Graduate School of Medicine and Pharmaceutical Sciences
(Pharmaceutical Sciences)
University of Toyama
Guide Book

Education philosophy

Graduate School of Medicine and Pharmaceutical Sciences (Division of Pharmaceutical Sciences) provides the curricula of master degree (M.S.) and doctor of philosophy (Ph.D.). The Graduate School collaborates with Institute of Natural Medicine, which is devoted in the study of Natural Medicines with cutting-edge scientific technology, and offers the unique graduate school program for the oriental and western medicine. The aim of our Graduate School is to cultivate creative scientists and advanced experts in the field of Pharmaceutical Sciences and Natural Medicine as well as Clinical Pharmacy through education and training by high level of research works.

Pharmaceutical Sciences Program

Master's course (2-year)

The aim of this course is to cultivate students with a wide range of knowledge and deep expertise, abundant medical creativity, and good comprehensive judgment with respect for human beings, so that it nurtures people who can contribute to the progress of people's health and academic research as researchers, educators, engineers, and specialists who are responsible for the development and dissemination of pharmaceuticals.

The Major of Pharmaceutical Sciences

Ph.D. course (3-year)

The aim of this course is to cultivate creative investigators who generate new knowledge in a subject of academic interest, and future leaders of Pharmaceutical Sciences. The programs are designed to provide the students with greater in-depth knowledge of the subject in Pharmaceutical Sciences, training in critical thinking, and the ability to identify issues accompanying the advance of science and technology. The students study individual research projects and learn also leading-edge knowledge and technique in Pharmaceutical Sciences. The graduate students in this course are expected to work for developing of basic life sciences in academic institutes, new drugs in pharmaceutical and related industries.

The Major of Pharmacy

Ph.D. course (4-year)

The aim of this course is to cultivate researchers or advanced pharmaceutists who are able to extend the field of Clinical Pharmacy, and future leaders of the field. The programs are designed to provide the students with greater in-depth knowledge of the subject in Clinical Pharmacy together with basic Pharmaceutical Sciences, training in critical thinking, and the ability to identify issues accompanying the advance of Medical and Pharmaceutical Sciences. The students study individual research projects learn also leading-edge knowledge and technique in Pharmaceutical Sciences. The graduate students in this course are expected to work for developing of Clinical Pharmacy in academic institutes, and to work as a leader of pharmaceutists in general hospitals. They are also expected to work as a specialist personnel of clinical trial in general hospitals and pharmaceutical industries.

About the Graduate School of Medicine and Pharmaceutical Sciences in University of Toyama (Pharmaceutical Sciences)

SAKAI Hideki, Ph.D.

Director, Faculty of Pharmaceutical Sciences Academic Assembly University of Toyama
Dean, Graduate School of Medicine and Pharmaceutical Sciences
Dean, School of Pharmacy and Pharmaceutical Sciences

The Graduate School of Medicine and Pharmaceutical Sciences in University of Toyama (Division of Pharmaceutical Sciences) is consisted of members of Faculty of Pharmaceutical Sciences and Institute of Natural Medicine. The Graduate School cultivates creative scientists and advanced experts through education and training with high level of research works. Based on a basic research in Chemistry, Physics, Biology, Pharmaceutics and Pharmacology, we promote education and research about "creation of new drugs", "understanding of new functions of drugs", "protection of the human body with drugs" and "application of modern science to the field of Natural Medicine". In education related to Clinical Pharmacy, Department of Hospital Pharmacy in the Toyama University Hospital is cooperating in the cultivation of highly skilled pharmacists. We are also focusing on clinical research in association with the other laboratories in different field of the graduate school.

In the Master's course of Pharmaceutical Sciences specialty, we provide the highest knowledge and technology in the field of Pharmaceutical Sciences for the students, and develop them to be able to push forward their studies by themselves under appropriate planning. Most of graduates of the course are working at academic institutes, pharmaceutical and related companies, government agencies, and general hospitals. Much to our pleasure, they are highly appreciated by the employers for their excellent abilities.

In the Ph.D. course of Life and Pharmaceutical Sciences specialty, the students promote the studies from Master's course and cultivate their creativity. The programs are designed to provide the students with the greater in-depth knowledge of the subject, training in critical thinking, and the ability to identify issues accompanying the advance of science and technology. The students are expected to become researchers who can generate new knowledge in a subject of academic interest and become leaders of Pharmaceutical Sciences in future. Most of graduates of the course are working at academic institutes for developing basic life sciences, at pharmaceutical and related industries for developing new drug, and at medical institutions for developing clinical studies. They are also highly evaluated by their employers.

In the 21st century of Japan, also worldwide, better medical care should be achieved for the aging society. Therefore, we need a lot of excellent professionals who can promote an active part in the cutting-edge of the Pharmaceutical Sciences. I do hope that highly motivated students will enter our Graduate School.

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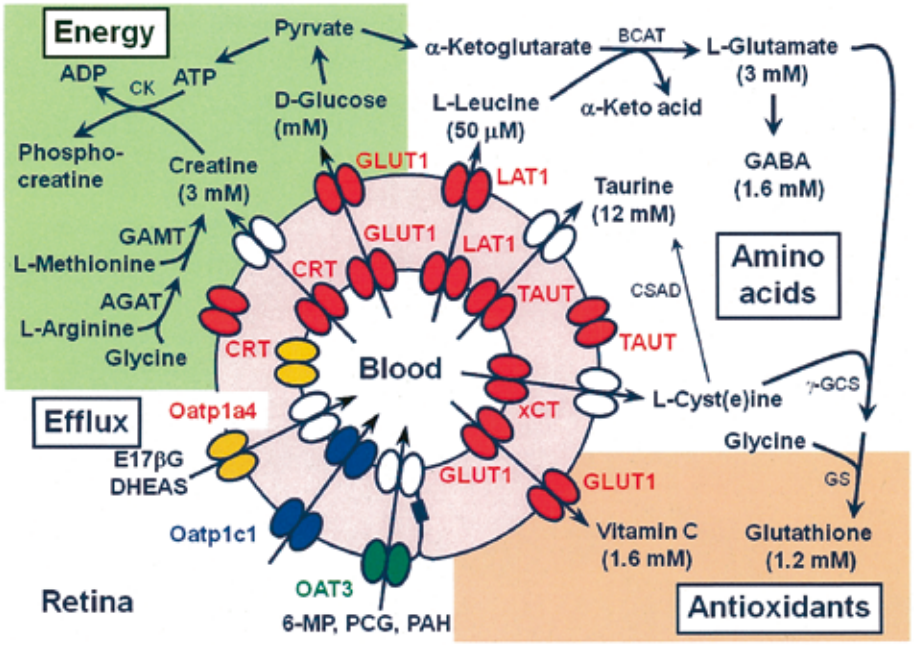
Laboratory of Biopharmaceutics

Professor HOSOYA Ken-ichi, Ph.D.
Associate Professor AKANUMA Shin-ichi, Ph.D.
Assistant Professor TEGA Yuma, Ph.D.

