Graduate School of Life Sciences, Ritsumeikan University

Principal Investigators

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Inorganic Catalysis Chemistry Laboratory

[INADA Laboratory]

Professor
INADA Yasuhiro

Research Overview

Our research aims to elucidate the mechanisms by which inorganic materials function as catalysts or battery components by observing them “in situ”: that is, in real time under actual operating conditions where their functions emerge. Through this approach, we hope to build a foundation for the strategic creation of high-performance inorganic functional materials. At facilities such as the university’s SR Center, we are advancing X-ray Absorption Fine Structure (XAFS) spectroscopy, a powerful technique for analyzing the electronic states and local structures of metal species under reaction conditions. Using experimental setups developed in-house, we track chemical state changes that occur during functional activation processes in a range of inorganic functional materials, including supported metal catalysts used for exhaust-gas purification and materials conversion, as well as electrode active materials involved in the operation of rechargeable batteries.

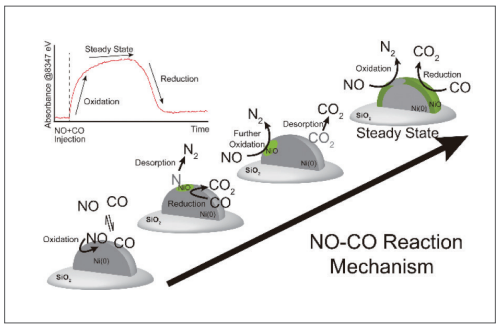
Research Themes

(1) Advanced development of XAFS spectroscopy

We have substantially improved the time and spatial resolution of XAFS spectroscopy and, ahead of the rest of the world, developed a dispersive XAFS (DXAFS) system capable of tracking reactions on millisecond time scales. We have also created a two-dimensional imaging XAFS system that can measure XAFS spectra across a relatively wide two-dimensional area simultaneously. Building on the technologies cultivated through these developments, we have gone on to design and install several novel experimental instruments at the SR Center. These include a VDXAFS system that combines one-dimensional spatial resolution with millisecond-scale time resolution, as well as a dual-element DXAFS system that enables two different elements to be measured at exactly the same moment.

(2) Elucidation of reaction mechanisms in supported metal catalysts

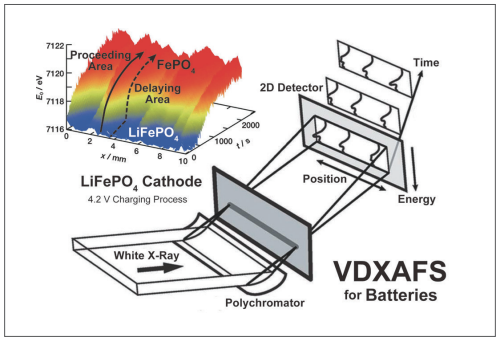
Using in situ XAFS spectroscopy, we analyze the chemical states of supported metal catalysts with metal species dispersed on solid oxides under reaction conditions. By systematically evaluating differences in reactivity of metal species associated with their metal elements, support materials, and metal particle sizes, we have clarified how the spatial distribution of oxide chemical species are within metal particles change during reactions. Furthermore, by dynamically tracking state changes during catalytic reactions with our independently developed time-resolved DXAFS method, we have succeeded in elucidating catalytic reaction mechanisms at the atomic level.



Reaction mechanism of the NO–CO reaction elucidated using time-resolved DXAFS spectroscopy

(3) Elucidation of spatial distribution of reactions in cathode active materials for rechargeable batteries

For active materials within composite electrodes during the charge and discharge processes of rechargeable batteries, we visualize chemical states using in situ two-dimensional imaging XAFS under electrochemically controlled conditions. These observations have revealed that reactions within electrodes are spatially inhomogeneous. In addition, by applying the VDXAFS method, we have observed dynamic changes in reaction distributions during rapid charge–discharge processes. We successfully reproduced these behaviors using model functions that include terms describing spatial propagation. This line of research has also been extended to the development of novel active materials, building on the material-synthesis technologies accumulated in our prior research.



Time and spatially resolved analysis of electrode reactions in rechargeable batteries

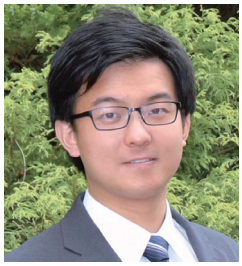
(4) Creation of catalytic and functional materials through the precise synthesis of metal clusters and nanoparticles

Metal clusters synthesized with precise control over the number of atoms are expected to exhibit unique properties and catalytic functions not found in conventional nanoparticles. By employing synthesis methods such as dendrimer-templated approaches and ligand-protected metal clusters, we aim to precisely synthesize metal clusters and metal nanoparticles and thereby create new classes of catalytic and functional materials.

Inorganic Electrochemistry Laboratory

[ORIKASA Laboratory]

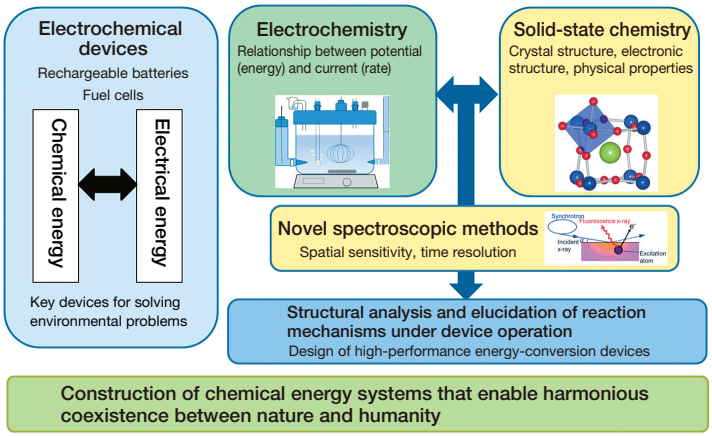
Professor
ORIKASA Yuki



Lecturer
ZHONG Chengchao

Research Overview

Electrochemical devices are systems that convert electrical energy and chemical energy into one another. Batteries used in smartphones and laptop computers are familiar examples from everyday life. In recent years, as energy and environmental problems have become increasingly serious, there has been growing momentum to scale up batteries for use as power sources for automobiles and to apply them as systems capable of storing electricity generated from renewable sources. Our research group is based in the academic fields involved in battery science: electrochemistry, solid-state chemistry, and synchrotron radiation science for reaction analysis. Drawing on these disciplines, we aim to analyze reactions occurring within devices and to design materials for high-performance energy-conversion devices.



Research Themes

(1) Elucidation of mechanisms at electrochemical reaction interfaces

In electrochemical devices, the primary reaction field is the interface between the electrode and the electrolyte. This region is estimated to be in the order of nanometers (10^{-9} meters), making the direct observation of phenomena extremely challenging. By combining electrochemical measurements that capture the relationship between energy and reaction rate with operando measurements that directly observe structures near the interface, we aim to elucidate previously unknown interfacial phenomena.

(2) Ion diffusion within solid electrode materials

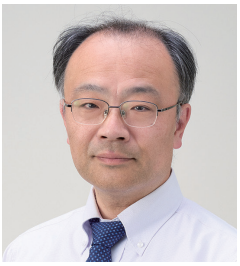
Electrodes in lithium-ion batteries are made of mixed conductors in which both electrons and ions move through the material. Understanding how easily ions diffuse within these materials is essential for battery design, yet accurately measuring this property is not straightforward. In this research, we work to visualize ion diffusion behavior using synchrotron X-rays and to develop methods for measuring ion diffusion coefficients.

(3) Establishing design guidelines for next-generation rechargeable-battery electrode materials

Rechargeable batteries for automotive applications are required to store more than twice the energy of current systems while operating safely and reliably over long periods. To achieve a breakthrough in battery design, we synthesize candidate materials for new battery systems and evaluate their performance. We also analyze the mechanisms that enable faster reaction processes, taking a solid-state chemistry perspective.

Functional Coordination Chemistry Laboratory

[KUWATA Laboratory]



Professor
KUWATA Shigeki

Research Overview

Within living organisms, a wide variety of chemical reactions proceed efficiently under mild conditions through the action of metalloenzymes, which are characterized by the cooperation between biomolecules – most notably proteins – and metal ions. To uncover the mechanisms underlying these processes, our research group designs and synthesizes original metal complexes based on coordination chemistry and organometallic chemistry, using them as structural and functional model compounds of metalloenzymes, and investigating their properties and reactivity in detail. Furthermore, we aim to develop methods for exploiting these metal complexes to convert abundant atmospheric resources such as nitrogen gas and carbon dioxide into useful chemicals, as well as to realize highly efficient and highly selective organic synthesis reactions.

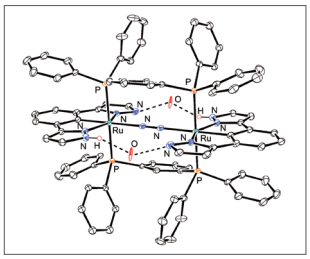
Research Themes

(1) Control of proton and electron transfer using multiproton-responsive ligands

Many redox reactions that occur in biological systems are accompanied by the movement of protons. To enable smooth proton transfer, we have designed and synthesized a variety of ligands incorporating multiple proton-responsive sites. Using these ligands, we study proton transfer that is coupled with electron transfer from the metal center to substrates coordinated to the metal. We are also working toward applications in the reductive conversion of dinitrogen and carbon dioxide molecules.

(2) Development of supramolecular metal complexes responsive to external stimuli

Using a supramolecular chemistry approach in which ligands and metal modules containing proton-responsive sites and redox-active sites are linked and structurally organized by multidentate ligands, we have synthesized metal complexes with a high degree of functional integration. These complexes not only encapsulate small inorganic molecules such as dinitrogen within internal cavities, but also exhibit structural flexibility in response to counter anions and coexisting ligands. We are currently exploring their application as catalysis.



Metal complex encapsulating a nitrogen molecule within a cavity surrounded by metals and proton-responsive sites

(3) Development of organometallic catalysts based on metal–ligand cooperation

Homogeneous catalytic reactions using organometallic complexes have become indispensable methodologies in modern organic synthesis. Focusing on new reaction mechanisms that rely on cooperative interactions between metals and ligands, such as multipoint activation and simultaneous activation of substrates, we are investigating hydrogenation reactions of carbonyl compounds and transformation reactions of unsaturated alcohols.

Bioinorganic Reaction Chemistry Laboratory

[KOSHIYAMA Laboratory]

Professor
KOSHIYAMA Tomomi

Research Overview

The integration of biomolecules such as proteins, DNA, and vesicles with non natural functional molecules has attracted increasing attention as a promising strategy for creating novel hybrid materials that combine the advantages of both components. However, the range of biomolecules that can be practically utilized remains limited because of issues related to stability and structural constraints. Moreover, the lack of detailed structural information about introduced molecules on biomolecular scaffolds has made it difficult to construct functional artificial systems in which multiple chemical processes such as energy transfer, electron transfer, and moleculartransport are closely integrated. Against this background, our research group focuses on the unique reaction environments provided by biomolecules, including proteins, protein assemblies, and lipid membranes. By hybridizing these biomolecules with metal complexes, we aim to control a wide variety of chemical processes, including catalytic reactions and molecular adsorption. In particular, by establishing molecular design strategies that enable precise control over the positioning, orientation, and aggregation state of metal complexes within biomolecular environments, we aim to achieve more sophisticated control of chemical reactions.

Research Themes

Artificial phospholipid bilayers (liposomes) and natural red blood cell membranes are used as lipid-membrane platforms for controlling metal-complex-based reactions. We are studying strategies for controlling the reactivity of metal complexes in lipid membranes by localizing them on the membrane surface, within the hydrophobic membrane interior, or in the hydrophilic internal aqueous phase.

(1) Control of the Reactivity of Metal Complexes Using Membrane Properties

By changing the phospholipid composition, we tune the local environment around metal complexes to control catalytic reactions such as oxygen evolution from water and carbon dioxide reduction. In addition, membrane phase separation is utilized to control the accumulation state of metal complexes within the membrane, leading to improved reaction efficiency.

(2) Control of MOF Formation Reactions Using Ion Channels

By regulating the influx rate of metal ions through ion channels, we control the size and morphology of metal–organic framework (MOF) crystals formed inside liposomes. The resulting MOF–liposome composites exhibit ion-adsorption and sensing properties.

(3) Functionalization of Red Blood Cell Membranes with Metal Complexes

To utilize natural lipid membranes as novel reaction platforms for metal complexes, we are developing methods for the functionalization of red blood cell membranes with metal complexes.

Photofunctional Physical Chemistry Laboratory

[KOBAYASHI Laboratory]

Professor
KOBAYASHI Yoichi

Research Overview

Developing materials that can efficiently harness the vast amount of solar energy reaching the Earth is a crucial challenge for moving beyond a society that simply consumes energy derived from fossil fuels, and toward a sustainable and prosperous future. Our research addresses this challenge by working with a wide range of materials, both organic and inorganic, and studying how their “functions,” such as color, light emission, and chemical reactivity, can be controlled using light and nanotechnology. Examples include organic molecular materials known as photochromic compounds, whose color reversibly changes upon light irradiation, as well as nanomaterials that emit different colors across the spectrum despite being composed of the same substance, simply by changing their size to the nanoscale. Such photo-functional materials are not only important in basic scientific research, but also closely connected to a variety of industries, including inks, printing, lenses, cosmetics and displays. We aim to contribute to wider society through the development of new photo-functional materials and analysis techniques.

Research Themes

(1) Development of novel photochromic molecules

Fast thermally reversible photochromic molecules, which change from colorless to colored upon light irradiation and rapidly return to the colorless state once the light is removed, are useful not only because of their color changes but also because of their rapid response as novel light-activated molecular switches. We are continuously developing new photochromic molecules with enhanced and novel functionalities.

(2) Creation of novel nanomaterials

The term “nano” refers to a scale of 10^{-9} meters, which is slightly larger than individual molecules. Materials at the nanoscale exhibit properties that are entirely different from those of isolated molecules or the solid materials we commonly encounter. We are developing novel nanomaterials that display unprecedented and complex light responses by combining organic molecules with inorganic materials.

