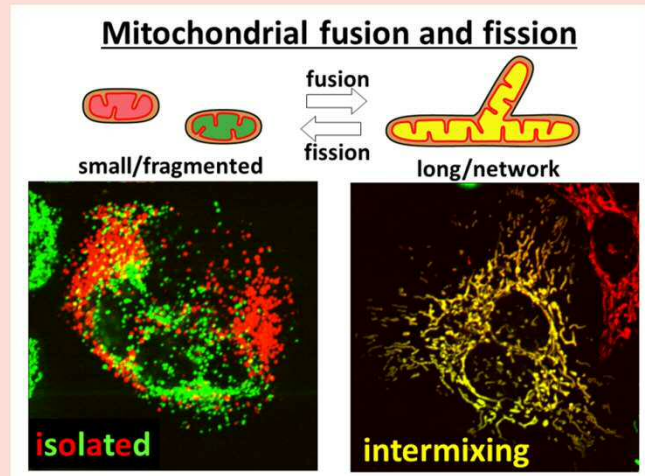
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[Research Area]

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.



Laboratory of Interdisciplinary Biology 1

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[Research Area]

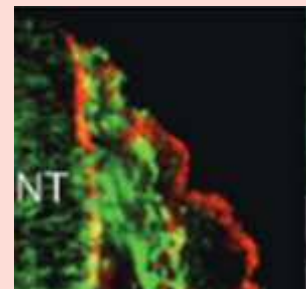
1) Molecular mechanism of photosynthetic light energy conversion (Hirozo OH-OKA)

Photosynthetic light energy conversion system is a key process carried out by pigment-associated protein complexes. In order to understand molecular mechanisms how light energy is converted into chemical energy, we have three research subjects; (a) molecular structure of type 1 reaction center and (b) photosynthetic electron transfer mechanism, and (c) molecular architectures for biological hydrogen productions.

2) Developmental mechanisms of neural crest cells (Kazuo ITO)
We study developmental mechanisms of neural crest cells of which migration and differentiation are attributable to characterization of the vertebrate body plan. We analyze their developmental mechanisms by using the mouse as a model system and the lamprey, the most primitive living vertebrate, from the viewpoints of molecular developmental biology and evolutionary developmental biology.

3) Mechanisms of cell 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.



Laboratory of Interdisciplinary Biology 2

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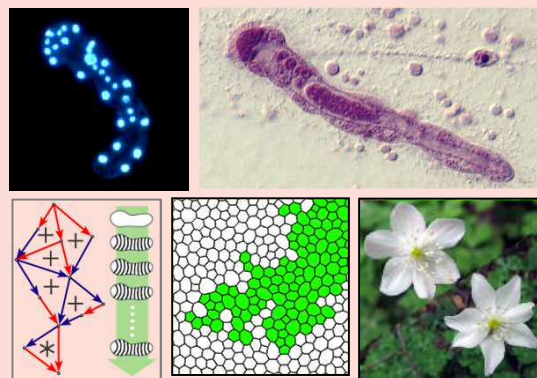
[Research Area]

1) Theoretical Biology (Koichi FUJIMOTO)

Using physics, mathematics and bioinformatics, our laboratory tries to understand the underlying mechanisms of biological processes in a wide spectrum ranging from microbes to animals and plants. Dr. Fujimoto studies how gene networks regulate animal and plant morphogenesis, and chemical and mechanical communications of cell populations. By computer simulations of mathematical models consistent with molecular genetics and bioimaging, our missions are to uncover the principles for the evolution of gene regulatory network (Bottom left figure), the collective decision making of cells (Bottom center), and the robust determination of organ numbers (Bottom right).

2) Biology of dicyemid mesozoans (Hidetaka FURUYA)

Dicyemid mesozoans (Phylum Dicyemida) inhabit the kidney of cephalopod mollusks. The dicyemid body consists of only 20 to 40 cells and represents the smallest number of cells in the animal kingdom. We pursue a synthetic biology of dicyemids, which includes systematics, phylogeny, development, ultrastructure, coevolution with cephalopod hosts.



Laboratory of Interdisciplinary Biology 3

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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.

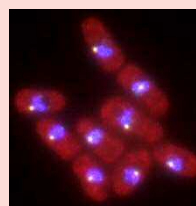


Replicated DNA visualized by incorporation of labeled nucleotides.

Molecular Mechanisms of Chromosome Rearrangements

– Takuro NAKAGAWA –

Human genome consists of 3.2 billion base pairs of DNA. DNA is fragile and keeps suffering various kinds of DNA damage including DNA double-strand breaks (DSBs) and stalled replication forks. Faithful repair of these damage is required to maintain genome integrity. When these damages are not properly repaired, gross chromosomal rearrangements (GCRs) such as translocation, truncation, and isochromosome formation take place. Chromosomal abnormality sometimes causes human genetics diseases including cancer. However, it remains unclear how GCRs occur in cells. To gain insights into the mechanism behind these events, we perform genetic studies using fission yeast and human cell lines.