The blood-tissue barriers including blood-retinal barrier form complex tight junctions of capillary endothelial cells and/or epithelial cells. Although these tight barriers prevent the free diffusion of substances between the circulating blood and the neural tissues, blood-tissue barrier efficiently supplies nutrients to the retina and brain and removes endobiotics and xenobiotics from the neural tissues to maintain a constant milieu. We investigate transport mechanism at the blood-tissue barrier, especially blood-retinal barrier to develop strategies aimed at drug delivery to the retina.



Blood-Retinal Barrier Transporters

Publications

1) Kubo *et al.*, Recent advances in drug and nutrient transport across the blood-retinal barrier. **Expert Opin. Drug Metab. Toxicol.**, 14, 513-531 (2018)
2) Shinozaki *et al.*, Comprehensive evidence of carrier-mediated distribution of amantadine to the retina across the blood-retinal barrier in rats. **Pharmaceutics**, 13:1339 (2021)
3) Jomura *et al.*, SLC6A and SLC16A family of transporters: contribution to transport of creatine and creatine precursors in creatine biosynthesis and distribution. **Biochim. Biophys. Acta Biomembr.**, 1864: 183840 (2022)
4) Tajima *et al.*, Freshly isolated retinal capillaries to determine efflux transporter function at the inner BRB. **J. Control. Release**, 343, 434-442 (2022)
5) Yamamoto *et al.*, Newly-established in vitro inner BRB spheroids to elucidate retinal Ang2-linked substance transfer. **J. Control. Release.**, 351, 8-21 (2022)

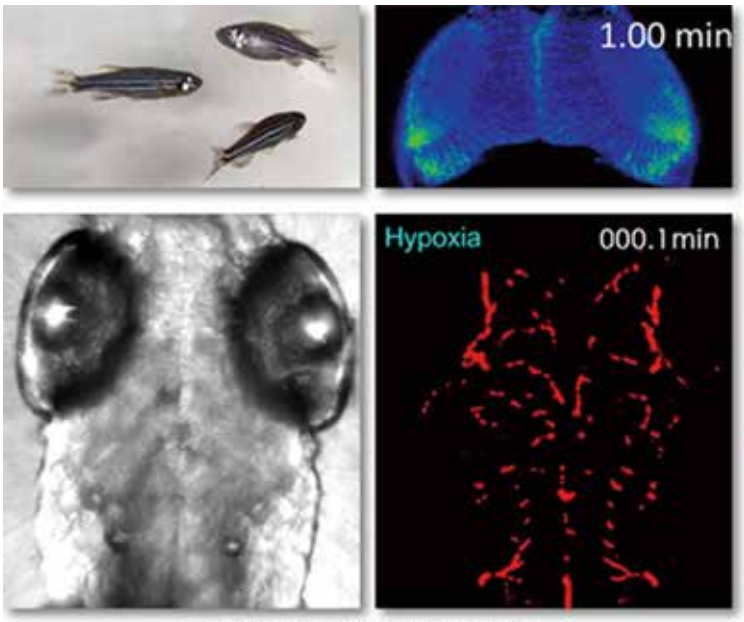
Laboratory of Applied Pharmacology

Professor KUME Toshiaki, Ph.D.
Associate Professor UTA Daisuke, Ph.D.
Assistant Professor SAWAHATA Masahito, Ph.D.

Neurodegenerative diseases such as Alzheimer's disease and Parkinson disease and brain diseases such as stroke are severe diseases to be overcome even in developed countries. However, the cause of these diseases was not uncovered and development of therapeutic drugs is not sufficient. Also, pain and itch are bio-warning signals and important for keeping healthy living, but patients often visit a doctor's office because of severe pain or itch. Analgesia is a goal for therapy in patients with chronic pain such as neuropathic pain, and itch relief is a main aim of treatment in patients with pruritic diseases such as atopic dermatitis. The purpose of our research is to contribute to the treatment of patients suffering neurodegenerative disease, brain disorders, pain or itch.

Main Research Subjects:

1. Elucidation of pathogenesis mechanisms of brain diseases, especially neurodegenerative diseases and brain ischemia
2. Establishment of novel animal models that exhibit the brain diseases and the sensory symptoms, such as itch and pain
3. Elucidation of the mechanisms of pain caused by herpes zoster pain / post-herpetic neuralgia, cancer pain, and anticancer drug
4. Search for cytoprotective, analgesic, antipruritic substances derived from foods and plants



Zebrafish model of brain ischemia


Mouse model of Herpes Zoster


Mouse model of atpic dermatitis

Laboratory of Biorecognition Chemistry

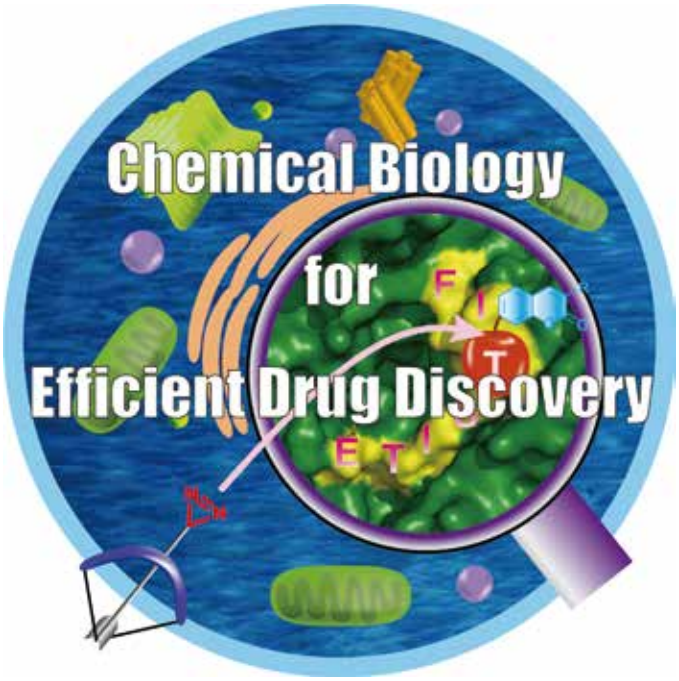
Professor TOMOHIRO Takenori, Ph.D.
Associate Professor TANIMOTO Hiroki, Ph.D.

Mission :

Excellent chemistry reveals new facts of life and that knowledge creates a new way of thinking. Innovative chemical biology tools coupled with advancement of performance in analytical instruments often leads to the discovery of bioactive materials that have never been seen before, and drastically changes the concepts in life science. In order to understand their physiological functions and relationship with diseases, and further to create and optimize new drugs, it is necessary to know the key signal-regulating protein. Despite its importance at the initial stage of drug discovery, the target protein identification of bioactive molecules is generally complicated, and indeed, the target of many drugs currently in use are not known. We have developed high-performance photochemical tools that are able to greatly simplify steps in protein identification process, and specify drug-interacting protein and its binding site in a short period. In addition, our click chemistry enables to convert a variety of biomolecules, DNAs, peptides and carbohydrates, into functional probes in a one-step manner. We hope to reveal off targets that lead to the discover of unexpected biomolecular network.