(3) Development of novel materials with nonlinear optical responses

In typical photochemical reactions, the extent of the reaction increases in proportion to the intensity of light. However, when special light sources or materials are used, nonlinear optical responses can be observed, in which the extent of the reaction increases dramatically with light intensity. Such nonlinear optical responses generally require high-intensity pulsed lasers, but our research focuses on developing functional materials that exhibit nonlinear responses even under weak, continuous light irradiation.

Organic & Biomolecular Chemistry Laboratory

[SOHTOME Laboratory]

Professor
SOHTOME Yoshihiro

Research Overview

Nucleic acids (DNA and RNA) found in living organisms – which have undergone billions of years of evolution – are composed of D-sugars, while proteins are primarily built from L-amino acids. We view the life processes promoted by these biological macromolecules, which act as chiral catalysts in nature, as a rich source of inspiration. Drawing inspiration from enzymes—nature's most efficient catalysts—we are designing new catalytic processes to make possible the creation of novel molecular architectures that have thus far eluded synthesis through current methods. Our quest extends beyond conventional boundaries as we also delve into the realm of Chemical Biology, in which we harness these unique molecules to modulate and control biological processes.
Central to our mission is the relentless pursuit of a deeper and more complete understanding of the complex mechanisms behind each reaction by using state-of-the-art analytical methods including spectral analysis, computational chemistry, and comparative quantitative analysis.

Research Themes

(1) Dynamic asymmetric catalysis

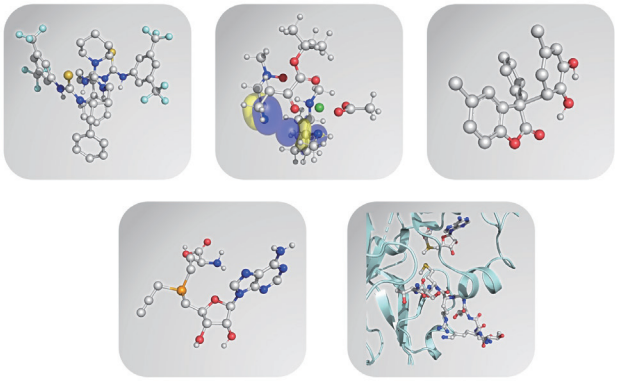
Catalytic asymmetric reactions are among the most ideal strategies for supplying novel chiral compounds that are essential in drug discovery. However, the transition states are extremely short-lived and cannot be directly detected. By combining experimental and theoretical chemistry, we pursue both the development of new reactions and the analysis of mechanisms. Furthermore, by introducing our own original concepts into newly elucidated transition states, we aim to expand this knowledge into the creation of novel catalysts and reactions. In particular, we focus on developing dynamic asymmetric reactions that, like enzymes, respond flexibly to reaction conditions and exhibit different functions.

(2) Oxidative molecular transformations using oxygen

In nature, enzymes enable a wide range of oxidation reactions using molecular oxygen (O_2). Natural products containing polar functional groups formed through oxidative enzymes also represent a valuable natural source of bioactive molecules that interact selectively with biological macromolecules. However, developing oxidation reactions that use O_2 under mild conditions remains a significant challenge. Our research aims to develop new oxidative molecular transformations that use oxygen as the oxidant, while also elucidating complex reaction mechanisms that cannot ordinarily be captured. In addition, we seek to identify and create highly bioactive molecules from among the novel compounds generated through our unique oxidative molecular transformations.

(3) Protein methylation

Synthetic chemistry and chemical biology are core research disciplines within chemistry and biology respectively, and chemical reactions play a central role in both. However, a substantial gap still exists between chemistry, which often focuses on purified reactions in flasks, and biology, which deals with life processes occurring in complex mixtures.
Using protein methylation as a model system and led by experts in organic synthetic chemistry, we aim to create and detect “the molecules we want,” “in the place where they naturally function,” and “in the minimum required amounts.” Specifically, by using our own designed molecules to hijack enzymatic reactions, we work to uncover previously hidden methylation reactions occurring within living systems. In parallel, we challenge ourselves to control biological processes through the development of original inhibitors.



Analytical Biochemistry Laboratory

[TAKAGI Laboratory]

Professor
TAKAGI Kazuyoshi

Research Overview

We have conducted fundamental studies, from a bioanalytical chemistry perspective, on several reactions in which redox enzymes produced by bacteria act as catalysts. In addition, from an applied bioelectrochemistry viewpoint, we investigate applications in bio-based batteries, biosensors, and bioreactors by coupling these enzymatic reactions with electrode processes.

Research Themes

(1) Re-examination and application of methanol and methylamine oxidation pathways in methylotrophic bacteria (Methylobacterium species, Paracoccus species, etc.)

Methylotrophic bacteria have long been known to grow using C1 compounds such as methanol and methylamine as their sole carbon and energy sources. In this research, we focus on enzymes produced by these bacteria, including methanol dehydrogenase (a PQQ-dependent enzyme), methylamine dehydrogenase (a TTQ-dependent enzyme), as well as aldehyde oxidoreductase (AOR) and formate dehydrogenase (FDH). These enzymes are purified and subjected to fundamental investigation from a bioanalytical chemistry perspective. Furthermore, we are building bioelectrocatalytic reaction systems that combine these enzymatic reactions with electrode reactions. We also explore applications such as bio-based batteries that use methanol, methylamine, or formic acid as biofuels, as well as biosensors designed for the detection of aldehydes.

(2) Re-examination and application of oxidation (oxidative fermentation) pathways of sugars and alcohols in acetic acid bacteria (Gluconobacter species, Acetobacter species, etc.)

Acetic acid bacteria inhabit environments rich in sugars and alcohols, such as floral nectar, fruits, and spoiled fruit wines. Their powerful substrate-oxidizing capabilities have long attracted attention in the field of agricultural chemistry and have been the subject of extensive research. In this work, we focus on enzymes produced by acetic acid bacteria, particularly alcohol dehydrogenase (ADH), and examine reactions involving reduced substrates that have not been previously investigated in detail. We are also studying purification methods for aldehyde dehydrogenase (AldDH), which has been considered difficult to purify. By coupling these enzymatic reaction systems with electrode reactions, we further explore the potential application to bio-based batteries that use glycerin, which is produced in large quantities as a by-product during biodiesel fuel purification, as a biofuel.

Polymer Materials Chemistry Laboratory

[TSUTSUMI Laboratory]

Professor
TSUTSUMI Osamu

Research Overview

The Laboratory of Polymer Materials Chemistry develops advanced optical, electronic, and photonic functional materials based on polymers, liquid crystals, and molecular assemblies.

Organic molecules offer a high degree of structural design freedom, enabling the creation of compounds with diverse functions. However, molecular design alone is often insufficient to achieve the sophisticated performance observed in biological materials. In biological systems, molecular structures, spatial organization, and orientational order are integrated across multiple spatial and temporal scales to maximize function. Inspired by this principle, our research focuses on controlling not only the molecular structures of constituent molecules but also their higher-order structures, including molecular arrangement, orientation, aggregation, and hierarchical organization. Through this approach, we aim to establish design principles for soft functional materials that exhibit advanced optical, luminescent, mechanical, and stimuli-responsive properties.

Our research is guided by the following questions:

- How can molecules be organized with precision?
- How can small molecules, polymers, and nanostructures be assembled into functional ordered systems?
- What optical, electronic, and mechanical functions emerge from controlled molecular organization?

Research Themes

(1) Luminescent liquid-crystalline materials

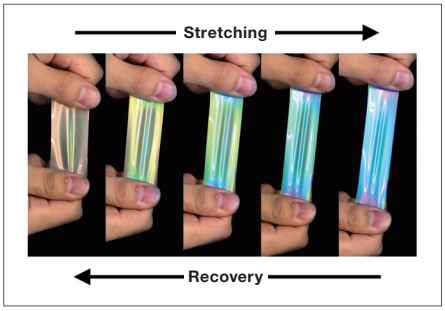
We develop luminescent materials whose emission properties are controlled by molecular aggregation and liquid-crystalline order. In particular, we investigate gold(I) complexes and related emissive molecular systems in which intermolecular interactions, including metal–metal and π–π interactions, strongly influence photophysical behavior.

By integrating luminescence with liquid-crystalline molecular organization, we aim to develop materials that exhibit anisotropic emission, room-temperature phosphorescence, circularly polarized luminescence, and near-infrared emission. These materials are relevant to next-generation optical devices, chemical sensors, information-security technologies, and soft photonic systems.

(2) Stimuli-responsive soft materials for sensing and photonics

We develop soft materials whose optical properties respond to external stimuli such as mechanical deformation, heat, and light. Representative examples include chiral-nematic liquid-crystalline polymers and elastomers that exhibit structural color changes in response to stretching, compression, or temperature variation.

These materials enable the visualization of strain, stress, temperature, and motion without complex electrical wiring. They are therefore promising platforms for strain sensors, tactile sensors, robotic skins, wearable devices, sports science, ergonomics, and Internet of Things technologies.



Mechanochromic response of a chiral-nematic liquid-crystalline elastomer film under tensile deformation, showing reversible structural color change during stretching and recovery.

(3) Functional soft materials through precise control of molecular orientation

We develop methods for controlling molecular orientation and higher-order structure during polymerization and self-organization processes. In particular, we have established photogradient polymerization as a strategy for inducing uniaxial in-plane alignment of the helical axis in chiral-nematic liquid-crystalline polymer films.

Precise control of molecular orientation is expected to generate new optical and photonic functions, including polarization control, structural color modulation, mechano-optical responses, and potentially optical vortex generation. By integrating molecular design, polymer synthesis, liquid-crystalline order, and photonic function, we aim to establish new design principles for multifunctional soft materials.

URL: http://www.ritsumei.ac.jp/lifescience/achem/tsutsumi/

Laser Photochemistry Laboratory

[NAGASAWA Laboratory]

Professor
NAGASAWA Yutaka

Research Overview

A chemical reaction involves changes in molecular structure, and molecular motion is closely linked to chemical reactivity. For example, the dissociation of a diatomic molecule is related to the stretching vibration of the bond between the two atoms. When this vibration periodically reaches its maximum bond length, dissociation can occur with a probability determined by quantum-mechanical tunneling. As a result, femtosecond time-resolved spectroscopic measurements reveal a stepwise increase in reaction products synchronized with each vibrational cycle. Torsional motion of molecular bonds is also thought to contribute to trans-cis isomerization reactions. In addition, polar solvents act as dielectric media that interact with solute molecules; rotational and translational diffusion of solvent molecules can alter the charge distribution of solutes and thereby influence chemical reactions.

In my laboratory, we observe chemical reactions using ultrafast time-resolved spectroscopy to uncover the fundamental principles of molecular motion that are the driving force of chemical reactivity. Our goal is to establish a foundation for the development of new reaction fields. In particular, we conduct fundamental research aimed at elucidating the processes of photosynthesis in plants and at developing new methods of light-energy conversion.

Research Themes

(1) Using ultrashort-pulse lasers, we observe chemical reactions on the femtosecond (10^{-15} second) timescale and elucidate the relationship between chemical reactions and molecular motions such as vibration, rotation, and diffusion.

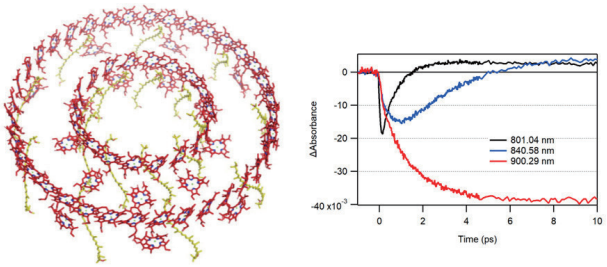
(2) In condensed systems including liquids, solids, amorphous materials, glasses, and polymers, we investigate how microscopic environments influence molecular motion, with the aim of developing new chemical reaction fields.

(3) We study the initial processes of photosynthesis (energy and electron transfer) using ultrashort-pulse lasers to elucidate their underlying principles and, in the future, to provide a foundation for the development of artificial photosynthesis.

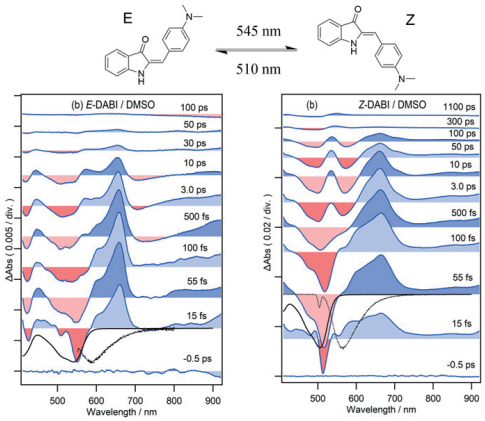
(4) Biological chemical reactions such as photosynthesis occur within the specialized environments provided by proteins. Using time-resolved spectroscopy with ultrashort-pulse lasers, we seek to clarify how proteins move and what kinds of reaction fields they create.

(5) We investigate the fundamental mechanisms of phenomena such as photochromism and solvatochromism, in which the color of a substance changes in response to light or solvent polarity.

(6) We study the physical properties of sugars as bioprotective substances against drying and freezing, as well as their effects on biological materials.



Energy transfer dynamics within the light-harvesting antenna LH1-LH2 complex.



Photoisomerization dynamics of hemiindigo.

Organic Materials Chemistry Laboratory

[HANASAKI Laboratory]

Professor
HANASAKI Tomonori

Research Overview

Our laboratory focuses on the synthesis of novel functional organic materials and the study of their physical properties. Our target materials are mainly soft materials such as liquid crystals, and our research is not limited to low-molecular-weight compounds but also extends to oligomers and polymers.
Through molecular-level design and synthesis, we systematically investigate the properties of these materials to clarify the structure–property relationships.
An overview of several of our research themes is given below.

Research Themes

(1) Studies on ER effect of liquid-crystalline materials

Certain materials exhibit a reversible change in their rheological properties upon the application and removal of an electric field. This phenomenon is known as the electrorheological (ER) effect, and such materials are referred to as ER fluids. In this study, aiming to develop novel ER fluids, we synthesize liquid-crystalline materials based on siloxane derivatives, as well as dual-frequency-driven liquid crystals of which molecular orientation can be controlled by changing the frequency of an applied alternating electric field, and we investigate their ER effects.