Fluorescent image of the fission yeast *Schizosaccharomyces pombe*: Localization of the centromere region of chromosomes that consist of DNA repeats.

Laboratory of Organic Biochemistry

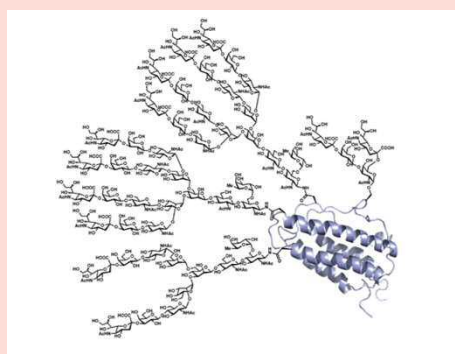
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[Research Interests]

- 1) Chemical synthesis of oligosaccharides
- 2) Chemical synthesis of glycoproteins and glycopeptides
- 3) Elucidation of oligosaccharide functions

The oligosaccharides of protein have been thought to concern with protein conformation, dynamics, protein trafficking and glycoprotein lifetime in blood. We have examined synthesis of homogeneous glycoproteins having human complex type oligosaccharide in order to evaluate oligosaccharide functions. We have synthesized several small glycoproteins (amino acids 40-76 residues), erythropoietin analogue (amino acids 166 residues), and co-stimulate glycoprotein of T-cell (amino acids 120 residues). In order to synthesize these glycoproteins, the polypeptide sequence of target glycoprotein were divided into several segments and these were synthesized by solid phase peptide synthesis. After prepared both glycopeptide-thioester and peptide, these were coupled by repetitive Native Chemical Ligation (NCL). After construction of

the glycosylated polypeptide chain, we examined folding experiments and evaluated effect of oligosaccharide during protein folding process. In addition, glycoproteins folded was analyzed its structure by NMR and CD spectra in order to evaluate conformational differences between glycosylated and nonglycosylated proteins. In our laboratory, we would like to elucidate oligosaccharide functions by use of such chemical approach.



Laboratory of Polymer Assemblies

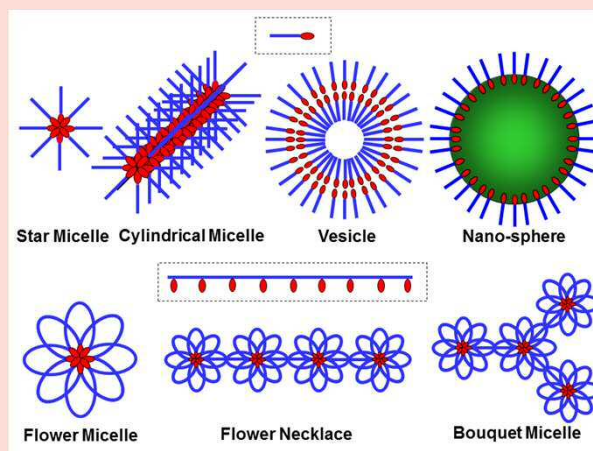
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[Research Interests]

The intramolecular attractive force among polymer molecules is necessary to construct polymer assemblies. Different kinds of attractive forces or interactions act among polymer molecules, the solvophobic interaction, electrostatic interaction, hydrogen bonding, and so on. Furthermore, the atomic groups, or functional groups, producing the attractive forces are arranged on the polymer chain in different ways. The variety of those polymer chemical structures provides a number of morphologies of polymer assemblies, as shown in the right scheme. Our laboratory aims at (a) synthesizing novel polymers forming unique assemblies, (b) characterizing the structure of polymer assemblies, (c) understanding the mechanism of the assembly formation, and (d) establishing the relationship between the structures and properties of polymer assemblies. Our final goal is to understand the structures and properties of assemblies constructed by both synthetic and biological macromolecules in a unified way.

The followings are the research themes which we are studying:

- 1) Polymer micelles formed by amphiphilic polymers.
- 2) Polymer complexes formed by amphiphilic polymers and various substances.
- 3) Polyion complexes formed by oppositely charged polyelectrolytes.
- 4) Conformation and molecular recognition of polysaccharides.



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Laboratory of Macromolecular Structure

Members Katsumi IMADA (Professor), Fumitoshi KANEKO (Associate Professor),
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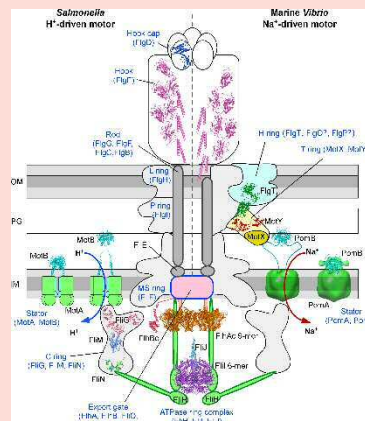
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[Research Area]

Biological process is driven by complex molecular machines composed of biological macromolecules. The flagellum, which is an organelle for bacterial motility, is one of those molecular machines. The flagellum is a huge protein assembly composed of a helical filamentous screw, a molecular universal joint, a highly efficient ion-driven motor and a protein export apparatus for self-construction. The Laboratory of Macromolecular Structure aims to provide fundamental understanding of operating principles and the self-assembly mechanism of biological macromolecular machines, such as the bacterial flagellum, through the studies of molecular structure at atomic resolution and reconstitution of the molecular machines. We also study structures of polymer complexes with low molecular weight compounds and the relationship between their structures and functions.