Main Research Projects :

1) Innovation of high-throughput approach for identifying drug-targets
2) Chemical tools for imaging and specifying biomolecules, and elucidating its binding site within protein
3) Development and application of bioorthogonal coupling reactions, including multicomponent conjugation
4) Rational drug discovery by affinity-based lead optimization



Laboratory of Cancer Cell Biology

Professor SAKURAI Hiroaki, Ph.D.
Associate Professor YOKOYAMA Satoru, Ph.D.
Assistant Professor ZHOU Yue, Ph.D.

Research Interests

Challenge to the unknown signaling networks in cancer cells

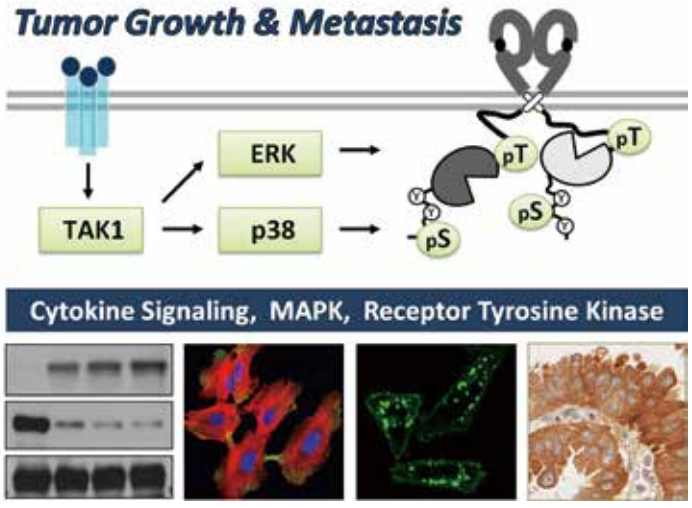
Besides conventional chemotherapy that kills dividing cells, the 21st century has seen the emergence of targeted therapy, resulting from the identification of signaling pathways in cells and their alterations in tumors. We try to identify the unknown signaling networks that regulate cancer cell proliferation, invasion and metastasis, especially by focusing on receptor tyrosine kinases and transcription factors.

Research Topics

1. Study on the molecular mechanisms of tumor progression via inflammatory signaling pathways
2. Study on the activation mechanisms of molecular targets in cancer therapy
3. Study on the intracellular signaling pathways in malignant progression of melanoma

Publications

1. Zhou Y. et al.: Crucial roles of RSK in cell motility by catalysing serine phosphorylation of EphA2. Nat. Commun. 6: 7679, 2015.
2. Tanaka T. et al.: Ligand-activated epidermal growth factor receptor (EGFR) signaling governs endocytic trafficking of unliganded receptor monomers by non-canonical phosphorylation. J. Biol. Chem. 293: 2288-2301, 2018.
3. Yokoyama S. et al.: SOX10 regulates melanoma immunogenisity through an IRF4-IRF1 axis. Canser Res. 81: 6131-6141, 2021.



Laboratory of Chemical Biology

Professor INOUYE Masahiko, Ph.D.
Associate Professor CHIBA Junya, Ph.D.
Assistant Professor OHISHI Yuki, Ph.D.

Chemical biology is a new area of biosciences, of which basis depends on chemistry. Our research group (Laboratory of Chemical Biology) is aiming at exploitation any common ground between life and molecules and at creation of an artificial life through the investigation of intermolecular interactions.

Main Research Projects

Creation of artificial DNAs :

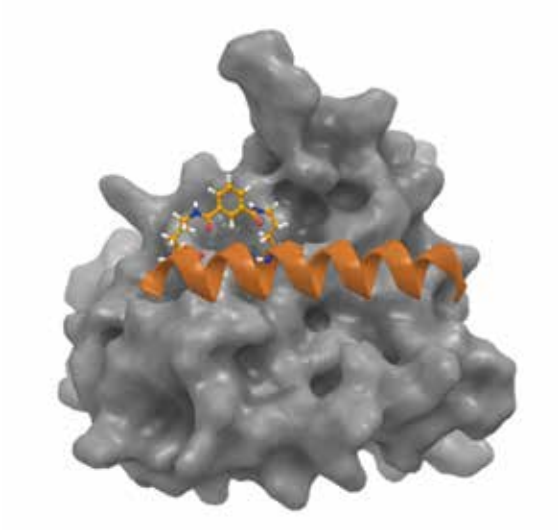
We create a new class of DNA-like oligomers made exclusively of nonnatural nucleosides with four types of nonnatural bases attached to a deoxyribose through *C*-glycoside bond. The artificial DNAs might be applied to a future extracellular genetic system with information storage and amplifiable abilities.

Regulation of protein functions :

A general method was developed for stabilizing α-helices of short peptides with our cross-linking agents. We aim at replacing proteins with the short helical peptides for intracellurar protein-biomolecule interactions in order to resolve unknown biological events at molecular level and to develop next-generation drugs.

Development of saccharide-recognition molecules :

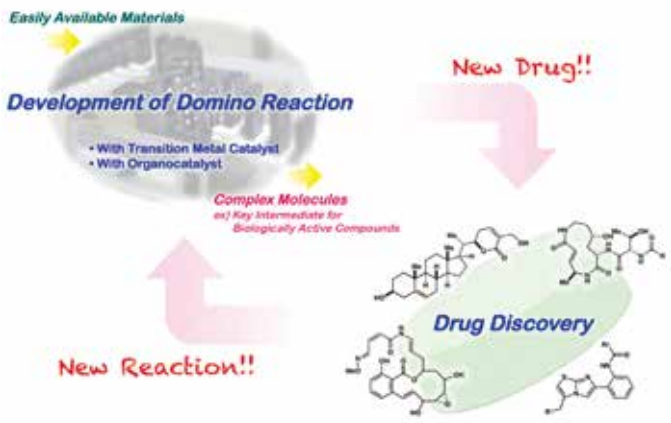
Various ethynylpyridine-based polymers and oligomers were designed and synthesized as conceptually new host molecules for saccharide recognition. We also apply the host molecules to mediators and catalysts for new reactions of saccharides and to materials of biological and industrial interest.



Laboratory of Synthetic and Medicinal Chemistry

Professor MATSUYA Yuji, Ph.D.
Associate Professor SUGIMOTO Kenji, Ph.D.
Assistant Professor TANIOKA Masaru, Ph.D.