(2) Synthesis of conjugated polymers in photoresponsive chiral liquid-crystal fields and studies of their helical structures

The addition of photoresponsive chiral compounds composed of photoresponsive units and axially chiral units to low-molecular-weight liquid crystals can induce a chiral liquid-crystal field with a helical structure. Using such a field, for example, electrochemical polymerization of ethylenedioxythiophene results in the formation of helical conjugated polymers. In this study, we aim to synthesize helical conjugated polymers using chiral liquid-crystal fields containing photoresponsive chiral compounds and to achieve precise control over their helical structures and spiral morphologies with light irradiation. In particular, we focus on the development of materials exhibiting circularly polarized luminescence.

(3) Ionic liquids with liquid-crystalline properties: structure and physical properties

Ionic liquids are composed entirely of cations and anions and remain in the liquid state at relatively low temperatures (below 100 °C), with distinctive properties such as extremely low vapor pressure. In this study, we focus on quaternary ammonium salt-type ionic liquids and synthesize novel ionic liquids with liquid-crystalline properties. Particular attention is paid to the effects of solvents such as polyhydric alcohols doped into the ionic liquids on their phase-transition behavior.

(4) Studies on polymeric surfactants

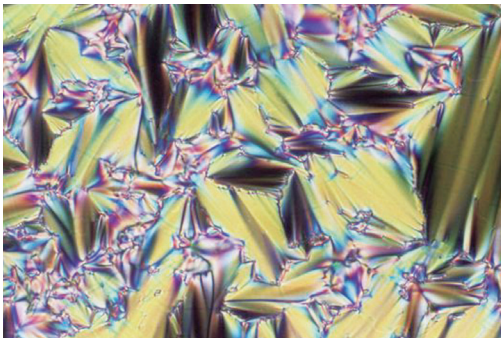
The synthesis of bead polymers by suspension polymerization is widely used in industry. However inorganic fine particles are often added to prevent coalescence during polymerization, and these particles need to be removed after the polymerization. In this study, we aim to synthesize amphiphilic block copolymers with various structures using controlled polymerization techniques and to apply them as coalescence inhibitors in suspension polymerization.

(5) Synthesis of spherical and film-type liquid-crystal elastomers and studies of their viscoelastic behavior under electric fields

We fabricate spherical and film-type elastomers containing liquid-crystalline units and investigate their viscoelastic behavior and shape changes under applied electric fields. Furthermore, by incorporating liquid-crystal units with dual-frequency drive characteristics (where the orientation mode depends on the frequency of an applied alternating electric field) into elastomers, we aim to develop advanced actuator materials which exhibit multiple and controllable deformation modes.

(6) Other research topics

In addition to the themes introduced above, our laboratory also conducts studies on the synthesis and physical properties of organic thin-film transistors(TFTs) and their alignment materials, polymeric silane coupling agents, and discotic liquid-crystalline molecules with luminescent properties.



Polarized optical microscopy image of a liquid-crystalline texture

Supramolecular Chemistry Laboratory

[MAEDA Laboratory]

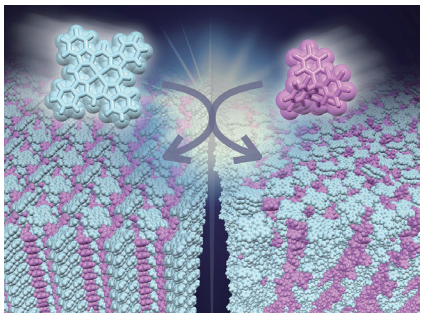
Professor
MAEDA Hiromitsu

Research Overview

Life processes are realized through the sophisticated use of strong covalent bonds and weak intermolecular interactions, which enable molecules to assemble into aggregates and higher-order structures. In my laboratory, we draw inspiration from the precisely designed structures and functions of biomolecules and use organic synthesis to construct molecules and assemblies that do not currently exist, with the aim of achieving physical properties and functionalities that surpass those found in natural systems. Guided by the idea that “molecules with previously unknown frameworks should exhibit features not found in existing molecules,” we synthesize new classes of functional dye molecules based on π-electronic systems. We then form and control supramolecular assemblies and nanoscale organized structures that possess capabilities absent in individual molecules – that is, systems in which “1 + 1 exceeds 2.” Through this approach, we seek to create new functions and concepts and ultimately to open up new directions in chemical science.

Specifically, we investigate the following research subjects using a wide range of spectroscopic techniques and surface analyses:

- Construction of supramolecular assemblies and nanoscale organized structures through molecular “programming” (i.e., designing molecular frameworks and introducing specific interaction sites), with subsequent development into functional materials
- Evaluation and control of affinity for specific metal ions or anions, with applications toward pharmaceuticals and sensors
- Evaluation and control of the electronic and photophysical properties of molecules and assemblies (such as what wavelengths of light they absorb or emit, and how efficiently they conduct electricity), with an eye toward device applications.



Research Themes

(1) Creation of functional bio-related molecules

We design and synthesize organic molecules that respond to or react with specific physical stimuli (such as light) or chemical species. Using these molecules, we explore molecular assembly, the formation of supramolecular polymers and dynamic covalent polymers, and the verification and evaluation of biological activity.

(2) Creation of organized structures based on metal ions

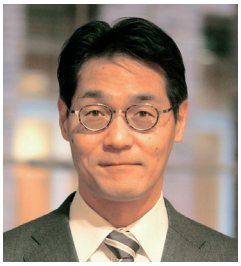
We design and synthesize organic molecules capable of using metal ions as “molecular glue.” Through metal-ion cross-linking, we have discovered the formation of polymers as well as cage-, spring-, and prism-like structures, and even luminescent nanoparticles.

(3) Development from stimulus-responsive nanoscale architectures to dimension-controlled materials

We design and synthesize π-electronic systems (receptors) with electronic and photophysical functions that mimic ion-channel structures, imparting high recognition ability toward anions and related species. We are developing these systems into fluorescent and circularly polarized light sensors that can switch between emissive and non-emissive states. By designing receptor molecules that enable assembly, we have also demonstrated the formation of stimulus-responsive soft materials such as supramolecular gels, liquid crystals, and vesicles. Furthermore, by constructing ion-pairing assemblies with controlled dimensionality through the ordered arrangement of charged species (cations and anions), we have established a concept for developing electronic and photophysical functional materials and devices that are unattainable with conventional systems – a concept that has received strong international recognition.

Plant Biochemistry Laboratory

[ISHIMIZU Laboratory]



Professor
ISHIMIZU Takeshi

Research Overview

Our laboratory aims to discover enzymes involved in the biosynthesis and degradation of plant glycans (complex carbohydrates) and to elucidate the glycan metabolism systems formed by the cooperative action of multiple enzymes. We also study the functions of plant glycans and their roles in processes such as differentiation and morphogenesis. Unlike other organisms, plants contain an overwhelmingly high abundance of glycans and an exceptional diversity of glycan structures. For this reason, fundamental research on plant carbohydrate components is expected to be a key factor in addressing future challenges related to food and energy supply. The knowledge gained in our laboratory contributes to plant-based energy production, increased food yields, and the development of functional foods that utilize carbohydrate components found in plants.

Research Themes

(1) Biosynthesis and degradation of plant flavonoid glycosides and their physiological functions

Plants produce a wide variety of specialized (secondary) metabolites to enhance their adaptation to the environment. These include alkaloids, which serve as lead compounds for new pharmaceuticals, and polyphenols such as flavonoids, which are used in cosmetics and food additives. Quercetin, a flavonoid found in Suntory's "Tokucha" beverage, induces the activation of lipid-degrading enzymes. Apiin (Fig. 1), a flavonoid glycoside produced in parsley and celery, has been reported to exhibit antioxidant activity and inhibitory effects on cancer cell proliferation, and is also thought to have anti-anxiety effects in humans. For these reasons, elucidating the functions of apiin is of considerable interest. Recently, our laboratory discovered the gene encoding an enzyme responsible for the biosynthesis of apiin. Based on this discovery, we are advancing our research into the biosynthetic mechanisms and physiological functions of flavonoid glycosides.

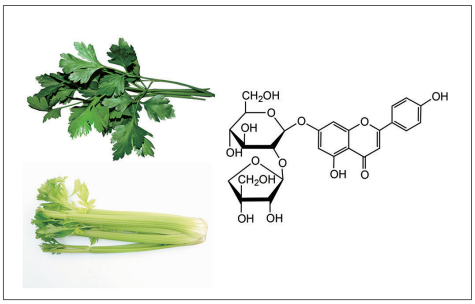


Figure 1. Flavonoid glycoside apiin found in parsley and celery

(2) Biosynthesis and degradation of plant cell-wall polysaccharides and their physiological functions

We are investigating the molecular mechanisms underlying the biosynthesis and degradation of plant cell-wall polysaccharides, particularly pectin (Fig. 2). Pectin is believed to play roles in plant growth, cell–cell adhesion, regulation of plant flexibility, and responses to pathogens. To understand the functions of pectin, it is essential to identify the genes encoding the enzymes responsible for its synthesis. Our laboratory has discovered one such enzyme, RG-I rhamnosyltransferase, along with its gene, thereby opening the way to elucidating the molecular mechanisms of pectin biosynthesis with its highly complex structure. By introducing mutations into this gene, we are also studying the physiological roles of pectin and have demonstrated, for example, that pectin synthesis is involved in plant growth. Taking a broader bioeconomy perspective, we aim to apply these findings to the cultivation of plants as energy and food resources, as well as to the industrial utilization of plant polysaccharides.

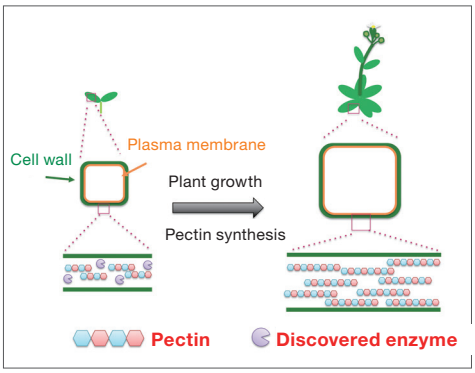


Figure 2. Synthesis of plant cell-wall pectin and plant growth

(3) Elucidation of mechanisms of secondary cell-wall pattern formation during xylem vessel differentiation

Xylem vessels are essential plant tissues responsible for transporting water and inorganic nutrients and for providing structural support to the plant body. The secondary cell walls formed in xylem vessel cells constitute woody biomass and are therefore expected to serve as renewable energy resources useful for realizing a sustainable society. Secondary cell walls are composed mainly of cellulose and form distinct characteristic patterns at different developmental stages through mechanisms dependent on the orientation of cortical microtubules beneath the plasma membrane. From the perspective of microtubule alignment control, we are analyzing in detail the mechanisms that determine these patterns.

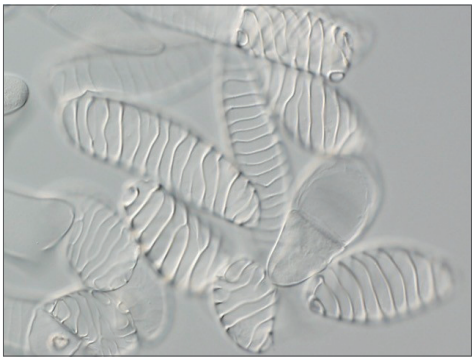


Fig. 3 Plant cells induced to differentiate into xylem vessel cells

Plant Molecular Biology Laboratory

[KASAHARA Laboratory]

Professor
KASAHARA Masahiro

Research Overview

Living organisms accurately perceive and respond to diverse environmental stimuli to adapt to their surroundings. These responses are mediated by molecular mechanisms that include sensors (or receptors) that detect environmental cues such as light, as well as low-molecular-weight compounds and signal transduction proteins that convey these signals within cells. Our laboratory primarily investigates the molecular mechanisms underlying cellular and organismal responses to light in plants.

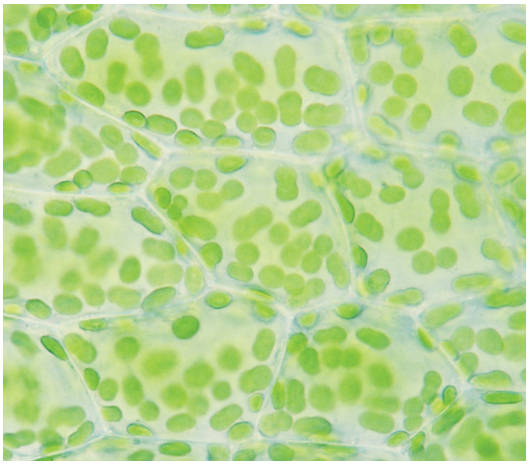
Research Themes

(1) cAMP signaling pathways in plants

Cells receive external environmental stimuli or signals from other cells and transmit this information intracellularly using specific signaling molecules. Cyclic AMP (cAMP) is known to be a major signaling molecule conserved across almost all biological taxa. Due to its importance, cAMP has long been studied in plants, particularly in angiosperms. However, plants were long considered a group in which the existence of cAMP and its synthesizing enzymes was ambiguous, leaving the physiological roles of cAMP signaling largely unknown. Recently, we discovered novel cAMP synthesis/degradation enzymes, referred to as CAPE (COMBINED AC with PDE), that are conserved in basal plant lineages, including bryophytes, ferns, gymnosperms, and charophyte algae. Interestingly, these enzymes are conserved in plants that undergo sexual reproduction via motile sperm, suggesting a close relationship with the evolutionary history of land plants. We analyze the plant cAMP signaling system from both physiological and evolutionary perspectives.

(2) Plant responses to the light environment

Plants utilize sunlight not only as an energy source for photosynthesis but also as informational input necessary for regulating growth and development. Physiological phenomena triggered by light as informational signals, such as phototropism and chloroplast movement, have been studied for a long time. Most photoreceptors that perceive light as information have already been identified, and the relationships between individual physiological responses and photoreceptors have been largely clarified. Nevertheless, the functions of some photoreceptors have not yet been fully elucidated, and our understanding of plant light responses remains incomplete. Our goal is to elucidate in detail the molecular mechanisms underlying plant light responses, including both the functions of less-characterized photoreceptors and the signaling processes that occur beyond photoreception.