- 1) Rotation mechanism of bacterial motor systems.
- 2) Self-constitution mechanism of bacterial motility machines.
- 3) Structural and functional studies on bacterial infection apparatus.

- 4) Structural and functional studies on environmental sensing units.
- 5) Study on the structure of polymer complex with small molecule and its formation mechanism.



Schematic drawing of the bacterial hook basal-body architecture

Department
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Laboratory of Supramolecular Functional Chemistry

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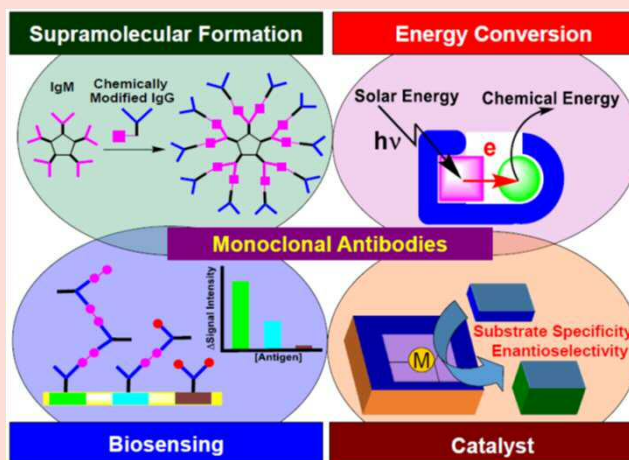
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[Research Interests]

- 1) Development of a high performance sensing element.
- 2) Construction of energy conversion and catalytic systems using hybrids of biomacromolecules with synthetic molecules.
- 3) Creation of functionalized supramolecular materials based on self-assembly of bio-related and/or synthetic polymers.

In biological systems, life processes are led by the unique behavior of macromolecules such as proteins and DNA. Molecular recognition by macromolecules plays an important role, for example, in substrate specificity of enzymes and antigen-antibody reactions in human life. Selective molecular recognition among macromolecules is achieved through a large number of weak interactions. We have focused our attention on the special behavior of antibodies, especially monoclonal antibodies, because they can recognize a larger and more complex compound with high specificity. In this laboratory, we develop novel supramolecular materials and construct functionalized sensing, catalytic, and energy conversion systems via specific molecular recognition of biomacromolecules and selective assembly of bio/synthetic molecules.



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.

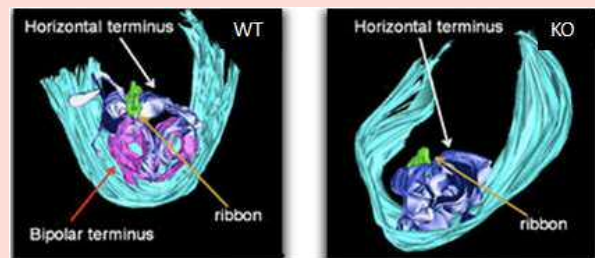


Figure. We previously identified pikachurin, an extracellular matrix-like retinal protein, and observed that it localized to the synaptic cleft in the photoreceptor ribbon synapse. Pikachurin KO mice showed improper apposition of the bipolar cell dendritic tips to the photoreceptor ribbon synapses, resulting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

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

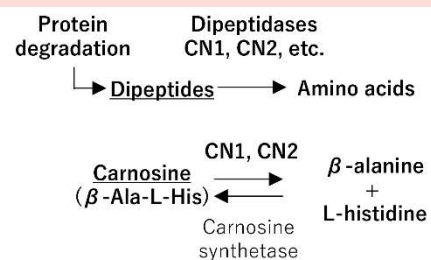


Fig. 1 Dipeptide breakdown and carnosine metabolism

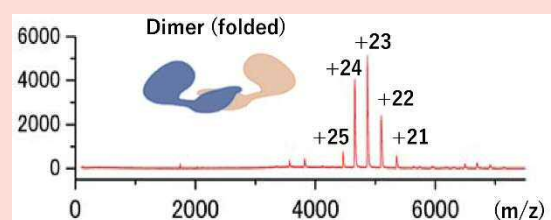


Fig. 2 ESI-MS analysis of CN2 dimer (106 kDa)

Laboratory for Molecular Biophysics

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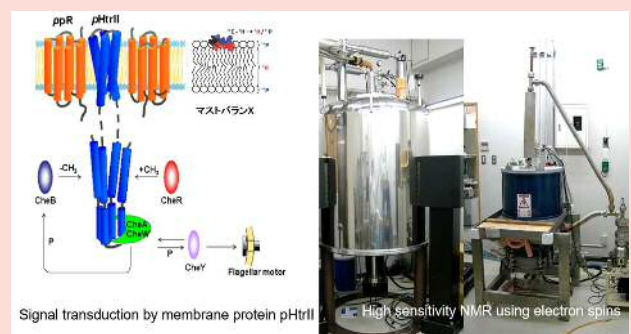
Home Page <http://www.protein.osaka-u.ac.jp/biophys/>

[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.