Technological innovations represented by Combinatorial Chemistry, High Throughput Screening (HTS), and Computer Aided Design for Drugs (CADD), have enabled the recent medicines production field to reform in various ways. In particular, Combinatorial Chemistry and HTS have sped up the medicines production research dramatically by increasing the number of compounds which one synthetic organic chemist can synthesize at a time. At the same time, it has enabled the researchers to evaluate the effectiveness of the compounds rapidly. Combinatorial Chemistry has been contributing to the compound library's synthesis with diverse ranges of substituents. However, if there is a case having a certain basic skeleton forms of pharmacophore, which is indispensable to exhibit biological activity, and you need to get diversity from the basic skeletons, it is difficult to get it through Combinatorial Chemistry. Also, to be able to obtain the unknown lead compound, there is no choice but to depend on the precedent synthetic method. Furthermore, even if CADD presumes the presence of a lead compound, if there is no actual compound, CADD is a pie in the sky. Thus, it is still necessary to have orthodox synthetic chemistry to be able to apply the new innovations to the production of medicine. As you can see, the significance of synthetic chemistry is increasing everyday in the drug production field. The problem we are facing today involving synthetic chemistry is not only the synthesis of natural resources with complicated structure as it was done in earlier times, but also basing the synthesis on synthetic technology to create compounds with better functions. That is the goal all prominent synthetic organic chemists are heading towards. Due to this current situation involving the production of medicines and synthetic chemistry, our laboratory sets our goals as developing new reactions to bring a form of innovation to synthetic chemistry, and production of medicines that are effective and safe.



Main Research Projects

1) Development of novel reactions utilizing organo- or metal-catalysts
2) Development of new reactions based on intramolecular silyl migration
3) Design and synthesis of new compounds effecting a central nervous system
4) Synthesis and SAR studies of small organic molecules for development of novel medicines for treatment of lifestyle related diseases
5) Synthesis of macrolide natural compounds having anti-tumor activities

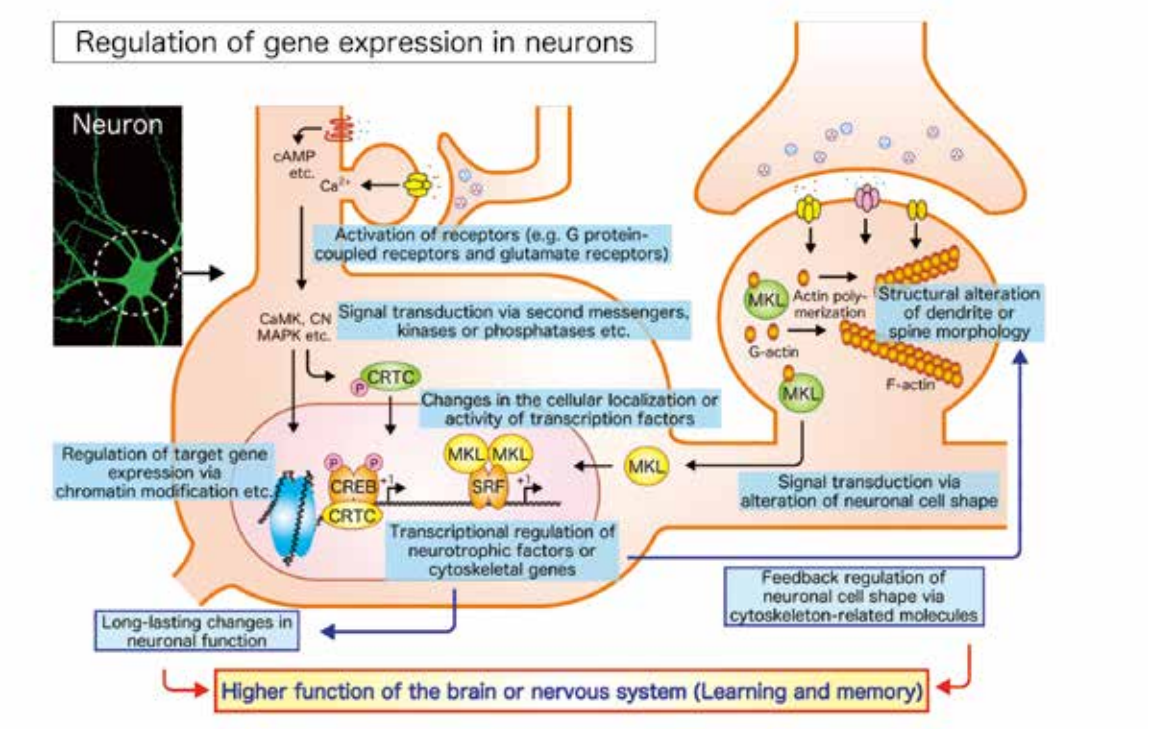
Laboratory of Molecular Neurobiology

Associate Professor TABUCHI Akiko, Ph.D.
Assistant Professor IHARA Daisuke, Ph.D.

Memory formation and behavioral events reflect the integration of several information in the nervous system, which receives a variety of signals from environmental stimuli. The memory consolidation is well established by repetitive training, suggesting that the brain is influenced by environment and experiences. At the cellular level, neurons, the basic units of the brain, are also influenced by extracellar stimuli and the signals propagate from the cytoplasm into a nucleus where gene expression are eventually regulated. Therefore, regulation of gene expression is very ideal for explanation of the long-lasting change in neuronal properties. In fact,

The long-term change in gene expression is required for memory consolidation and maintenance.

Our laboratory speculates that the regulation of gene expression in neurons is an initial, but critical process of the "memory" and the dysregulation of this process is causative of neurological disorders. Thus, we aim at elucidating the molecular mechanism by which gene expression is regulated via extracellular stimuli, which triggers neuronal activity.



Publications (selected):

Tabuchi & Ihara Neurochem Res. (2022)
Gao *et al*. Redox Biol. (2021)
Mizukoshi *et al*. BBRC. (2020)
Fukuchi *et al*. Sci Rep. (2019)
Kaneda *et al*. Sci Rep. (2018)
Fukuchi *et al*. Sci Rep. (2017)
Fukuchi *et al*. J Neurosci. (2015)
Ihara *et al*. Neuropharmacology (2012)
Tabuchi & Ihara Front Mol Neurosci. (2021)
Ishibashi *et al*. J Neurochem. (2021)
Miyata *et al*. BBRC (2020)
Kikuchi *et al*. J Neurochem. (2019)
Ihara *et al*. Cell Struct Funct. (2017)
Kikuchi *et al*. BBRC (2017)
Fukuchi *et al*. J Biol Chem. (2015)
Ishikawa *et al*. J Biol Chem. (2010)

Laboratory of Gene Regulation

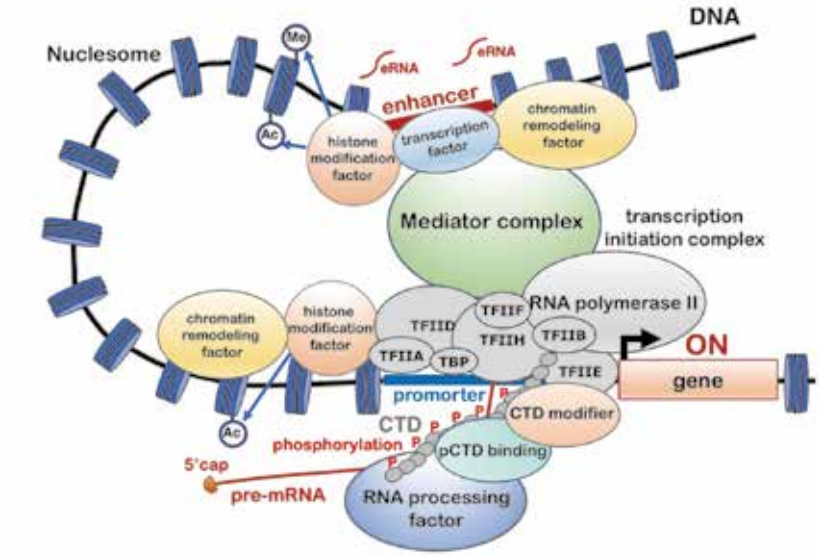
Associate Professor HIROSE Yutaka, Ph.D.
Assistant Professor TANAKA Aki, Ph.D.