Plant cells and chloroplasts

Plant Biotechnology Laboratory

[TAKEDA Laboratory]

Professor
TAKEDA Atsushi

Research Overview

Even plants suffer from diseases, and reducing yield losses of agricultural crops caused by disease is a critically important challenge. Our laboratory aims to develop crops with enhanced resistance to viruses, viroids, and bacterial pathogens by leveraging biotechnology. As fundamental research, we investigate the infection mechanisms of plant viruses, viroids, and plant pathogenic bacteria, as well asplant immunity. We also conduct RNAi-based and Cas9-based screening to identify host factors required for viral infection. As applied research, we develop Cas9-mediated plant gene knockout systems and produce disease-resistant plants through genome editing without the introduction of foreign genes.

Research Themes

(1) Development of novel screening systems in plants and identification of host factors for viruses and viroids

Given that many plant RNA viruses possess only four to six genes, it is assumed that numerous plant genes (hereafter referred to as host factors) are involved in viral infection. Moreover, viroids, which lack protein-coding genes altogether, rely entirely on host factors for their replication. Identifying host factors required for pathogen infection is crucial for understanding the mechanisms of viral and viroid infection and is also expected to contribute to the development of disease-resistant crops based on recessive resistance. Despite extensive attempts using model plants, only a limited number of host factors have been identified through forward genetic screening, such as TOM1 and TOM3 for Tobacco mosaic virus. This scarcity is thought to be due to the essential nature of many host factors, whose disruption leads to lethality, as well as functional redundancy, which prevents phenotypic manifestation upon disruption of a single gene. To overcome these limitations, our laboratory is developing RNAi- and Cas9-based screening systems capable of bypassing these obstacles. Using these systems, we aim to identify novel host factors essential for the replication of plant viruses and viroids.

(2) Molecular basis of the plant immune system and mechanisms of immune suppression by pathogenic bacteria

Plants possess an innate immune system to protect themselves from pathogens. Plant immune responses involve dynamic changes in the expression of thousands of genes; however, the molecular mechanisms underlying this large-scale and coordinated gene expression regulation remain poorly understood. Our lab's research focuses on signaling molecules such as plant hormones and transcription factors involved in plant immunity, with the aim of elucidating how changes in gene expression lead to enhanced disease resistance. Some pathogens inject virulence factors, known as effectors, into plant cells to suppress immune responses and establish infection. To clarify how pathogens manipulate the plant immune system, we seek to identify the host targets of these effectors. Based on the insights obtained, we aim to develop technologies to strengthen plant immune systems and to neutralize the functions of pathogen effectors.

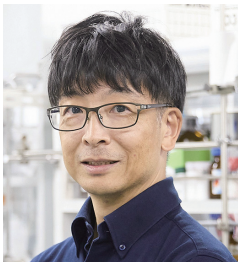
(3) Development of gene knockout systems in plants and generation of disease-resistant crops

In principle, disrupting host factors required by pathogens in agricultural crops can confer disease resistance. To achieve this in practice, detailed genomic information and reliable methods for targeted gene disruption are required for each crop species. As genome sequencing has progressed for many plant species, host factors identified in model plants have been shown to be conserved across diverse crops. At the same time, genome editing technologies, such as Cas9, have been rapidly advancing. As a result, it is becoming possible to confer disease resistance to crops without producing genetically modified organisms in the conventional sense. By fully utilizing biotechnology, our laboratory aims to generate solanaceous crops with resistance to viruses, viroids, and bacterial pathogens.

Biotechnology Course

Biomolecular Chemistry Laboratory

[TAKEDA Laboratory]



Professor
TAKEDA Yoichi

Research Overview

Our research focuses on chemical approaches to elucidate the structure and function of biomolecules, with particular emphasis on glycans and lipid molecules. In our studies of glycoprotein quality control mechanisms in the endoplasmic reticulum (ER), we synthesize diverse glycan structures and investigate their interactions with glycan-recognizing proteins to clarify the roles of glycans in protein folding and trafficking. In addition, to understand membrane lipid dynamics and signaling mechanisms, we conduct chemical synthesis and functional analysis of lipids, including photoaffinity probes. We are also engaged in the synthesis of complex glycan fragments that constitute plant cell walls and in the characterization of enzymes involved therein using these synthetic tools. Through this research, we aim to achieve a molecular-level understanding of the precise interactions among biological macromolecules.

Research Themes

(1) Analysis of glycoprotein quality control mechanisms

Many proteins synthesized in the endoplasmic reticulum undergo glycosylation during translation, and their glycan structures are continuously modified by various glycosidases and glycosyltransferases present in the ER. The glycan structures on glycoproteins are thought to reflect the folding state of the protein moiety, and lectin chaperones in the ER specifically recognize these glycan structures to facilitate protein folding and transport. By constructing glycans with diverse structures and analyzing their interactions with glycan-recognizing proteins, we aim to elucidate the maturation process of glycoproteins in the ER.

(2) Chemical synthesis of membrane lipid probes

Biological membranes function not only as stable and functional compartments that maintain cellular architecture but also play essential roles in signal transduction and selective transport mediated by membrane-embedded proteins. To analyze the biosynthesis and regulatory mechanisms of membrane lipids, we perform synthetic studies of various lipid molecules, including photoaffinity lipid probes.

(3) Creation of novel functional molecules using rare sugars

Rare sugars such as allose and allulose are known to suppress postprandial blood glucose levels. Using these rare sugars as starting materials, we explore their application as functional sweeteners by synthesizing novel disaccharides and oligosaccharides. Thus far, we have established a method for 1,2-cis-selective glycosylation of an allose residue onto an allulose residue using an intramolecular aglycon delivery approach, and have also successfully synthesized a sucrose-mimicking disaccharide, α-D-allopyranosyl-(1→2)-β-D-allulofuranoside. We are currently pursuing the development of more efficient glycosylation methods.

(4) Synthesis of glycans constituting plant cell walls

Plant cell walls are composed of complex combinations of polysaccharides and associated low-molecular-weight compounds. We synthesize glycan fragments of pectin, which constitute plant cell walls, and use them as molecular tools to characterize the properties of glycosidases and glycosyltransferases involved in cell wall biosynthesis.

Structural Bioscience Laboratory

[MATSUMURA Laboratory]

Professor
MATSUMURA Hiroyoshi

Research Overview

In recent years, global environmental degradation, food shortages caused by population growth, and the spread of illnesses such as cancer and infectious diseases have become major concerns. Our laboratory seeks to address these challenges by elucidating the functions, structures, and dynamics of enzymes and proteins at 0.1-nanometer resolution and by developing methods to control their activities through enzyme engineering and drug discovery. Our research targets include supramolecular complexes involved in carbon dioxide fixation pathways in photosynthesis, enzymes widely used in food processing, cosmetics, and pharmaceutical production, and enzymes and proteins associated with cancer and infectious diseases. By combining fundamental life-science techniques such as enzyme analysis, genetic manipulation, microbial handling, and protein engineering with new methodologies including X-ray crystallography, crystallization, high-speed AFM (atomic force microscopy), phage display, yeast surface display, and computational science, we investigate biological mechanisms at the molecular level. In addition, through active collaborations with universities, companies, and research institutes overseas, including partners in the United States, we conduct mechanism-driven research and technology development aimed at contributing to environmental improvement, solutions to food supply challenges, enhanced quality of life, and drug discovery.

Research Themes

(1) Elucidation of the molecular mechanisms of the photosynthetic CO_2 fixation pathway

We are investigating the molecular mechanisms of the CO_2 fixation pathway (the Calvin cycle) in photosynthetic organisms with the goal of further improving photosynthetic efficiency. Recently, we identified a prototype of the plant photosynthetic mechanism in methanogenic archaea, providing fundamental insights for harnessing photosynthetic functions. Furthermore, we have determined the three-dimensional structure of the Calvin cycle regulatory complex by combining X-ray crystallography and small-angle X-ray scattering, enabling us to elucidate its regulatory mechanism at the molecular level. Based on these findings, we aim next to develop plants with enhanced photosynthetic efficiency. In parallel, we focus on RuBisCO, the CO_2-fixing enzyme that limits photosynthetic efficiency. A hybrid RuBisCO composed of the small subunit (RbcS) from C_4 plants and the large subunit (RbcL) from rice exhibits a substantially higher catalytic rate, although the reason for this enhancement is unknown. To clarify the mechanism, we have determined the crystal structure of the hybrid RuBisCO using X-ray crystallography, and are now uncovering the structural basis for its increased catalytic turnover. These insights are expected to contribute to future solutions for food and energy challenges associated with global population growth.

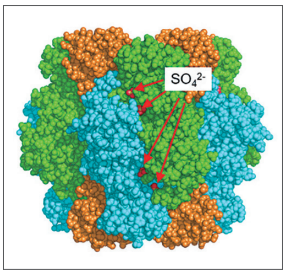


Figure 1. Three-dimensional structure of RuBisCO

(2) Research on industrially valuable enzymes

The plant Eucommia ulmoides accumulates large amounts of trans-polyisoprene (TPI), a natural rubber, in its leaves, bark, and fruits. TPI is attracting attention as a petroleum-independent resin material for industrial applications. However, the amount of TPI accumulated in plant tissues remains insufficient from the perspective of production cost and commercial viability. There is a need to enhance TPI accumulation or control its molecular weight and distribution in order to add new value. This requires a detailed understanding of the molecular mechanisms underlying TPI biosynthesis, which has remained unclear.

We therefore focused on novel enzymes involved in TPI biosynthesis and performed structural analyses to elucidate their reaction mechanisms. Specifically, we analyzed enzymes responsible for synthesizing long-chain TPI polymers (TPT) and those producing short-chain TPI (approximately several hundred Daltons; FPS). Analysis of the structure of these enzymes revealed that the TPT dimer forms a compact, box-like structure containing a tunnel extending from the interior to the exterior of the molecule, whereas the FPS dimer adopts a twisted, open structure in which the tunnel is blocked by neighboring molecules. Based on these observations, we hypothesize that TPT synthesizes high-molecular-weight TPI by forming a compact, box-shaped dimer that serves as a tunnel through which the polymer can be continuously extruded. We are currently testing this hypothesis through extensive mutational analyses.

In addition, we are engineering β-galactosidase (BgaDD) from Bacillus circulans, one of the most widely used industrial enzymes. BgaDD produces galacto-oligosaccharides (GOS), which are utilized as prebiotics that improve bowel function and are widely used as functional food ingredients. However, BgaDD has broad specificity for long glycans, and generates GOS with a broad range of chain lengths (2–10 sugars), whereas trisaccharide GOS exhibit the highest prebiotic activity. To selectively enhance trisaccharide GOS production, we are modifying the enzyme using a combination of artificial binding proteins, structure-guided amino acid substitutions, and random mutagenesis. We also aim to extend these approaches to enzymes used in food processing, cosmetics, and pharmaceutical synthesis.

(3) Elucidation of cell division mechanisms and drug discovery targeting infectious diseases

During bacterial cell division, the protein FtsZ forms a ring-shaped polymer along the inner surface of the cell membrane; contraction of this ring drives membrane invagination. FtsZ simultaneously undergoes two opposing processes – attaching (polymerization) and detaching (depolymerization) – yet how a single protein accomplishes these contradictory functions remained unknown. To address this question, we determined the crystal structure of FtsZ from methicillin-resistant Staphylococcus aureus (MRSA). Remarkably, two significantly different conformations of GDP-bound FtsZ were observed within the same crystal (Figure 2). This was the first demonstration of such distinct conformations in a single FtsZ species, leading us to propose a model in which conformational transitions drive the polymerization-depolymerization cycle.

Since FtsZ is essential for MRSA proliferation, it is an attractive anti-MRSA drug target. By introducing known FtsZ inhibitors into the crystals, we found that these inhibitors bind selectively to only one of the two observed conformations (Structure A in Figure 2), demonstrating conformation-specific binding. Furthermore, in collaboration with Rutgers University in the United States, we developed a novel antibacterial compound, TXA6101, which binds to FtsZ in drug-resistant MRSA strongly and in a previously uncharacterized mode. This new binding mode allows TXA6101 to inhibit drug-resistant forms of FtsZ that exhibit reduced affinity for conventional inhibitors.

We further evaluated the inhibitory effects of TXA6101 against other pathogenic bacteria previously considered resistant to FtsZ inhibitors, and found that TXA6101 was effective against several of these organisms. Going forward, we will continue to examine the binding structures and inhibitory activities of various compounds and, in collaboration with Rutgers University, pursue the development of next-generation inhibitors.

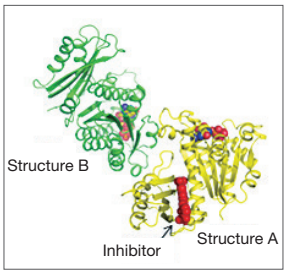


Figure 2. Two distinct conformations of FtsZ observed within the same crystal (Structure A, yellow; Structure B, green), and an inhibitor bound exclusively to Structure A.

Applied Molecular Microbiology Laboratory

[MIHARA Laboratory]

Professor
MIHARA Hisaaki

Lecturer
AONO Riku

Research Overview

Long before the term “biotechnology” was coined, humans had already been utilizing microorganisms and the enzymes they produce. The diverse capabilities of microorganisms can be applied across a wide range of fields, including solutions to environmental and food-related challenges, pharmaceutical development, and high-tech industries. Many novel microorganisms and enzymes remain undiscovered.
In our laboratory, we employ approaches from biochemistry, microbiology, molecular microbiology, protein engineering, and genetics to elucidate the diverse and unique metabolic mechanisms of microorganisms and to explore their practical applications.

Research Themes

(1) Studies on selenoproteins containing the “21st amino acid”

The UGA codon, which normally functions as a stop codon, can be translated into selenocysteine, the 21st amino acid, via a specialized mechanism. Proteins containing selenocysteine are collectively known as selenoproteins and are widely distributed across organisms ranging from microorganisms to humans, where they play essential roles such as antioxidant defense. How is the UGA codon translated? We are investigating this unusual mechanism, with particular focus on archaea, whose systems remain poorly understood. At the same time, we analyze the unique functions of selenoproteins.