Laboratory of Organelle Biology

Members Masato NAKAI (Associate Professor)

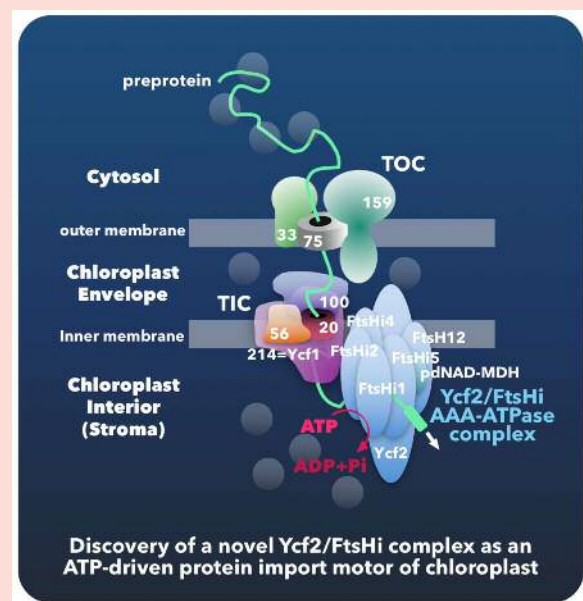
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[Research Interests]

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 translocons 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.



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

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[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).

Department
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Laboratory of Protein Folding (Institute for Protein Research)

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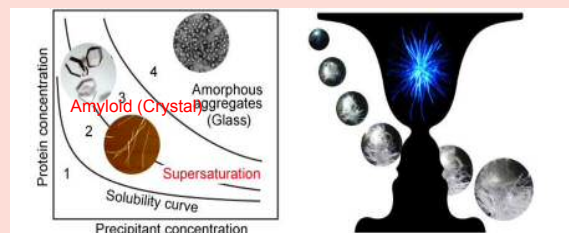
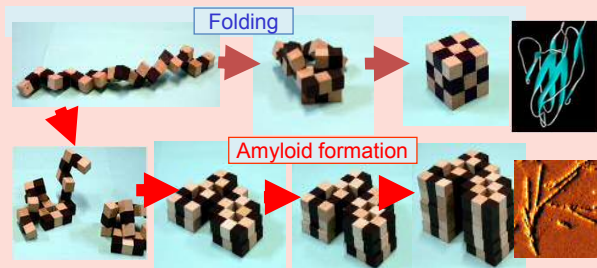
Home Page <http://www.protein.osaka-u.ac.jp/physical/>

[Research Area]

- 1) Folding and stability of proteins.
- 2) Mechanism of formation of amyloid fibrils.
- 3) Comprehensive understanding of protein folding and misfolding

Protein folding is a process in which an extended polypeptide chain acquires a unique folded conformation with biological activity. Clarifying the mechanism of protein folding is essential to improve our understanding of the structure and function of proteins. It is also important because many critical biological processes and disease states involve protein misfolding and aggregation reactions. We study the conformational stability and the mechanisms of protein folding and misfolding with various approaches including spectroscopies (NMR, fluorescence, CD), physicochemical measurements (calorimetry, analytical ultracentrifugation) and fluorescence microscopy.

We found that ultrasonication effectively breaks supersaturation and forces fibrillation. By constructing a HANdai Amyloid Burst Inducer (HANABI), which combines the use of ultrasonicator and microplate reader, we study the ultrasonication-forced fibrillation of various amyloidogenic proteins.



Laboratory of Supramolecular Crystallography (Institute for Protein Research)

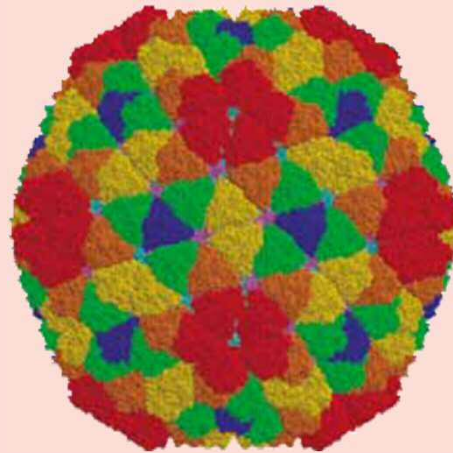
Members Atsushi NAKAGAWA (Professor), Mamoru SUZUKI (Associate Professor), Eiki YAMASHITA (Associate Professor), Hirotaka NARITA (Specially Appointed Assistant Professor)

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

[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 and X-ray free electron laser.
- 3) Development of data processing algorithm of diffraction data from micro-crystals.