Lab Members

Decoding genomes ～ the blueprints of life

Recent studies have revealed that various differentiated tissues and organs can be reprogrammed to become pluripotent stem cells by regulating gene expression. Expression of genetic information stored in the cell nucleus is regulated by transcription and by its intimately related processes such as chromatin modification and RNA processing. We are mainly studying on the following three subjects to aim to decipher regulatory mechanisms of human gene expression and pathogenic mechanisms of human diseases caused by misregulation of gene expression program.

Machinery for mRNA gene expression in eukaryotes



Main Research subjects

1. Study on the molecular mechanism of transcription initiation by RNA polymerase II (Pol II)

We study on the transcription initiation complex consist of Pol II and the general transcription factors through protein modification and structural change.

2. Study on the role of Mediator complex in controlling gene expression

Mediator complex is the huge protein complex, which transduces the regulatory signals from various transcription factors to the transcription initiation complex, has central roles in maintenance of homeostasis and in cellular differentiation. We study on the regulatory mechanism for gene expression by the kinase module of Mediator.

3. Study on the coordinated regulatory mechanism of gene expression through the C-terminal domain of Pol II (the CTD)

The CTD of Pol II is subjected to dynamic phosphorylation during transcription process and serves as a scaffold for various RNA processing factors and chromatin modification factors. We study on the coordinated mechanism of gene expression through regulation of phosphorylation of the CTD, especially focus on the functions of CTD kinases and phosphatases.

Laboratory of Molecular Cell Biology

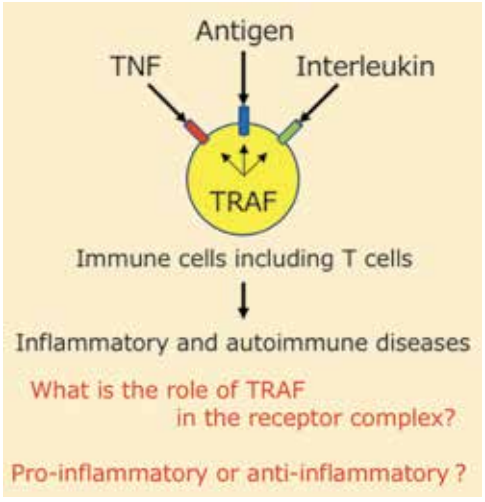
Professor SO Takanori, Ph.D.
Associate Professor MORITA Masashi, Ph.D.
Assistant Professor KUNIISHI Mari, Ph.D.

Understanding the cellular and molecular mechanisms governing immunity and inflammation

Our laboratory investigates how cellular proteins regulate signal transduction, metabolic reactions, and organelle functions and seeks to understand how dysfunction of these cellular events leads to the development of diseases in the immune and nervous system.

Elucidation of novel cytokine receptor signaling in immune cells that is regulated by TRAF and TNF family molecules

The mammalian tumor necrosis factor (TNF) receptor-associated factor (TRAF) is composed of six family molecules that contain characteristic C-terminal TRAF domains. It has been demonstrated that intracellular TRAFs, which associate with a range of receptors expressed by immune cells including T-lymphocytes, control signal transduction via these receptors in both positive and negative ways and in a context-dependent manner. However, the molecular mechanisms by which TRAFs control signaling function of these receptors remain obscure.



It is well known that TRAFs bind to the TNF receptor family molecules such as OX40 and control pro-inflammatory signaling in immune cells. Surprisingly, we have identified a novel anti-inflammatory function of TRAFs in the IL-6-receptor signaling. TRAF2 and TRAF5 bind to the signal transducing receptor gp130 and limit the signaling activity in CD4+ T cells.

We aim to understand novel and uncharacterized signaling functions of TRAFs and TNF family molecules in the context of inflammatory and autoimmune diseases.

Understanding the molecular function and pathology of ABC protein subfamily D

ATP-binding cassette (ABC) protein subfamily D is composed of four family molecules, ABCD1 to ABCD4. We study the molecular mechanisms of substrate transport across membranes mediated by ABCD proteins in peroxisome and lysosome, and also analyze defective transporter activities of ABCD proteins in disease settings. Dysfunction of peroxisomal ABCD1 is responsible for X-linked adrenoleukodystrophy (X-ALD) that is characterized by the inflammation in the cerebrum and the progressive demyelination. We analyze the process of neurodegeneration in the brain that is driven by immune cells lacking expression of ABCD1.

Main research project

1. Elucidation of novel pro-inflammatory cytokine signaling mechanisms regulated by TRAF family molecules
2. Elucidation of regulatory mechanisms of TNFR family molecules in CD4+ T cells
3. Elucidation of molecular pathology of X-linked adrenoleukodystrophy

Laboratory of Medicinal Bioresources

Associate Professor TAURA Futoshi, Ph.D.
Assistant Professor LEE Jung-Bum, Ph.D.

Our research interests are ; 1) the structures, reaction mechanisms and physiological regulation of the enzyme proteins catalyzing natural products biosynthesis in higher plants, and 2) the signal transduction mechanisms involved in the enhancement of secondary metabolites production in response to various external stimuli in plant cells. We attempt to understand the physiological, biochemical and molecular regulation of plant secondary metabolism for the development of novel methodology to improve the production of useful natural products of pharmaceutical significance (*in vitro* cell culture, catalytically-modified enzyme proteins, and transgenic plants).

At present, special attention is focused on the elucidation of signaling pathway of jasmonic acid, a plant hormone derived from fatty acid which evokes the biosynthesis of various defense-related natural products. We study how plants perceive and respond to this external signal by modifying their cell physiological programs to produce diterpene and sesquiterpene compounds. We have identified a new molecular network for Ca^{2+} signal transduction in plants which leads to the enhanced production of the plant secondary metabolites. Recently, we have also found that, at downstream these early signaling events, plants respond to the stimulation with jasmonic acid by post-translational modification of plant-specific monomer GTP-binding proteins, Rac/Rop GTPases, followed by the plasma membrane-oriented translocation of these mediators. An attempt is made to 'manipulate' these signaling processes in higher plant cells for the control of natural products biosynthesis employing various transgenic plants.



Left, Seedlings of *Atropa belladonna* germinated under sterilized conditions as the host for transformation experiments ; **Center**, Generation of transformed hairy root tissues from leaf segments of *A. belladonna* by co-expression of root-forming *rol*-cluster with plant Ca^{2+}-cascade related genes ; **Right**, Regenerated young seedlings of *A. belladonna* transformed with Rac/Rop GTPase genes encoding unique monomeric GTP-binding proteins of higher plants.