(2) Elucidation of unique microbial metabolisms and survival strategies

The amount of carbon dioxide released from soils by microbial activity is estimated to be approximately seven times greater than that emitted by human activities. In addition, microbially produced dimethyl sulfide emitted from the oceans serves as a major nucleus for cloud formation in the atmosphere. These examples illustrate the profound impact of microbial metabolism on the global environment. We view the diversity of microbial metabolic pathways as survival strategies shaped by environmental adaptation and are working to elucidate previously uncharacterized metabolic systems.

(i) Microbial roles in the global sulfur and selenium cycles

We investigate, at the gene and protein levels, the metabolic mechanisms of bacteria involved in sulfur and selenium cycling in the environment. We have also discovered a novel bacterial strain, BKC1, from soil on the BKC campus that can utilize organic selenium compounds. We are currently working to elucidate the metabolic mechanisms underlying this unique capability.

(ii) Exploring the evolution of respiratory enzymes that sustain life (archaeology through enzymology)

The distant ancestor of mitochondrial respiratory chain complex I in human cells is believed to be an ancient respiratory enzyme, hydrogenase. However, the evolutionary continuity between these enzymes – the so-called “missing link” – remains unresolved. Using genomic analyses supported by supercomputing resources, we are attempting to uncover this missing link in modern respiratory enzymes.

Enzyme Technology Laboratory

[WAKAYAMA Laboratory]

Professor
WAKAYAMA Mamoru

Research Overview

The Enzyme Technology Laboratory focuses on applying the functions inherent to living organisms, particularly microorganisms, to the fields of food, environment, resources, and energy. With respect to microbial functions, we focus on the catalytic activities of enzymes, which serve as the driving force of metabolism, and pursue comprehensive research on enzyme-based production of valuable compounds. Our research spans from basic to applied studies on enzymes, including the exploration of microorganisms capable of producing useful enzymes, construction of high-level enzyme production systems, analyses of enzyme structure and function, and functional enhancement through enzyme modification. In parallel, we develop technologies for producing valuable substances via fermentation processes that utilize whole microbial functions. Furthermore, by understanding fermentation at the molecular level and applying genetic, molecular biological, and biochemical approaches, we conduct research aimed at controlling fermentation processes.

Previous Research Achievements

We have successfully developed an enzyme particularly effective for producing the high-value and high-demand D-tryptophan, through our studies on the structure and function of N-acyl-D-amino acid amidohydrolase, which is an enzyme useful for optical resolution production of D-amino acids that are increasingly important as raw materials for pharmaceuticals such as antibiotics and chemotherapeutic agents.
In the food-related field, collaborative research elucidated the higher-order structure of a salt-tolerant glutaminase, a useful enzyme for the production of L-glutamic acid, a key umami component found in many foods, thereby providing a foundation for understanding salt-tolerance mechanisms. Additionally, we studied the structure and function of γ-glutamyltransferase derived from Pseudomonas species, an enzyme involved in the synthesis of theanine – an umami component of tea that has recently attracted attention for its physiological functions – and clarified its higher-order structure through collaborative research. We also developed an asparaginase derived from Bacillus subtilis, a food microorganism, as a food-additive enzyme capable of suppressing the formation of acrylamide, a carcinogenic and toxic compound present in large amounts in processed foods such as fried potatoes, and demonstrated its practical utility.
In the field of enzymes integrally related to food, environment, and resources/energy, we have conducted extensive research on polysaccharide-degrading enzymes, including chitinases that degrade chitin, which, alongside cellulose, is one of the most abundant yet underutilized biomass resources on Earth, and α-/β-glucanases that degrade α-/β-glucans abundant in fungi such as mushrooms and yeasts. Our work encompasses enzyme development, structural and functional analyses, production of useful compounds such as lactic acid from unused biomass, and agricultural applications such as pathogen control.
In parallel with our research on enzymes, we proposed a novel fermented seasoning, “Rakusho,” based on milk as a primary ingredient, and established a basic production method for it. Currently, production-scale brewing experiments are underway through collaboration with industry. Rakusho has a unique flavor profile, and we hope it will develop into a seasoning appreciated the world over.
In recent years, we have engaged in fundamental research on the physiological functions of acetic acid bacteria-a key microorganism in acetic acid fermentation-focusing on stress tolerance against ethanol, acetic acid and oxidation.

Future Research Directions

Our research has primarily targeted the application of microbial enzymes across diverse fields and the development of fermented foods centered on food-associated microorganisms. Moving forward, we aim to further promote collaborative research with external partners and to actively advance and expand our ongoing research initiatives.

Research Themes

(1) Research on fermentation

- Development of novel utilization methods for by-products generated in dairy processing and sake brewing
- Exploration of D-amino acid–producing lactic acid bacteria, studies on D-amino acid metabolic enzymes, and research aimed at their application in foods
- Biochemical and molecular biological approaches to elucidate ethanol and acetic acid tolerance mechanisms in acetic acid bacteria

(2) Research on amino acid and peptide metabolic enzymes

- Development of enzymatic methods for synthesizing functional peptides from non-proteinogenic amino acids such as D-amino acids
- Research aimed at advanced utilization of peptide- and protein-metabolism-related enzymes in foods
- Development of enzymatic methods for D-amino acid quantification and research on improving enzyme functionality

(3) Research on polysaccharide metabolic enzymes

- Research on the production and functionality of α-1,3-glucan oligosaccharides using α-1,3-glucanase
- Research on advanced utilization of α-1,3-glucans through chemical modification
- Exploration of microorganisms producing novel α-1,3-glucanases and development of their applications
- Research on plant-derived β-1,3-glucanases and their inhibitory substances

Microbial Genome Dynamics Laboratory

[TAKEMATA Laboratory]

Associate Professor
TAKEMATA Naomichi

Research Overview

Genomic DNA forms a highly organized three-dimensional structure within the cell. We study how genome organization mechanisms are linked to their functions in archaea, a group of microorganisms believed to be the origin of eukaryotes. Through these efforts, we aim to advance both the evolutionary understanding of archaeal genomes and their industrial applications.

Research Themes

(1) Elucidating the organizational principles of eukaryote-like chromatin in archaea

One of the most distinctive features of eukaryotes is their ability to form a three-dimensional genome structure based on chromatin. Chromatin is a fibrous structure primarily composed of nucleosomes, in which DNA is wrapped around histone proteins. This structure is further organized into higher-order architectures such as topologically associating domains (TADs) and DNA loops through the action of various chromatin factors, including the Structural Maintenance of Chromosomes (SMC) complexes. In eukaryotes, these structures are tightly regulated by diverse proteins, enabling precise control of genome functions such as transcription, replication, and repair.
To understand how eukaryotic chromatin originated, we study microorganisms known as archaea. Archaea are thought to be the prokaryotic ancestors of eukaryotes and possess homologs of eukaryotic chromatin factors, including histones and SMC complexes. This suggests that archaeal genomes may form complex chromatin-like structures resembling those present in the ancestors of eukaryotes. By leveraging molecular genetics and next-generation sequencing (NGS) approaches, we aim to elucidate the structural and functional properties of such “archaeal chromatin” and thereby gain insight into the origins of eukaryotic chromatin.
To date, we have investigated the structure and function of archaeal genomes by adapting genome-wide three-dimensional structure analysis methods such as Hi-C/3C-seq to hyperthermophilic archaea (Takemata et al., Cell 2019; Takemata & Bell, Molecular Cell 2021). Currently, we are particularly focused on understanding the formation mechanisms and functional roles of TAD-like domain structures generated by archaeal SMC complexes (Yamaura et al., Nature Communications 2025). In addition, we have recently initiated studies on archaeal histones. In archaea, DNA–histone complexes resembling eukaryotic nucleosomes are known to form; however, their physiological functions remain largely unclear. Notably, archaeal histones lack the intrinsically disordered “tail” regions that are crucial for the function of eukaryotic histones, and when and how these evolutionary differences arose remains unknown. We aim to uncover the roles of archaeal histones in regulating genome structure and function, and to explore the evolution of histones through an experimental evolution approach in which eukaryotic histone tails are fused to archaeal histones.

(2) Elucidating how hyperthermophilic archaea maintain chromatin functionality at high temperatures

Organisms with optimal growth temperatures above 80 °C are known as hyperthermophiles, and many of them belong to the domain Archaea. These organisms, which thrive in environments so hot that life would normally be considered impossible, have long fascinated researchers, yet their biological properties remain incompletely understood. In particular, it remains a longstanding mystery how hyperthermophiles maintain the structural and functional integrity of chromatin under high-temperature conditions that readily cause DNA denaturation and damage.
To address this question, we are focusing on reverse gyrase, a unique DNA topoisomerase found in hyperthermophiles.

(3) Efforts toward the application of archaeal genomes

Archaea inhabit not only high-temperature environments but also a wide range of extreme environments. In addition, they possess many unique metabolic pathways that are not found in other domains of life. These characteristics hold significant potential for future biotechnological applications. By understanding the operating principles of archaeal genomes and manipulating or modifying them, we aim to enhance and apply the extreme environment tolerance and distinctive metabolic pathways inherent to archaea.

Tissue and Organ Function Analysis Laboratory

[AMANO Laboratory]

Professor
AMANO Akira

Research Overview

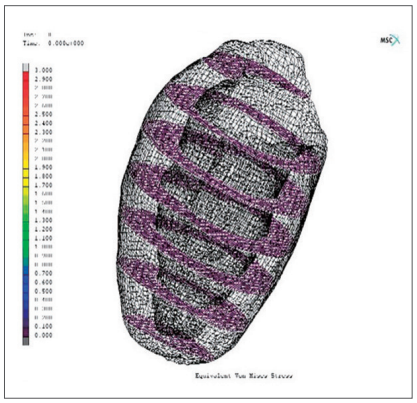
In the fields of medicine and life sciences, significant progress has been made in understanding biological functions by focusing on the elucidation of fine structures and mechanisms underlying life phenomena. However, it has become increasingly clear that biological systems are extremely complex and that overall functions emerge from nonlinear interactions among numerous factors. To aim understanding of such integrated mechanisms, expectations are growing for simulation-based approaches that construct models by integrating known phenomena and mechanisms, enabling the analysis of tissue-, organ-, and organism-level functions.

The Tissue and Organ Function Analysis Laboratory studies biological functions with a focus on relationships that have been relatively underexplored in life sciences: specifically, the relationships between cells and tissues, and between tissues and organs. We do so by constructing and analyzing simulation models to elucidate biological phenomena, with a particular focus on the heart as a target organ. Using cardiomyocyte models that incorporate detailed intracellular functional components, we reproduce and analyze contractile properties of myocardial tissue composed of many cells, responses to ischemic conditions, organ-level circulatory dynamics, and organism-level regulatory mechanisms such as the baroreceptor reflex.

Research Themes

(1) Simulation of biological functions in the heart, myocardial tissue, and retina

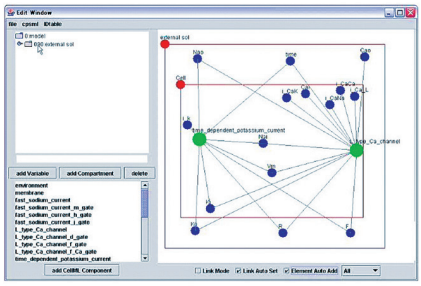
In cardiomyocytes, electrical stimulation induces action potentials that elevate calcium concentrations, which in turn generate contractile force. This contractile force raises intraventricular pressure and drives blood ejection into the arteries. These processes are not governed by one-way causality but involve multilevel interactions and feedback control systems. For example, the properties of individual cells differ from those observed at the tissue level. Our laboratory analyzes relationships between electrical excitation conduction in the heart and contractile force generation, as well as relationships between single-cell contractile properties and myocardial tissue contraction properties integrated with the heart and circulatory system as a whole. In addition, we construct detailed electrophysiological models of retinal rod cells, horizontal cells, bipolar cells, and neurons, with a particular goal of reproducing electrical properties suitable for medical applications.



Left ventricular model

(2) Software environment for biological function simulation

Many researchers in life sciences are not specialists in mathematics or software, and this creates substantial barriers especially for modeling at tissue and organ scales. Our laboratory is developing a software environment that allows non-software specialists to integrate, modify, and edit multiple elemental models. This environment also supports large-scale tissue- and organ-level simulations using high-performance computing systems.



Model editing tools

Information Biology Laboratory

[ITO Laboratory]

Professor
ITO Masahiro

Research Overview

Our aim is to elucidate the mechanisms of development, aging, and immunity comparative analyzes based on information science to large-scale life science data. This includes datasets relating to epigenomics, genomics, transcriptomics, proteomics, metabolomics, and phenomics datasets.

Research Themes

(1) Understanding the functional system of the SARS-CoV-2–specific protein ORF8 through data-driven science and experimental validation in molecular biology

The pandemic SARS-CoV-2, which began in January 2020, continues to cause infectious disease worldwide as of March 2024, more than four years later. To control and treat the disease, it is essential to understand the functions of the proteins encoded by SARS-CoV-2. Within infected cells, SARS-CoV-2 synthesises four types of structural protein, sixteen types of non-structural proteins, and seven types of accessory protein. In March 2020, we reported that ORF8 and ORF7b are SARS-CoV-2-specific accessory proteins [1].

The human immune system efficiently eliminates infected cells by selectively promoting degradation of MHC class I (MHC-I) molecules in response to viral attack (Figure 1A). Killer T-cell receptors recognize specific signals presented by MHC-I peptide complexes and induce death of virus-infected cells through release of cytotoxic substances (Figures 1A and 1B). When a virus infects a cell, antigens are presented on the cell surface by MHC class I molecules, followed by recognition of the antigens and damage to infected cells by CD8-positive T cells (killer T cells) (Figure 1C). The ORF8 protein interferes with antigen presentation in this process and reduces the recognition and elimination of virus-infected cells by cytotoxic T lymphocytes (CTLs) [2]. Specifically, in the endoplasmic reticulum, the ORF8 protein binds to the MHC-I complex and promotes its translocation to autolysosomes and subsequent degradation, thereby functioning as a strong negative regulator of MHC-I (Figure 1C) [3] and inhibiting the removal of infected cells that support viral replication.