Macromolecule assemblies, consisting of proteins, nucleic acids, and other substances, play key roles in all living system. Our laboratory works on structure determination of biological macromolecular assemblies using X-ray diffraction technique. Development of tools for X-ray crystallography of biological macromolecular assemblies, including the synchrotron radiation beamline at SPring-8, is also one of our mainworks.



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

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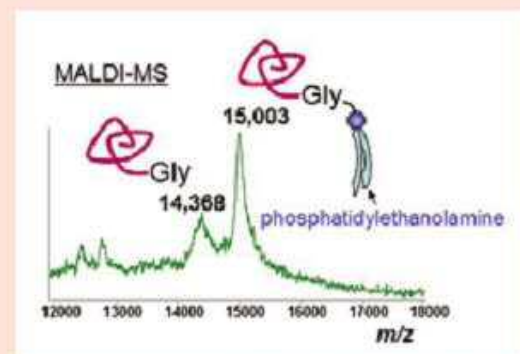
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[Research Programs]

- 1) Development of chemical/analytical methods and softwares for analyses of protein primary structures.
- 2) Hardware development for high-sensitivity MS.
- 3) MS analysis of post-translational modifications.
- 4) Development of a chemical derivatization method for high sensitive detection of sugar chains of glycoproteins.
- 5) Development of chemical and separation methods for proteomic analysis.
- 6) Study on fragmentation of peptides and carbohydrates in MS.

Mass spectrometry (MS) is a well accepted technique for the analyses of chemical structures of biological compounds. We have been working to develop methods for determining primary structures and post-translational modifications of proteins by 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 proteomics research. We

also apply the above developed methods to the structural analysis of micro quantities of peptides, proteins, and their related substances.



PE : phosphatidylethanolamine

Laboratory of Genome and Chromosome Functions

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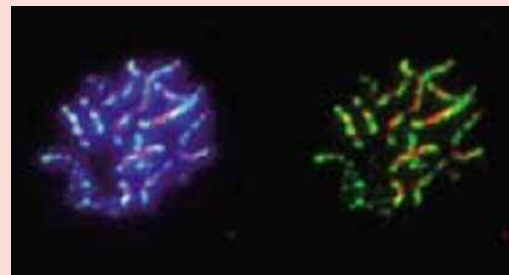
[Research Area]

[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

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 morphogenesis. Malfunction 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 and biochemical 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)

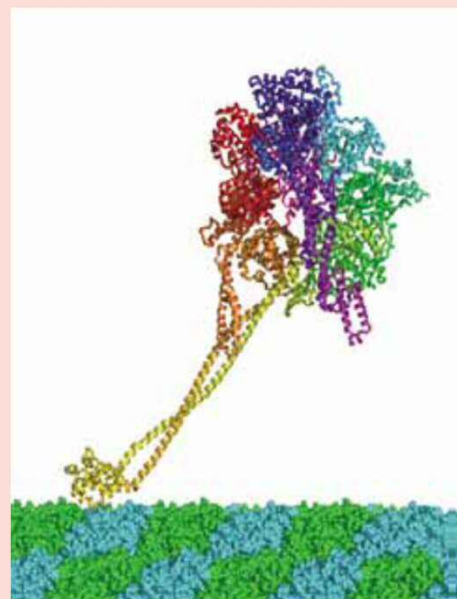
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Home Page <http://www.protein.osaka-u.ac.jp/crystallography/EngHP/>

[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

Laboratory of Protein Organic Chemistry

(Institute for Protein Research)

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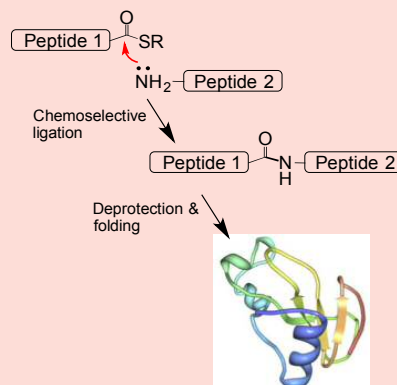
Home Page <http://www.protein.osaka-u.ac.jp/organic/index.html>

[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.

Laboratory of Nuclear Network

(Institute for Protein Research)

Members Junko KANO (Associate Professor)

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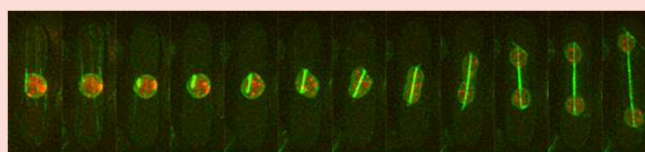
Home Page <http://www.protein.osaka-u.ac.jp/icr/network>

[Research interest]

Elucidation of the functions of chromosome ends, telomeres and subtelomeres

Chromosomes contain genetic information and regulate the bases of biological activities. Deletion or duplication of chromosomal regions results in cell death, tumorigenesis, or serious diseases. Therefore, it is important not only for the elucidation of principals of life but also for the clarification of the mechanisms of human diseases to study chromosomal functions. Telomere, which exists at the end of a linear chromosome, plays important roles in chromosome integrity. Recent studies have revealed that telomere regulates cell senescence and life span, and that it is important for meiosis and preservation of species. We are studying the molecular mechanism of the functions of telomere-binding protein complexes using genetics, molecular biology, biochemistry and cell biology.