Laboratory of Synthetic and Biomolecular Organic Chemistry

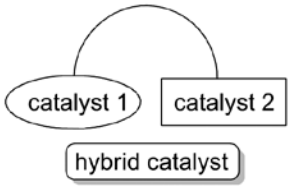
Professor YAKURA Takayuki, Ph.D.
Associate Professor OKITSU Takashi, Ph.D.
Assistant Professor KASAMA Kengo, Ph.D.

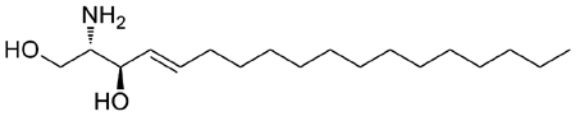
Research Interests

Research within the Yakura (SBOC) Group is focused on the study of green chemistry and synthetic organic chemistry. A portion of this research is directed toward the developing new environmentally benign procedures for the production of pharmaceuticals, flavors and fragrances, and agrochemicals. We are also interested in the development of new synthetic methods and their application to the synthesis of biologically active natural products.

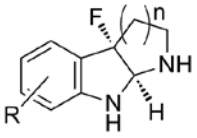
Emphasis is presently placed on the following four research projects.

1) Development of novel environmentally benign catalytic oxidations based on the hypervalent iodine chemistry : to design and synthesize new hybrid catalysts with a new concept.
2) Synthetic studies towards the total synthesis of natural products such as serine palmitoyl transferase inhibitor sphingofungins and anti-trypanosomal actinoallolides using stereoselective rhodium catalyzed carbenoid reactions.
3) Development of the novel approach for the synthesis of sphingosine derivatives and its application for the drug design based on the sphingolipids.





sphingosine

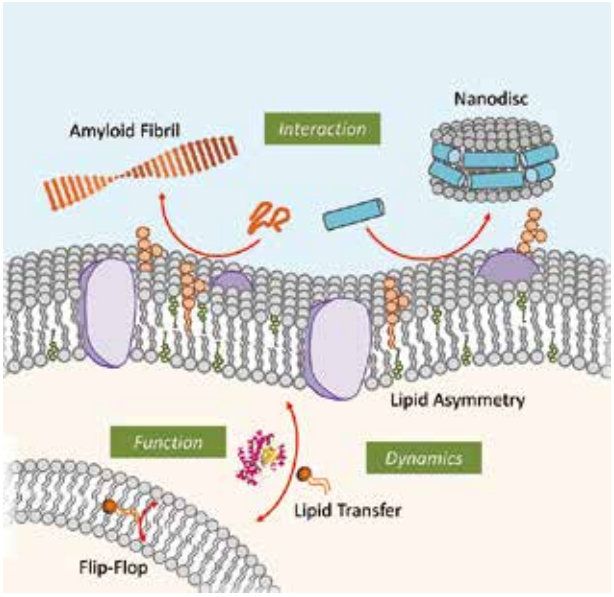


organofluorine compound

Laboratory of Biointerface Chemistry

Professor NAKANO Minoru, Ph.D.
Associate Professor IKEDA Keisuke, Ph.D.
Assistant Professor NAKAO Hiroyuki, Ph.D.

The aim of the research in our laboratory is to develop a new field in pharmaceutical science by elucidating colloid chemical aspects of the heterogeneous, complex system of biocolloids based on the physical chemistry, to construct a rational methodology for developing new drugs harmonious with the complicate biocolloidal systems in our body, and to produce and educate researchers who can put above matters in practice. Especially, we are clarifying several intermolecular interactions on lipid membranes. Our current research projects are listed below.



1. Interbilayer transfer dynamics of lipids

Intracellular and intercellular lipid transport plays an important role in maintaining homeostasis. However, quantitative discussions on lipid dynamics have not been carried out well in cell systems as well as even in cell-free systems. This is because no rational dynamics measurement methods were available. We use phospholipid vesicles (liposomes) to kinetically analyze the intervesicular lipid transfer, using fluorescence resonance energy transfer (FRET), intermolecular excimer fluorescence, and neutron scattering. Currently, we are trying to apply them as assay systems for proteins with lipid transfer activity.

2. Flip-flop of phospholipids

The lipid composition of the plasma membrane is greatly different between the cytoplasmic side and the outer side of the bilayer. Disruption of the plasma membrane asymmetry is directly linked to cell death. In the endoplasmic reticulum, on the other hand, newly synthesized phospholipids are introduced into the cytoplasmic side of the lipid bilayer, and then rapidly transferred (flipped) to the luminal leaflet to maintain the balance of the number of lipids between both leaflets. We are conducting research to evaluate the rate of the phospholipid flip-flop using fluorescence quenching and neutron scattering, and to clarify the factors involved in the promotion of the flip-flop.

3. Nanodiscs

High-density lipoprotein (HDL) is a colloidal particle in the blood responsible for the reverse cholesterol transport system, which transports peripheral cholesterol to the liver. HDLs are produced by the liver and peripheral cells and become disc-shaped initially when produced. These discoidal particles can be also created artificially (which are called nanodiscs) using phospholipids and apolipoprotein A-I (apoA-I), which is a major protein component in HDL, or amphiphilic polypeptides having a similar structure to apoA-I. Nanodiscs are not only physiologically important but are also being applied to membrane protein remodeling tools and drug delivery systems. We are elucidating the structure of nanodiscs using fluorescence spectroscopy, dynamic light scattering, and transmission electron microscopy.

4. Membrane curvature and protein-membrane interaction

Biological membranes greatly change the curvature of the membrane during processes such as membrane fusion. Many proteins have been found to induce or recognize the curvature of the membrane. By using vesicles with different sizes (curvatures), we are evaluating how curvature changes the membrane environment and how it affects the interaction with proteins. It was clarified by the isothermal titration calorimetry that the enthalpy of the membrane increases with the increase in the curvature. We also found that the binding of amyloid β protein to the membrane and amyloid fibrillation are promoted in high curvature membranes. We are conducting research aimed at elucidating the physiological significance of changes in the membrane curvature.

Laboratory of Structural Biology

Professor MIZUGUCHI Mineyuki, Ph.D.
Associate Professor OBITA Takayuki, Ph.D.
Assistant Professor YOKOYAMA Takeshi, Ph.D.

In the living organism, a protein molecule folds into its three-dimensional structure that is encoded in its sequence. Since the function of a protein is closely linked to its structure, experimental determination of the protein structure is a matter of high importance. In order to study the protein structures, we are using nuclear magnetic resonance (NMR) spectroscopy, X-ray crystallography, and neutron crystallography.

The aim of our study is to understand the structure and function of proteins which are fundamentally important in disease onset and progression. Under some conditions, proteins fail to fold correctly, or to remain correctly folded, and this failure can result in a wide range of diseases. One group of diseases, known as amyloidoses, is caused by the deposition of misfolded proteins in a variety of organs. Amyloid fibrils have been the target of increasing attention because of their central role in several human pathologies, including Alzheimer's disease and transthyretin-related amyloidosis. Our research interests also center on the structural bases for the formation of amyloid fibrils by transthyretin using a combination of X-ray crystallography, neutron crystallography and other biochemical methods. In particular, neutron protein crystallography is an experimental method of directly locating hydrogen atoms that are essential for protein's structure and function.