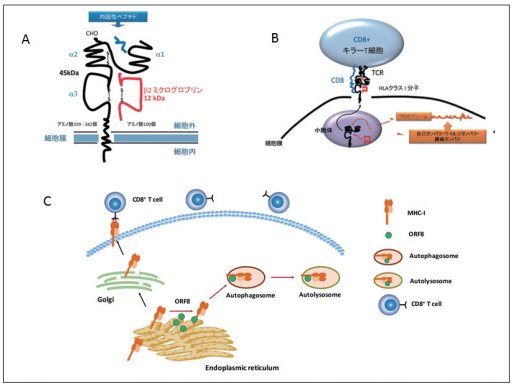


Figure 1: A. Molecular model of MHC-I; B. Cellular response; C. Function of ORF8 in killer T cells of the adaptive immune system
The ORF8 protein mediates degradation of MHC-I via an autophagy-dependent pathway.
A, B: Inoko H. et al., *Ishoku/ketsueki kansagaku [Transplantation and Hematologic Immunology]*, Kodansha, pp. 24-39 (2004)
C: Reference [3]

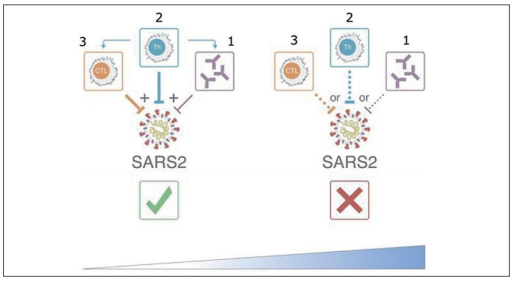


Figure 2: Three types of cells involved in antigen-specific immune responses
1. B cells that produce antibodies; 2. helper T cells; and 3. killer T cells all function cooperatively, and this coordination is important for host defense during the acute phase of SARS-CoV-2 infection (left).
With aging, naïve T cells decrease, and when this cooperative function is lost, the risk of severe disease increases (right). The horizontal axis indicates age.
Reference [5]

In SARS-CoV-2 variants identified in the United Kingdom, ORF8 exhibits genetic mutations. Since mutation or deletion of ORF8 leads to reduced SARS-CoV-2 infectivity and replicative capacity within the host and attenuated pathogenicity, ORF8 has been suggested to act as a trigger of immune responses [2].

Proteomic analyses determined a group of host proteins (332 in total) that interact with the various SARS-CoV-2 proteins [4]. Among these, ORF8 had the largest number of binding partners, with 47 interacting proteins. Many of these proteins are involved in glycoprotein biosynthesis processes associated with endoplasmic reticulum stress and the ubiquitin-dependent ER-associated degradation pathway, and also include the receptor IL-17RA, which binds IL-17A associated with CD4-positive T cells (helper T cells) [5]. Following SARS-CoV-2 infection, nonspecific innate immune mechanisms act first, after which specific adaptive immunity is induced. In adaptive immunity, B cells that produce antibodies, killer T cells that destroy virus-infected and cancer cells, and helper T cells that assist various immune responses play key roles (Fig. 2) [5]. Based on this, we proposed the hypothesis that the onset and severe progression of COVID-19 are caused by ORF8 inducing autoimmune abnormalities in killer T cells and helper T cells.

We have already advanced verification of this hypothesis. Through phylogenetic profile analysis of 446 SARS-CoV-2 ORF8-binding proteins, we identified that (a) ORF8-binding proteins acquired during vertebrate evolution act on complement and blood coagulation; (b) ORF8-binding proteins acquired in animals and chordates contribute to negative regulation of interferon-β originating from the extracellular matrix; and (c) ORF8-binding proteins acquired in eukaryotes function as negative regulators of antigen presentation in leukocytes.
In other words, we clarified that ORF8-binding protein groups acquired at different stages during human evolution contribute to regulation of multiple functions, thereby exerting complex effects on the control of adaptive immunity, innate immunity, and tissue repair [6].
In our present research project, by fully leveraging both data-driven approaches and molecular biological approaches, we will further advance understanding of the functional systems of SARS-CoV-2-specific proteins that are useful for elucidating the mechanisms of COVID-19 onset and for developing therapeutic strategies.

[1] Fahmi M, Kubota Y, Ito M. Infect Genet Evol. 2020, 81,104272.
[2] Su YCF et al. mBio. 2020, 11, e01610-20.
[3] Zhang Y et al. PNAS, 2020, 118, e 2024202118.
[4] Gordon DE et al. Nature 2020, 583, 459–8.
[5] Moderbacher RC et al. Cell. 2020, 184, 996-1012.
[6] Takatsuka H, Fahmi M et al. Front Med. 2022, 9, 824622.

(2) Elucidation of gonad formation mechanisms, germ cell differentiation, and mechanisms regulating embryogenesis in nematodes through integrated genetic and information-biological approaches

The hermaphroditic nematode Caenorhabditis elegans reproducibly forms a U-shaped gonad. Focusing on gametogenesis during development, sperm are produced at the end of the larval stage (from the end of the L3 larval stage to the L4 stage), after which oocytes are produced upon reaching adulthood to generate fertilized eggs for the next generation.
We have previously demonstrated that (a) the transcriptional regulatory PAF1 complex contributes to promotion of epidermal morphogenesis and oocyte maturation; and (b) three types of Class I HDAC (histone deacetylase) complexes, known as negative transcriptional regulators, play essential roles in control of fertilized egg size and embryogenesis [7 - 9].
In this project, in addition to genetic approaches, we perform comparative transcriptome analyses between simple gene knockdown animals and transgenic nematodes rescued in a tissue- or cell-type-specific manner. By focusing on gene groups whose expression is specific to particular tissues, we classify them into gene groups that function cell-autonomously and gene groups that function non-cell-autonomously and contribute to inter-tissue interactions, and have succeeded in identifying multiple genes. We are currently elucidating their functions and molecular interaction networks in order to clarify the molecular mechanisms underlying cell differentiation, fertilized egg formation, and morphogenesis. In addition, we are advancing spatiotemporal regulation analyses with ensured objectivity using AI-based image analysis.

[7] Kubota Y, Ota N et al. Genes Cell, 2022, 27, 409-420.
[8] Unno T et al. Genes Genom, 2022, 44, 343-357.
[9] Kubota Y, Ohnishi Y et al. Genes Genom, 2021, 43, 553-565.

(3) Elucidation of anti-aging mechanisms and prevention of neurological diseases

Because nematodes have a short lifespan of approximately 20 days and show little individual variation in developmental and aging processes, research using nematodes has led the field of aging and anti-aging studies worldwide. In our laboratory, we are analyzing the roles of extracellular matrix molecules in maintaining feeding function, as well as the effects of sulfur dioxide gas, which is expected to influence mitochondrial metabolism. By using age-related organelle-level changes across various organs and tissues as indicators, these studies aim to elucidate the molecular mechanisms that extend healthy lifespan.
We are also conducting fundamental research aimed at disease prevention using pathological models by screening for genes that alleviate cytotoxicity caused by the APP family, which are major causative factors of Alzheimer's disease. Furthermore, we are advancing integrative analyses that combine findings obtained from model organisms with data science approaches using big data derived from human disease information.

Brain Network Information Laboratory

[KITSUKAWA Laboratory]

Professor
KITSUKAWA Takashi

Research Overview

Our research is conducted with the aim of elucidating the mechanisms of information processing in the brain. Brain function is supported by neural circuits formed by neurons; therefore, if the composition and operating principles of these neural circuits can be clarified, the mechanisms of neural information processing should become apparent. Indeed, through many years of progress in neuroscience, a great deal has already been learned. It is becoming clearer year by year which events specific groups of neurons in different regions of the brain respond to. Different brain regions are responsible for different types of information, such as vision, hearing, and olfaction. This is one of the most significant differences between information processing in the brain and in computers.

If we can clarify in detail what types of neurons exist, where and how they are located, and when and how they become active, the overall structure of neural information processing circuits should gradually come into view. However, neural circuits are extremely complex. A single neuron receives inputs from thousands of different neurons and at the same time sends outputs to thousands of other neurons, making it difficult to experimentally investigate what kinds of processing are actually being performed. How, then, should neural information processing at a fine level be understood? One powerful method is computer-based neural circuit simulation. In this approach, neurons are virtually connected within a computer, and the types of information processing that can emerge are analyzed. In the Brain Network Information Laboratory, we combine neuroscience and computer simulation to pursue elucidation of neural information processing mechanisms.

Research Themes

(1) Elucidating brain rhythm control mechanisms from neural activity in rhythmically running mice

In the brain, rhythmic activity known as brain waves is recorded. These brain wave rhythms may serve as the framework for neural information processing. For example, brain wave rhythms appear to play important roles in memory storage and retrieval. Therefore, if we can clarify how the brain controls these rhythms, the mechanisms of brain information processing should become clearer. Based on this idea, we focused on controlling brain rhythms through movement. Specifically, we trained mice to perform complex continuous stepping movements and searched for neurons that respond to rhythmic aspects of this behavior. As a result, we identified rhythm-responsive neurons in a brain region called the basal ganglia. By describing the activity of these neurons in detail, we are analyzing how the basal ganglia contribute to brain rhythm regulation.

(2) Elucidating brain rhythm generation mechanisms through simulation of basal ganglia neural circuits

Many studies, including those in our own lab, have investigated neural circuits of the basal ganglia and demonstrated the existence of circuits that perform characteristic functions. Among these, we focus on two antagonistic neural circuits – the direct and indirect pathways – which together constitute part of a loop that links the cerebral cortex and the basal ganglia. By reproducing neurons that model these neural circuit groups within a computer, we use simulation to analyze how rhythm-responsive neurons, such as those described above, function within these circuits.

(3) Elucidating neural information representation through neural activity responding to multisensory stimuli

Sensory information such as visual, olfactory, and auditory inputs enters the brain through separate pathways and is ultimately integrated. For this integration to occur, information must be transmitted/received and shared between related brain regions. Therefore, analyzing the response properties of neurons that respond to multisensory information is expected to lead to understanding of the information representation strategies adopted by the brain and the modes of information transfer between regions. Accordingly, we record neural activity from the brains of mice performing multisensory discrimination tasks and analyze how information is represented within the brain.

Computational Structural Biology Laboratory

[TAKAHASHI Laboratory]

Professor
TAKAHASHI Takuya

Research Overview

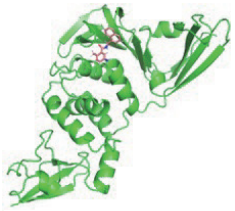
Living systems are composed of tissues, cells, and intracellular organelles, and biological phenomena arise from the diverse functions of a vast number of biomacromolecules. Enzymes and other biomolecules regulate complex biological reactions by adopting specific three-dimensional structures. The fundamental information determining these structures is encoded in DNA as nucleotide sequences.
Recent advances in the analysis of DNA sequences and protein structures have led to the accumulation of large amounts of primary sequence and three-dimensional structure data. As a result, bioinformatics has rapidly developed in areas such as structure–function prediction.

Research Themes: Linking Structural Information to Biological Function

Our laboratory aims to elucidate how three-dimensional structures are formed from primary sequence information and how their functions emerge. The applications of this research are wide-ranging, including drug discovery, drug delivery system design, functional protein design, and the elucidation of transcription mechanisms.
To achieve these goals, we employ a variety of approaches, including physicochemical theories based on experimental data, informatics methods such as database analysis, molecular simulations, and free energy calculations. We also utilize external supercomputers for large-scale computations.
The main research topics are as follows:

1) Analysis of protein–drug interactions using large-scale MD simulations and AI

We perform large-scale molecular dynamics (MD) simulations based on the VcMD method, an extended ensemble approach, to predict binding structures (binding sites) and binding affinities between target proteins, such as SARS-CoV-2 PLpro, and drug molecules (e.g., the inhibitor GRL0617).
Because these simulations generate enormous structural datasets, we analyze them using AI techniques, including machine learning methods such as t-SNE and DBSCAN. This allows us to investigate multiple binding modes and the contributions of loosely bound states to binding affinity.
We are also conducting virtual screening using generative AI tools (e.g., DiffDock) to efficiently identify promising drug candidates.



SARS-CoV-2 PLpro & GRL0617

2) Elucidation of drug delivery systems

Drugs must permeate biological membranes to reach their target sites within cells. We evaluate drug stability in micelle-based drug delivery systems using steered MD simulations and the WHAM method to calculate free energy changes.

3) Analysis of biological phenomena based on free energy calculations

In addition to computationally expensive large-scale MD simulations, physicochemical methods exist to evaluate intermolecular binding strengths. We employ a method that combines small-scale MD simulations with statistical mechanics of liquids to calculate binding free energies.
Using this approach, we analyze systems such as PLpro, botulinum toxin complexes, and diphtheria toxin complexes to evaluate complex stability and validate our methodology.

4) Protein structure formation and transcription mechanisms

Research on intrinsically disordered proteins (IDRs) has advanced in recent years. For example, phosphorylation of IDR regions in transcription factors has been shown to regulate DNA binding through the formation of self-inhibitory structures.
Our laboratory focuses on the TGIF1–DNA system and uses large-scale simulations with the VcMD method to elucidate phosphorylation-dependent structural changes and protein–DNA interactions.

5) Hydration dynamics and biomolecular structure/function

Understanding interactions between water and biomolecules remains a fundamental challenge. Since direct observation of individual water molecules around proteins is difficult, we use MD simulations to investigate hydration dynamics theoretically.
For example, organisms in cold environments maintain viability through antifreeze proteins that bind to ice crystal surfaces and inhibit their growth. Designing proteins with enhanced antifreeze activity has potential applications in organ preservation and food science.
Our laboratory analyzes the structure and dynamics of surrounding water to clarify these mechanisms and also develops in-house analysis programs.

Biomolecular Network Laboratory

[TERAUCHI Laboratory]

Professor
TERAUCHI Kazuki

Research Overview

The Biomolecular Network Laboratory aims to elucidate the mechanisms by which biological systems are regulated through the functions and interactions of biomolecules within cells. Using photosynthetic microorganisms, primarily cyanobacteria and photosynthetic bacteria, as model organisms, we investigate the molecular mechanisms underlying environmental adaptation, circadian clocks, and photosynthesis.