Subtelomere is a telomere-adjacent chromosomal domain. The knowledge about telomere has recently accumulated, but functions of subtelomere are largely unknown. However, it is thought that subtelomeres are important for human health because minute deletion or duplication of subtelomere DNA causes human severe diseases. Furthermore, the structure of human subtelomere is remarkably different from those of great apes, such as chimpanzee, bonobo and gorilla, suggesting the possibility that subtelomeres play some roles in evolution and diversity. We are analyzing structures and functions of the subtelomeres in fission yeast, humans and great apes.



Department
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Laboratory of membrane Protein Chemistry

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Intracellular membrane fusion is a fundamental and conserved biological reaction which is vital for vesicle trafficking between cellular compartments, organelle morphology, hormone secretion, and neurotransmission. Fusion is regulated by specific proteins and lipids: SNAREs, SNARE chaperones, Rab GTPases, and phosphoinositides. However, it is unclear how they act together to drive membrane fusion. We have been studying this vital membrane fusion machinery in eukaryotic cells and recently developed reconstituting proteoliposomal fusion with purified components. Our current projects attempt to dissect the ternary synergy of two SNARE chaperone systems and phosphoinositides which is essential for physiological fusion through catalyzing the SNARE complex assembly and remodeling the assembled SNARE complexes. In our future directions, we will further explore the molecular machinery of not only membrane fusion but membrane fission/budding and deformation, by this powerful system of reconstituting proteoliposomes with defined components.

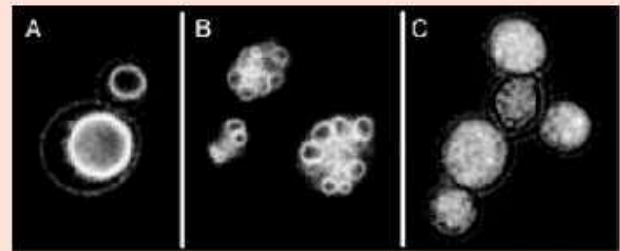


Figure: Yeast vacuoles as a model for intracellular membrane fusion. Yeast vacuoles (lysosomes in mammals) change their organelle morphology through membrane fusion (from C to A) and fission (from A to C) processes to respond the extracellular environments and/or cell cycles.

Department
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Laboratory of Cell Systems

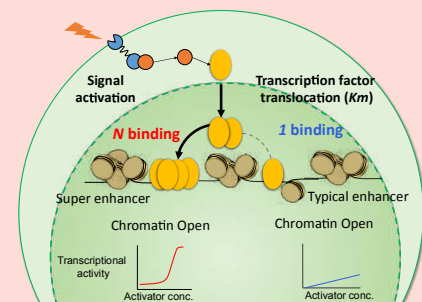
(Institute for Protein Research)

Members Mariko OKADA (Professor), Shigeyuki MAGI (Assistant Professor), Suxiang ZHANG (Assistant Professor), Keita Iida (Assistant Professor)**TEL·FAX** TEL: 06-6879-8617 · FAX:06-6879-8619**e-mail** mokada@protein.osaka-u.ac.jp**Home Page** http://www.protein.osaka-u.ac.jp/cell_systems/pg18.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.



Laboratory of Nanobiology

(Institute for Protein Research)

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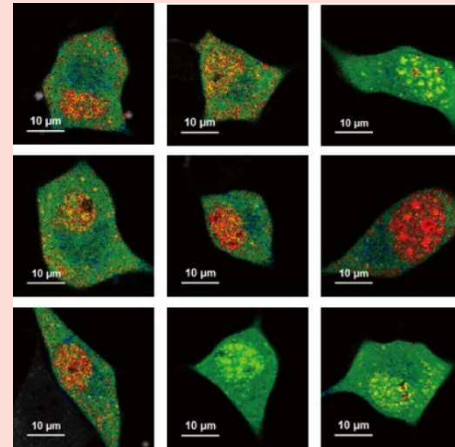
Home Page URL: <http://www.protein.osaka-u.ac.jp/nanobiology/en/index.html>

[Research Interests]

Inside the cells, many kinds of bio-molecules are involved in the biological process. Although the basic design, the genome, is almost identical, the tiny gene expression differences in the level, the timing and the spatial area make us different from other 7.4 billions of peoples. To understand the molecular mechanism underlying these differentiations, we have developed new technologies, especially in the field of biological imaging. Currently, we focused on the single molecule imaging of gene expression at molecular and super-complex layer, and revealed some secrets of the gene expression control. For higher biological layer, the cell layer, we recently developed a super-resolution imaging technique for intracellular temperature, which allowed us to detect unexpected temperature difference in the nucleus and the cytoplasm, leading us to open the door of thermal biology.