Another aim of our study is to understand the molecular machinery of ESCRT (Endosomal Sorting Complex Required for Transport) system in cell division using X-ray crystallography, NMR and other biophysical methods. Previous studies showed that ESCRT complexes are conserved in archaea and plays a key role in cell division. We determined the crystal structure of archaeal Vps4 in a complex with ESCRT-III, and revealed a unique shape of the interaction to facilitate the function. Currently, we are focusing on the interaction between Vps4 and ESCRT-III proteins in yeast.

We are also working on the medicinal chemistry, including lead discovery, structure-activity relationship study and structure-based drug design. One ongoing project is discovery of a natural product inhibitor of amyloidogenesis of transthyretin. Development of a small molecule, which binds to transthyretin and increases the molecular stability, is an efficient strategy for suppressing the amyloid fibril formation of transthyretin. Another project is drug discovery in cancer. The molecular targets are death-associated protein kinase 1 and bromodomain-containing protein 4.

Laboratory of Pharmaceutical Physiology

Professor SAKAI Hideki, Ph.D.
Associate Professor SHIMIZU Takahiro, Ph.D.
Assistant Professor FUJII Takuto, Ph.D.

In the Laboratory of Pharmaceutical Physiology, we study about ion-transporting proteins in epithelial cells by using physiological, biochemical, and pharmacological techniques. We focus on:

1. Structure and function of transportsome in gastrointestinal cells.
2. Pathophysiological function of ion pumps, transporters, and ion channels in cancer cells.
3. Volume-regulated anion channel VRAC/VSOR.
4. Physiological properties of transient receptor potential (TRP)-related channels.

Our recent publications on these topics are as follows:

Structure and function of transportsome in gastrointestinal cells

1. Inhibition of gastric H^+,K^+-ATPase by new dihydropyrazole derivative KYY-008. (2021) *Biochem. Biophys. Res. Commun*. 567: 177-182.
2. High-resolution label-free 3D mapping of extracellular pH of single living cells. (2019) *Nat. Commun.* 10: 5610.
3. Non-morphogenic effect of Sonic Hedgehog on gastric H^+,K^+-ATPase activity. (2019) *Biochem. Biophys. Res. Commun*. 518:605-609.
4. Inhibition of gastric H^+,K^+-ATPase activity in vitro by dissolution media of original brand-name and generic tablets of lansoprazole, a proton pump inhibitor. (2018) *Chem. Pharm. Bull. (Tokyo).* 66:896-900.

Pathophysiological function of ion pumps, transporters, and ion channels in cancer cells

1. Cardiac glycosides stimulate endocytosis of GLUT1 via intracellular Na^+,K^+-ATPase α3-isoform in human cancer cells. (2022) *J. Cell. Physiol.* 237: 2980-2991.
2. Survival of detached cancer cells is regulated by movement of intracellular Na^+,K^+-ATPase. (2021) *iScience* 24: 102412.
3. Pathophysiological properties of CLIC3 chloride channel in human gastric cancer cells. (2020) *J. Physiol. Sci*. 70:15.
4. Crosstalk between Na^+,K^+-ATPase and a volume-regulated anion channel in membrane microdomains of human cancer cells. (2018) *Biochim. Biophys. Acta Mol. Basis Dis.* 1864:3792-3804.

Molecular candidates for volume-sensitive anion channels

1. The relationship between actin cytoskeleton and membrane transporters in cisplatin resistance of cancer cells. (2020) *Front. Cell Dev. Biol.* 8: 597835.
2. Impaired actin filaments decrease cisplatin sensitivity via dysfunction of volume-sensitive Cl^- channels in human epidermoid carcinoma cells. (2020) *J. Cell. Physiol.* 235: 9589-9600.
3. Volume-sensitive outwardly rectifying Cl^- channels contribute to butyrate-triggered apoptosis of murine colonic epithelial MCE301 cells. (2015) *J. Physiol Sci.* 65:151-157.

Physiological properties of TRP-related channels

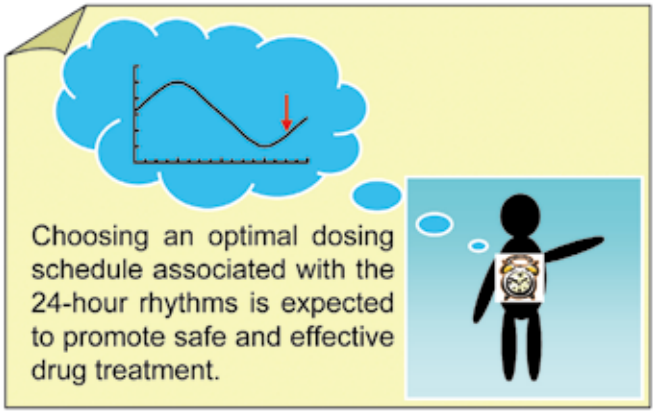
1. Regulation of TRPV1 channel activities by intracellular ATP in the absence of capsaicin. (2022) *Biochim Biophys Acta Biomembr*. 1864: 183782
2. The asparagine 533 residue in the outer pore loop region of the mouse PKD2L1 channel is essential for its voltage-dependent inactivation. (2017) *FEBS Open Bio.* 7:1392-1401.

Laboratory of Medical Pharmaceutics

Professor TO Hideto, Ph.D.
Asistant Professor INOUE Daisuke, Ph.D.
Asistant Professor SETO Yoshihiro, Ph.D.

Our aim is to provide patients with safe and effective medicinal treatment after giving careful consideration to the characteristics of drugs, proposing medication that is able to fulfill its potential as much as possible and to prove the hypothesis. As a methodology to achieve this purpose, we have focused on "Chronotherapy". The biologic functions of most living organisms are organized along an approximate 24-hour time cycle or circadian rhythm. For example, synthesis of cholesterol and cortisol showed clear 24-hour rhythms with a peak at night and a peak in the morning, respectively. Moreover, it has been reported that there are 24-hour rhythms for asthma attacks and morning stiffness in rheumatoid arthritis patients. Chronotherapy is defined as the administration of medications in accordance with biological rhythms in order to optimize therapeutic outcomes and/or control adverse effects. These effects arise from the 24-hour rhythms found in elements of cellular physiology such as the cell cycle, receptors, hormones and enzymes. It has been reported that many drugs such as antitumor drugs, antidepressants, and analgesic drugs show rhythm-dependent differences in their effects and pharmacokinetics.

We have studied the chronopharmacology and chronotherapy of antitumor agents and antirheumatic drugs in animals and in patients. Based on this evidence, we have obtained very interesting findings that facilitate the selection of an optimal dosing schedule associated with the 24-hour rhythms expected to promote safe and effective drug therapy. Further elucidation of these mechanisms is also expected to facilitate the development of new drugs targeting the 24-hour rhythms. Our research theme is shown below.