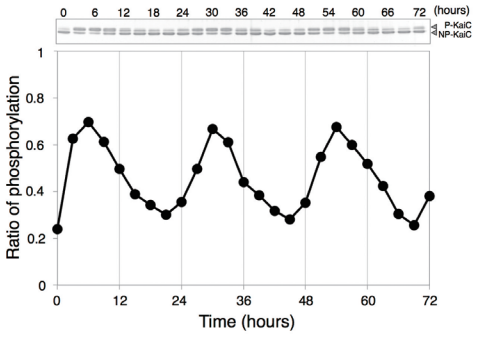
Research Themes

(1) Circadian clock

Circadian rhythms are approximately 24-hour oscillations in gene expression and physiological activities observed in nearly all organisms on Earth. Cyanobacteria, despite being prokaryotes, possess an intrinsic circadian clock that enables them to synchronize cellular activities with the Earth's day–night cycle, making them the simplest known organisms with a circadian timing system. Our laboratory aims to elucidate the molecular mechanisms of circadian clocks using an in vitro reconstitution system composed of the three clock proteins KaiA, KaiB, and KaiC.

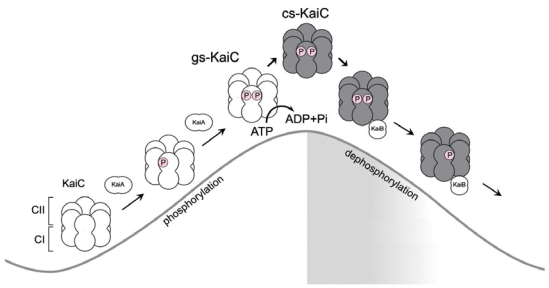
(2) Environmental responses of photosynthetic organisms

Cyanobacteria inhabit a wide range of environments across the globe and exhibit remarkable adaptability to changing environmental conditions. We seek to clarify the molecular mechanisms underlying this adaptability. Because light is a critical environmental factor for photosynthetic organisms, cyanobacteria possess diverse light-sensing and light-responsive systems. In addition, some cyanobacteria thrive in anaerobic environments such as paddy fields and estuarine sediments. We are also investigating the molecular basis of adaptation to low-oxygen conditions.



(3) Photosynthesis

Photosynthesis is a multistep photochemical process that converts solar energy into chemical energy. Having existed for more than three billion years, it is one of the most fundamental biological processes supporting life on Earth. Despite significant technological advances, humanity has yet to develop an energy conversion system that surpasses the efficiency and sophistication of photosynthesis. Our laboratory investigates the reaction mechanisms and evolutionary origins of photosynthesis using primitive photosynthetic organisms, including cyanobacteria and photosynthetic bacteria, as model systems. We study the structure and function of pigments and proteins involved in photosynthesis, as well as experimental evolutionary approaches aimed at reconstructing ancestral photosynthetic systems.



Biological Computation Laboratory

[TOGASHI Laboratory]

Professor
TOGASHI Yuichi

Research Overview

Our goal is to theoretically elucidate the mechanisms by which living systems process information: in other words, the principles of "computation" performed by biological systems. Individual molecular machines operating within cells can themselves be regarded as elementary devices for information processing. Likewise, the behavior of ecosystems can be viewed as collective information processing at the population level. By focusing on the underlying physical principles of phenomena across different hierarchical levels from microscopic to macroscopic, we aim to achieve an integrated understanding through mathematical models that are as simple and transparent as possible.

Research Themes

Although a wide range of objects and phenomena can be considered targets within the broad concept of "information processing" or "computation," we place particular emphasis on the following topics.

(1) Relationship between structural dynamics and function of nucleic acid–protein complexes

When considering molecules responsible for information processing within cells, nucleic acids are among the first to come to mind. Many proteins also act as molecular machines on nucleic acids. Their functions are dictated not only by static structures: motions and mechanical properties are also considered to play important roles. Accordingly, we conduct research on the structural dynamics of nucleic acid molecules and nucleic acid-protein complexes, primarily using molecular dynamics simulations. For example, chromatin structure within the nucleus affects gene expression through processes of information search and readout. That is, DNA can be regarded not merely as an information carrier but as part of an information-processing machine. From this perspective, we are advancing mathematical modeling studies of chromatin structural dynamics.
In related work, we also examine the effects of chemical modifications on the mechanical properties of DNA and nucleosomes. Recently, we have focused on translation initiation mechanisms in the ribosome, evaluating interactions between RNA strands and between RNA and proteins, as well as developing methods for such analyses. We are also working on improving computational efficiency and speed of simulations through coarse-grained models.

(2) Collective motion and self-organization in cell populations and living systems

Entities that move autonomously are collectively referred to as "active matter." When large numbers of active matter units aggregate and interact locally with nearby entities, ordered collective motion – such as long-range alignment of movement – can emerge spontaneously. Such collective behavior is observed in many biological systems. For example, flocks of birds and schools of fish can be observed in everyday life. Similar phenomena also occur at more microscopic levels, such as cell migration. In particular, collective cell movement enables self-organization of larger-scale structures and is essential for tissue formation and morphogenesis. Using such phenomena as examples, we attempt to reproduce collective motion and structural self-organization processes using theoretical models and computer simulations, with the aim of elucidating the rules underlying these behaviors.

(3) Minorities and small numbers in chemical reaction systems, cell populations, and ecosystems

Cellular behavior is not governed by majority rule, but is strongly constrained by genes encoded in DNA, which exist as a very small number of molecules. Since we first demonstrated that small numbers or low densities of molecules in catalytic reaction systems can induce nontrivial phase-transition-like phenomena, we have continued to consider the significance of small numbers of molecules in biological systems. Similar issues arise for minority cell populations within tissues or organisms. For example, experiments have reported the existence of "leader cells" that guide the collective migration of cell populations. Using simple mathematical models, we investigate the relationship between leader properties and collective behavior, as well as whether leaders can be detected from observed group behavior. Furthermore, we focus on phenomena driven by minority individuals in ecosystems and societies, aiming to extract mathematical structures common across hierarchical levels – that is, independent of specific physical realizations such as actual molecules.

(4) Problems concerning heat and temperature in crowded intracellular environments

In recent years, reports have suggested that intracellular temperature is not uniform – for example, that the nucleus may be at a higher temperature than the cytoplasm – sparking ongoing debate regarding the validity and causes of such observations. This issue cannot be ignored from the perspective of cellular function regulation. However, direct observation of heat transfer processes within cells is difficult due to limitations in spatiotemporal resolution. As a complementary approach to experiments, we have begun attempts to clarify aspects of heat transfer by performing molecular dynamics simulations of models that mimic intracellular environments. Because many biological macromolecules undergo structural changes or phase transitions near ambient temperatures, we also examine latent heat associated with these transitions and changes in thermal conductivity.

(5) Improvement of microscopic image data analysis methods

In collaboration with experimental researchers, we analyze single-molecule fluorescence imaging data. More recently, we have also been working on automation and labor-saving approaches for three-dimensional electron microscopy images using machine learning-based image processing, as well as state estimation through combination with mechanical models.

Plant Molecular Physiology Laboratory

[FUKAO Laboratory]

Professor
FUKAO Yoichiro

Research Overview

Plants are unable to move from the place where they are rooted. Consequently, they are constantly exposed to various environmental stresses and have evolved diverse strategies to cope with such stresses. In our laboratory, we aim to elucidate the molecular mechanisms underlying stress tolerance in plants exposed to environmental stresses such as deficiencies of essential minerals and plant diseases. We are also conducting research on the scientific elucidation of grafting and on the use of grafting technology to avoid environmental stresses and enable stable crop production.

Research Themes

(1) Elucidation of zinc homeostasis maintenance mechanisms in plants

Plants absorb almost all essential minerals from the soil. Therefore, mineral-deficient soils reduce crop yield. Zinc is deficient in approximately 50% of cultivated land worldwide. Our laboratory is particularly focused on elucidating the mechanisms that maintain zinc homeostasis. In recent years, integrated omics analyses combining quantitative proteomics and microarray analyses conducted in our laboratory have suggested that, in plants sensing zinc deficiency, the expression of various peptides is induced and contributes to zinc deficiency tolerance and maintenance of zinc homeostasis. Until now, plant zinc homeostasis mechanisms have been understood mainly through elucidation of the functions of transcription factors and zinc transporters; however, it has been shown that peptides play an important role as signaling molecules between organs and tissues.

(2) Scientific verification of graft establishment

Grafting is an agricultural technique indispensable for the cultivation of fruit trees and vegetable crops. Although grafting has been developed in Japan, sufficient scientific verification studies have not yet been conducted. To further advance grafting technology, we are conducting basic research aimed at elucidating the mechanisms by which grafting is successfully established, as well as research to apply the knowledge obtained from these studies to actual crop production.

(3) Elucidation of biological membrane functions in plant environmental stress tolerance

The membrane surrounding cells senses external stimuli and changes and transmits signals into the cell. Scattered throughout this cell membrane are minute lipid-protein aggregation units known as nanodomains. It has become clear that nanodomains change their dynamics in response to external stimuli and regulate the activity of proteins localized within them. Membranes surrounding intracellular organelles have also been shown to be important for the expression of organelle functions when plants are exposed to stress. By elucidating the functions and roles of biological membranes in plants using *Arabidopsis thaliana* and *Marchantia polymorpha*, we aim to deepen understanding of plant environmental stress tolerance.

(4) Analysis of regulatory mechanisms of autophagy activation and degradation target selection in plants

Autophagy, a process that degrades intracellular components, is induced in response to various environmental stresses. This process plays an important role in plant growth under stress conditions. We have discovered that portions of chloroplasts are selectively degraded by autophagy when plants are grown under phosphate deficiency together with excess nitrogen. We are working to elucidate how autophagy is activated and how specific targets are selected. Through these studies, we aim to advance understanding of how plants respond to environmental stress.

Bioinformatics Course

Life Systems Design Laboratory

[HIMENO Laboratory]

Associate Professor
HIMENO Yukiko

Research Overview

The heart acts as a pump that circulates blood throughout the body by synchronizing the contractile force of billions of cardiomyocytes. Each individual cell that makes up the heart also has its own distinct role. For example, ventricular cardiomyocytes that form the ventricular wall (Figure 1) possess well-developed contractile fibers that appear as striations, and they are capable of generating strong contractile force along the direction of these fibers. In contrast, sinoatrial node pacemaker cells isolated from the pacemaker region located at the boundary between the right atrium and the vena cava (Figure 2) exhibit rhythmic electrical activity known as automaticity, which determines the heartbeat rhythm of the entire heart. In this way, diverse cells with different characteristics cooperate to exert pump function as a single organ. Underlying this cooperation is close intercellular communication mediated by electrical signals. By viewing life activities as a system composed of multiple hierarchical levels and expressing their mechanisms through models, we aim to propose new forms of life for the future.

Research Themes

(1) Representing cellular functions using mechanistic models (physiome)

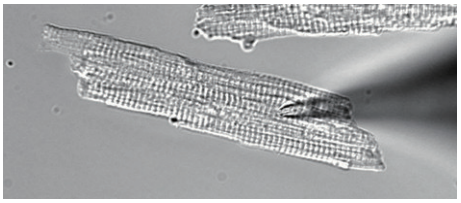
Based on experimental data obtained through electrophysiological and other means, we describe and integrate the relationships observed in experiments using ordinary differential equations to construct mathematical models that reproduce physiological phenomena observed at the cellular level, and analyze their underlying mechanisms. In addition, we develop simulators that account for metabolism, including the balance between energy supply and consumption, which serves as the source of cellular activity.

(2) Understanding bodily functions as systems (systems biology)

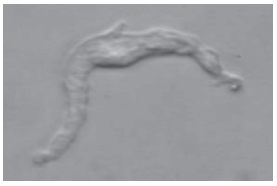
We refine the constructed mathematical models using multimodal biological data that have become newly accessible through advances in information technology. Furthermore, by personalizing mathematical models using genetic information and biological measurement data obtained from individuals, we create biodigital twins in virtual time and space, and perform simulations to predict the effects of treatment, drug administration and rehabilitation individually.

(3) Contemplating the mechanisms that support life processes (ELSI: Ethical, Legal, and Social Issues)

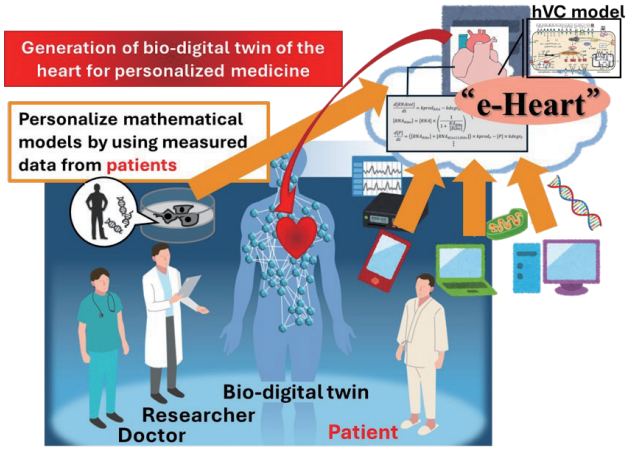
Rapid advances in science and technology in the life sciences are poised to substantially transform the very concept of life itself. In dialogue with diverse fields, we consider frameworks for comprehensively evaluating health, medicine, and welfare in order to protect each individual life. We aim to design a society in which people with disabilities, aging-related conditions, illnesses, and differences support one another and live together in a more comfortable and inclusive way.



ventricular muscle cell



SA node pacemaker cell



Bio-digital twin

Functional Microbiology and Bioinformatics Laboratory

[INOUE Laboratory]

Lecturer
INOUE Masao

Research Overview

Recent advances in technology have made it possible to decode microbial genome sequences at an astonishing pace. Yet within this vast "treasure trove" of data lie many layers of information that remain unexplored. In my laboratory, we make use of supercomputers to develop analytical methods for deciphering the record of biological evolution embedded in microbial genomes, which spans some four billion years. Building on insights obtained through these computational analyses, we also carry out experiments with the goal of discovering previously unknown microbial functions and genes.