We are imaging biological process at three different biological layers: the molecule, the super-complex and the cell.

- 1) Analysis of interaction between biomolecules using zero-mode waveguides (ZMWs)
- 2) Reconstitution of transcription super-complex using DNA origami
- 3) Imaging of intracellular temperature



Intracellular local temperature measurement image using fluorescence lifetime imaging microscope. The difference in color represents the difference in temperature. There was a large temperature difference inside the cell.

Laboratory for Advanced Brain Functions

(Institute for Protein Research)

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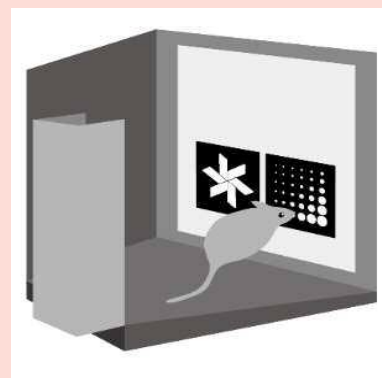
Home Page <http://www.protein.osaka-u.ac.jp/en/laboratories/adbancedbrainfunctions>

[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



Laboratory of Oncogene Research

(Research Institute for Microbial Diseases)

Members Masato OKADA (Professor), Shigeyuki NADA (Associate Professor),
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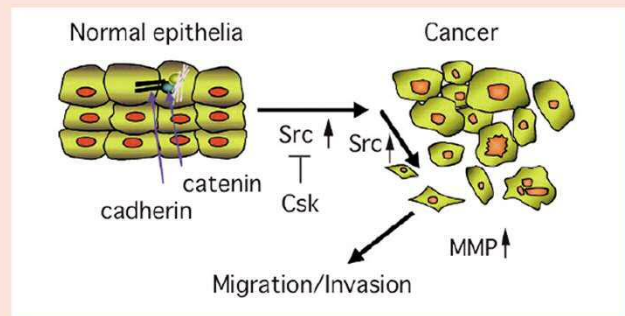
Home Page <http://www.biken.osaka-u.ac.jp/biken/oncogene/index.htm>

[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 cells often have elevated SFK activity, suggesting the potential 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.

Laboratory of Cellular Regulation

(Research Institute for Microbial Diseases)

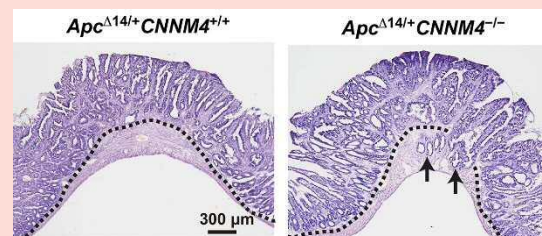
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[Research Interests]

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).

Cancer Biology

(Research Institute for Microbial Diseases)

Members Eiji HARA (Professor), Sugiko WATANABE (Associate Professor),
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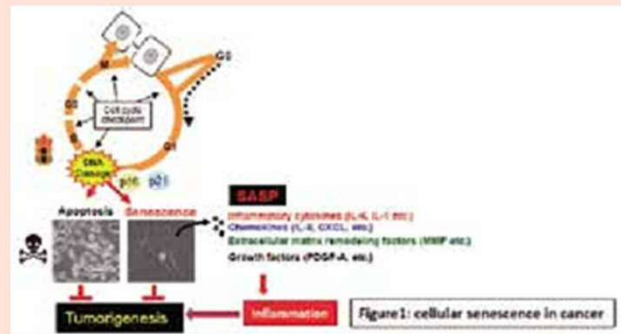
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[Research interests or Research Area]

Understanding the molecular mechanisms linking aging and cancer

Cellular senescence is the state of irreversible cell cycle arrest that can be induced by a variety of potentially oncogenic stimuli and has therefore long been considered to suppress tumorigenesis, acting as a guardian of homeostasis. Emerging evidence, however, reveals that senescent cells also promote secretion of various inflammatory and pro-proliferative factors. This newly identified senescence-associated phenotype termed SASP is likely to be associated with homeostatic disorders including cancer. It is therefore quite possible that accumulation of senescent cells during aging or obesity *in vivo* may contribute to aging- and/or obesity-associated cancers. By conducting the following studies, we aim to clarify the molecular mechanisms underlying aging- and/or obesity-associated cancer.