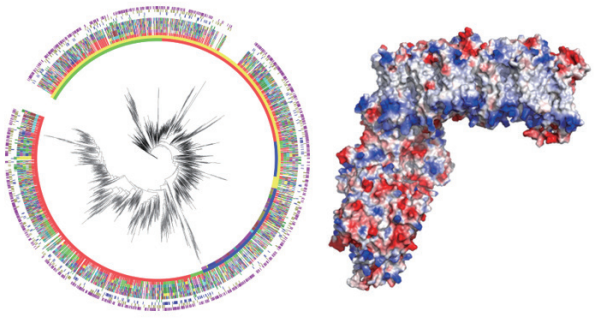
Research Themes

(1) Evolution and functions of primitive energy-metabolism enzymes

How did today's metabolic systems emerge from the metabolism of microbial ancestors on the early Earth? In this project, we focus on so-called primitive energy-metabolism enzymes, such as carbon dioxide-reducing enzymes and hydrogen-producing hydrogenases, which are thought to have been used by life at least four billion years ago. By investigating how their functions have evolved over time, we aim to clarify key steps in metabolic evolution. Because these energy-metabolism enzymes have diversified throughout Earth's history, this research not only sheds light on the origins of life and the transition of metabolic systems, but may also lead to the discovery of novel enzymes or microorganisms with potential applications in addressing environmental and energy-related challenges.

(2) Molecular mechanisms underlying the maintenance and diversification of genetic information in bacteria

DNA metabolism is a driving force of evolution, producing two seemingly opposing outcomes: the preservation of genetic information and its diversification. Bacterial cells lack a nucleus, so how is their genomic DNA folded, and how do DNA metabolic processes take place within the cell? In this project, we focus on the interactions among the DNA-binding proteins found in many bacteria. By reconstructing DNA metabolic processes in test-tube experiments, we aim to reveal how these systems operate.



Integration of evolutionary and structural information of microbial genes.

Stem Cell and Regenerative Medicine Laboratory

[KAWAMURA Laboratory]

Professor
KAWAMURA Teruhisa

Research Aim

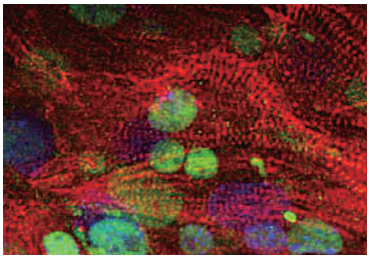
Molecular mechanisms of somatic cell reprogramming and stem cell differentiation, and their application to regenerative medicine

Research Themes

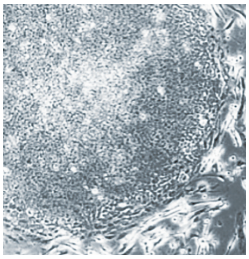
1) Elucidation of regulatory mechanisms underlying reprogramming from somatic cells to iPS cells
2) Establishment of regenerative medicine approaches to induce different cell types from iPS cells or mature cells
3) Generation of genetically modified mice by genome editing and embryo manipulation, and elucidation of mechanisms of cardiac morphogenesis
4) Construction of vision regeneration models using iPS cell technology (R-GIRO research hub)
5) Analysis of cardiovascular regeneration and adult tissue imaging (joint graduate program in collaboration with the National Cerebral and Cardiovascular Center)

Research Overview

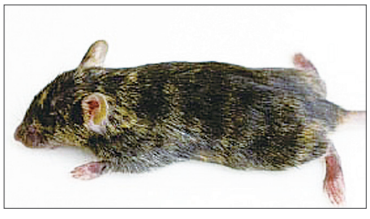
The human body is composed of several hundred types and tens of trillions of cells. However, these were all originally formed from a single totipotent cell that proliferates and changes its properties through the process of differentiation and development. Out of the tens of thousands of human genes, just a few are sufficient to reprogram our mature cells into artificial pluripotent cells, known as induced pluripotent stem (iPS) cells. Furthermore, recent advances in genome editing technology have made rewriting genetic information far easier than previously imaginable. Driven by these remarkable advances in science and technology, our laboratory aims to academically understand the phenomena of reprogramming, differentiation, and development, ensuring the safe and appropriate medical application of these technologies. To date, we have succeeded in identifying cell populations with a high probability of reprogramming during the induction process (iPS cell precursor cells), as well as cardiomyocyte precursor-like cell populations, and have identified various pathways and key molecules involved in reprogramming and differentiation. In addition, through research collaborations both within and outside the university, we have conducted studies on cardiac morphogenesis during the embryonic period, as well as research on the construction of vision regeneration models using retinal differentiation technologies. Furthermore, we have established a joint graduate program with the National Cerebral and Cardiovascular Center, advancing collaborative research on cardiovascular development and regeneration using mice and small fish species. These outcomes (see reference articles 1-8) are expected to contribute to the development of safe and efficient regenerative medicine technologies.



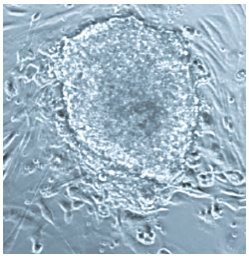
Cardiomyocytes generated from iPS cells



Undifferentiated iPS cells



Chimeric mouse generated from iPS cells



Undifferentiated mouse iPS cells

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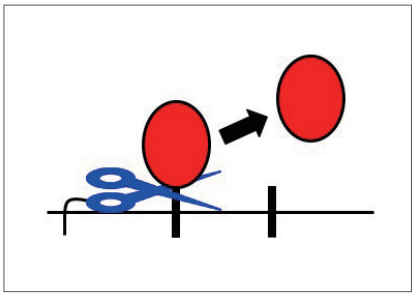
Protein Modification Biology Laboratory

[SHIRAKABE Laboratory]

Professor
SHIRAKABE Kyoko

Research Overview



Living organisms are composed of various organic compounds such as DNA, RNA, proteins, carbohydrates, and lipids. Among these, proteins serve as the primary driving force that gives rise to life phenomena. This is because proteins possess a property not shared by other compounds: their activity and cellular localization can change dynamically through modifications. Among the various modifications that proteins undergo, we focus on ectodomain shedding (referred to below simply as “shedding”), a process in which membrane proteins embedded in the cell membrane are cleaved, and their extracellular domains are released as soluble forms. Shedding can exert a wide variety of effects on organisms depending on the membrane protein that is cleaved. For example, shedding of signaling molecules dramatically expands the locations where those molecules can function, while shedding of receptors for signaling molecules blocks signaling by reducing the number of receptors on the cell surface. In addition, shedding of adhesion molecules disrupts adhesion structures and weakens cell-to-cell adhesion. In other words, shedding is a highly influential modification mechanism that controls not only the function of the membrane protein being cleaved, but also the functions of the cells expressing it. Abnormalities in shedding are known to cause a variety of diseases, including cancer, inflammatory diseases, and neurodegenerative disorders, and elucidating the regulatory mechanisms and functional significance of shedding is indispensable for understanding the pathogenesis of these diseases and for developing therapeutic strategies.

Research Themes

(1) Analysis of the mechanisms determining shedding susceptibility of membrane proteins

The enzymes responsible for shedding have low substrate specificity, and no similar amino acid sequences are found at the cleavage sites of shedding-susceptible membrane proteins. Therefore, we perform proteomic screening of shedding-susceptible membrane proteins and aim to elucidate the molecular mechanisms that determine shedding susceptibility through comparative analyses of these proteins.

(2) Elucidation of the functional significance of shedding

Through our previous studies, we have demonstrated that there are multiple membrane proteins whose shedding susceptibility switches depending on the presence or absence of alternative exons. To clarify what functional significance this regulation of shedding susceptibility by alternative splicing has, we conduct analyses using fluorescent reporters that monitor alternative splicing and exon-specific conditional knockout cells.

(3) Analysis of the mechanisms determining susceptibility to intramembrane proteolysis within transmembrane domains

After shedding, many of the membrane-anchored shedding products are further cleaved within their transmembrane domains. This cleavage within the transmembrane domain is referred to as “intramembrane proteolysis,” but many aspects of its regulatory mechanisms remain unclear. We have obtained preliminary results indicating that there are transmembrane domain sequences with differing susceptibilities to intramembrane proteolysis. Through comparative analysis of these sequences, we aim to elucidate the regulatory mechanisms of intramembrane proteolysis.

Context-dependent Cell Immunology Laboratory

[TACHIBANA Laboratory]

Professor
TACHIBANA Masashi

Research Overview

Although immune checkpoint blockade (ICB) therapy shows remarkable efficacy against various cancer types, its effectiveness is observed in only approximately 20-30% of patients. There is a strong demand for the development of combination therapies to overcome resistance and for the identification of biomarkers that can predict therapeutic efficacy. Myeloid-derived suppressor cells (MDSCs) emerge under tumor-bearing conditions and inflammatory pathological states and promote cancer progression by suppressing antitumor immune responses. In fact, tumor regression is observed in tumor-bearing mice when MDSCs are depleted, and a high abundance of MDSCs has been found in patients who do not respond to ICB therapy. These observations suggest that MDSCs exacerbate cancer progression through mechanisms distinct from those targeted by ICB therapy, indicating that MDSCs are important target cells in cancer immunotherapy. However, many aspects of the molecular mechanisms underlying MDSC differentiation, proliferation, and functional activation remain unclear.
To date, our laboratory has revealed that epigenetic regulatory mechanisms and nutrients such as glutamate play important physiological roles in MDSC differentiation, proliferation, and functional expression, and we are currently working to elucidate the detailed mechanisms involved.

Research Themes

1) Epigenetic regulatory mechanisms in MDSCs
2) Enhancement of the immunosuppressive capacity of MDSCs by glutamate
3) Exacerbation of pneumonia mediated by MDSCs due to aging and disease

Pharmacology Laboratory

[TANAKA Laboratory]

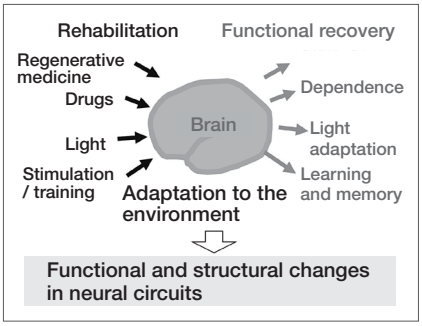
Professor
TANAKA Hidekazu

Research Overview

The activities necessary for sustaining our lives and the mental activities connected to our personality as “humans” are thought to depend largely on precisely constructed neural circuits in the brain. Neurons formed during the process of bodily development extend long neurites, and neural circuits are woven as these neurites encounter one another and adhere in a lock-and-key manner (synaptic connections). Even after neural circuits are established, repetition of parts of this process leads to strengthening and rewiring of synaptic connections. Such mechanisms are presumed to underlie the rich adaptability of the brain, including learning and memory, as well as drug dependence and functional recovery through rehabilitation (see Figure). We seek to understand the molecular mechanisms involved in these processes.

Research Themes

(1) Dynamic changes in the structure and function of neuronal synapses
  (a) Investigating the roles of adhesion molecules that regulate synapse formation
  (b) Exploring how adhesion molecules are involved in neural activity dependent changes in synaptic structure and function
  (c) Clarifying how synaptic structures and synapse related molecules are involved in brain disorders such as depression
(2) Analysis of microglia and adhesion molecules functioning in cerebral infarction and recovery through rehabilitation



Medical Physiology and Metabolism Laboratory

[MUKAI Laboratory]

Professor
MUKAI Eri

Research Overview

Diabetes mellitus is a complex metabolic disease characterized by chronic hyperglycemia and is increasing worldwide. Our laboratory investigates the mechanisms underlying the development of diabetes and explores effective strategies for its prevention and treatment. We focus particularly on pancreatic β-cell function, glucose metabolism, nutritional factors, and exercise-based interventions, using molecular, cellular, and physiological approaches.

Research Themes

(1) Mechanisms of insulin secretion in pancreatic β cells

We investigate the molecular mechanisms regulating insulin secretion in pancreatic β cells, particularly the roles of glucose metabolism and oxidative stress. Our studies focus on how reactive oxygen species (ROS) impair β-cell function and how cells defend against oxidative stress under diabetic conditions.

(2) Food components and natural compounds with glucose-lowering effects

We examine the effects of food-derived compounds and nutrients on blood glucose regulation. Our research includes the identification of natural products that improve glucose metabolism, insulin secretion, or insulin sensitivity.

(3) Anti-inflammatory food components under diabetic conditions

We study inflammation associated with diabetes in pancreatic β cells, muscle, and adipose tissue, and explore food components that suppress inflammatory responses under diabetic conditions.

Health Policy and Management Laboratory

[MORIWAKI Laboratory]

Associate Professor
MORIWAKI Kensuke

Research Overview

Health Technology Assessment (HTA) is a form of policy analysis that evaluates the societal impact of introducing medical technologies such as pharmaceuticals, with the aim of providing scientific evidence to support decision-makers. In particular, evidence regarding the cost-effectiveness of medical technologies (whether they provide value commensurate with their price) has become a major focus of interest. In recent years, HTA agencies have been established in many countries, and evaluations of various medical technologies have been conducted.

Evaluation results are utilized in accordance with each country's healthcare system for decision-making at multiple levels, including clinical-level decisions such as treatment selection, as well as healthcare policy-level decisions such as reimbursement coverage and price setting. In Japan, a full-scale cost-effectiveness evaluation system for medical technologies was introduced beginning in fiscal year 2019, and going forward, it is necessary to promote medical technology assessment through collaboration among the Ministry of Health, Labour and Welfare, industry, universities and other research institutions.

In line with these international trends, our research activities aim to disseminate evidence that supports clinical and healthcare policy decision-making. By making use of statistical analyses based on real-world data and simulations using mathematical models, we evaluate the social value of medical technologies, including their cost-effectiveness.

Research Themes

1. Cost-effectiveness evaluation of medical technologies (malignant tumors, cardiovascular diseases, geriatric diseases, rare diseases, etc.)
2. Evaluation of the additional clinical benefit of medical technologies (network meta-analysis, MAIC, STC, etc.)
3. Methodological research on statistical analysis and model-based analysis for cost-effectiveness evaluation
4. Application of cost-effectiveness analysis in medical decision-making
5. Utilization of real-world data in health technology assessment (claims databases, etc.)
6. Conceptualization and quantification of diverse value dimensions in health technology assessment