Laboratory of Biomolecular Science and Reaction

(The institute of Scientific and Industrial Research)

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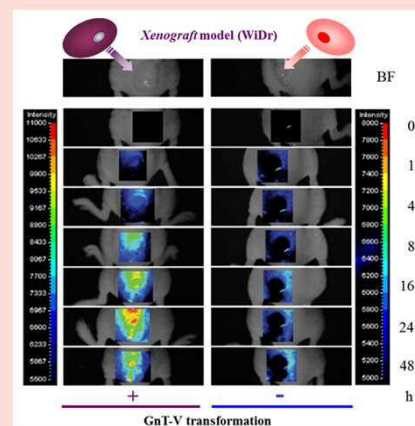
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[Research Interests]

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)

Laboratory of Biohistory

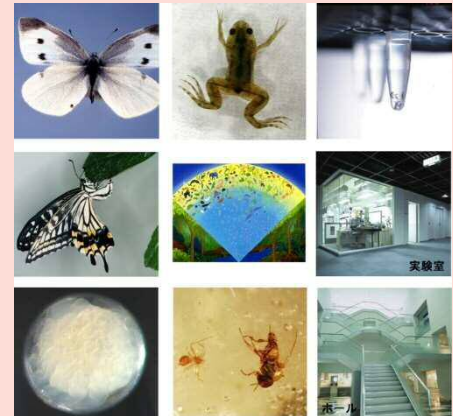
(JT Biohistory Research Hall [BRH])

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[Research Themes]

- 1) Insect's feeding preference and speciation: Molecular mechanism of the host plant selection of swallowtail butterflies.
- 2) Vertebrate body patterning: How does the well-patterned morphology is generated in terms of ontogeny and phylogeny?
- 3) Interaction and evolution between insects and plants: Evolutionary and ecological study of the fig and fig wasp mutualism.
- 4) Evolution of developmental programs and cell structure/function: Experimental study using the *Drosophila* and spider models.
- 5) Science communication and production: Presenting and sharing biological research among many people.

BRH performs the studies on evolution and development of organisms, and the study of how to spread science throughout society. The above-mentioned themes are carried out in five research groups. The staffs and other BRH members including Dr. Keiko Nakamura (Director General), Dr. Shin-ichi Nishikawa (Advisor) and researchers work together in supervising graduate students.



Laboratory of Cellular Structure and Function

Members	Yasushi HIRAOKA (Professor), Tokuko HARAGUCHI (Professor), Yuji CHIKASHIGE (Associate Professor)
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[Research Subjects]

(1) Chromosome/nuclear structure in fission yeast

We are examining molecular and structural bases for nuclear functions with a special interest in chromosome dynamics during the progression of meiosis.

(2) Nuclear structures in mammalian cells

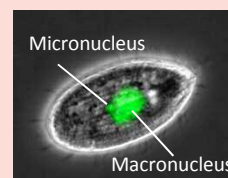
We are examining molecular and structural bases for nuclear functions with a special interest in nuclear envelope dynamics during the progression of mitosis.

(3) Nuclear structures in Tetrahymena

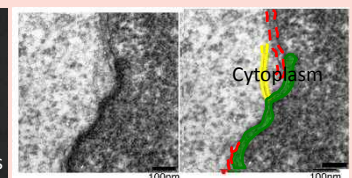
The ciliated protozoa have two functionally and structurally distinct nuclei in a single cell. We are examining molecular and structural bases of such “nuclear dimorphism”

(4) Development of imaging technology

We have developed a method of CLEM (correlative light-electron microscopy) combined with live cell imaging, called “Live CLEM”, to observe the molecular dynamics in living cells at high-resolution.



Tetrahymena



Reforming nuclear envelope (NE) in mitosis
(Red:NE, Green: BAF, Yellow: a single microtubule)

Laboratory of Biomolecular Informatics

(RIKEN Center for Biosystems Dynamics Research)

Members Tomoya KITAJIMA (Guest Associate Professor), Hidehiko INOMATA (Guest Associate Professor)

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[Research Interests]

1) The Mechanism of Chromosome Segregation in Oocytes (Kitajima).

We study chromosome segregation during meiosis in oocytes and during mitosis in early embryos. We will reveal distinct mechanisms for chromosome segregation during these cell divisions, taking advantage of techniques for live imaging, micromanipulation and genetic engineering methods. This study will provide insights into chromosome segregation errors in oocytes and embryos, a leading cause of pregnancy loss and congenital disease. The findings will be exploited to collaborative studies with reproductive medicine (Fig.1).

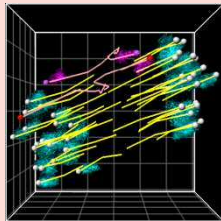


Fig 1: Chromosome segregation error in the aged oocyte.

2) The understanding and regulation of morphogen-mediated patterning (Inomata).

Developmental processes take place through the exchange of information by cells within the constrained spatial environment of the embryo. In our research we will seek to gain a understanding into process of pattern formation via morphogen gradient. Further, we are also working to develop methods for regulating the morphogen distribution in vivo. By using such methods, we plan to gain a deeper understanding of developmental systems (Fig.2).

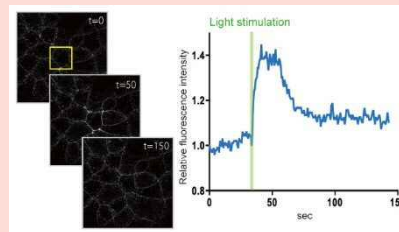


Fig 2: Spatiotemporal regulation of morphogen distribution