Research theme

- Translational research for clinical application of chronotherapy
- Application of chronotherapy for individualized medicine
- Development of new products for optimal chronotherapy
- Establishment of a methodology of medicinal treatment based on scientific evidence
- Development of new drugs targeting factors regulating the circadian rhythm of morbid states
- Nasal formulation development and therapeutic application for CNS diseases by hose-to-brain drug delivery system

Laboratory of Plant Resource Sciences

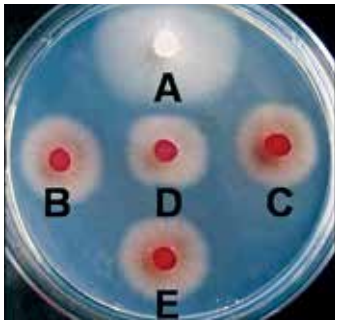
Associate Professor TAURA Futoshi, Ph.D. (concurrent post)
Assistant Professor YAMAMURA Yoshimi, Ph.D.

Medicinal Plant Secondary Metabolism: Diversity, Function and its Evolution

It is widely recognized that higher plant cells are rich sources of a variety of natural products for medicinal use. Numerous attempts have been made to secure and/or stimulate the productivities of these important secondary metabolites of plant cells; such as enhancement of the activities of biosynthetic enzymes of desired compounds with molecular biological and horticultural techniques, cultivation of plants in vitro and manipulation of the primary or secondary metabolism under artificially controlled conditions, and development of protection methods for medicinal plants against various environmental stresses.

1, *Scoparia dulcis* L. produce various unique diterpenes its leaves

2, Capsaicin-rich pepper (*Capsicum* L., Kahatto Ace)



3, Plant pathogen *Fusarium verticillioides*. (A, wild-type; B-E, pathogenic gene-deletion mutants) diterpenes its leaves

Left, *Scoparia dulcis* L. produce various unique diterpenes its leaves; **Center**, Capsaicin-rich pepper (*Capsicum* L., Kahatto Ace); **Right**, Plant pathogen *Fusarium verticillioides*. (A, wild-type; B-E, pathogenic gene-deletion mutants)

Research Topics

1. Elucidation of the biosynthetic machinery of the unique secondary metabolites in medicinal plants
2. Hybrid Breeding, improving the production of secondary metabolites in medicinal plants
3. Characterization of virulence mechanism in pathogenic fungi and establishment of the molecular basis for plant defense mechanism

Lab Members

Yoshimi Yamamura	Assistant Professor	Degree : Ph.D. Research Areas : Plant Physiology, Plant Pathology, Plant Molecular Biology

Laboratory of Clinical Pharmacology

Professor SASAOKA Toshiyasu, M.D., Ph.D.
Lecturer WADA Tsutomu, M.D., Ph.D.

[Research Interests]

The goal of our research is to understand the mechanism of development of type 2 diabetes mellitus (T2DM) and diabetic complications, and to provide a novel strategy for the prevention and treatment of these diseases. We are moving toward the goal by investigating the mechanism of peripheral and central insulin resistance and by examining novel drug effects in the following in vitro and in vivo studies, using transgenic mice and knockout mice.

1. Analysis of mechanisms underlying the development of insulin resistance :

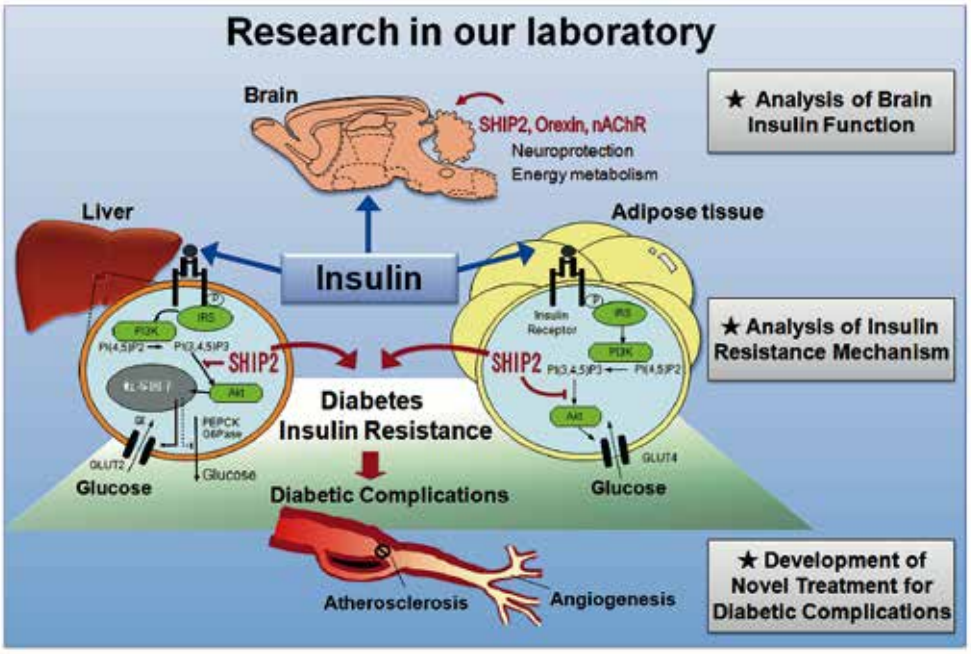
Our laboratory studies the impacts of protein and lipid phosphatases, including SHIP2 that we identified, and adrenal and sex steroid hormones on the development of insulin resistance.

2. Analysis of central action of insulin and hypothalamic neuropeptide for energy homeostasis :

We are investigating how the systemic glucose and lipid metabolism, and energy expenditure are regulated by brain insulin and orexin via humoral and neuronal pathways.

3. Development of novel treatment for T2DM and diabetic complications :

We are conducting studies to develop novel therapeutic approaches for the treatment of T2DM, diabetic complications and diabetes-related neurological disorders including Alzheimer's disease and depression.



Laboratory of Clinical Pharmacokinetics

Professor HASHIMOTO Yukiya, Ph.D.

The clinical pharmacologists (-kinetists) are charged with the obligation to quantify the dose-response relationship (pharmacokinetics and pharmacodynamics) of clinically useful drugs. Clinical pharmacokinetic studies are performed to determine the rational use of medicines according to patient characteristics, such as the disease and genotype of drug metabolizing enzymes (transporters), and to predict the influence of pharmacokinetic drug interactions.[1,2)]

We have recently proposed a new design/analysis approach for the patient-oriented clinical pharmacokinetic trial.[1,3,4)] The routinely treated patients often take drugs once daily or twice daily repetitively. The clinical practice-resembling pharmacokinetic trial may have less ethical problems, and its feasibility can be relatively high.[1)] We have performed the simulation for the exploratory clinical pharmacokinetic trial, in which blood is sampled at two time points corresponding to the peak and trough concentration following repetitive oral drug administration to 10-30 subjects.[1,3)] The simulation study indicated that the oral clearance (CL/F) value is estimated accurately by the naive trapezoidal method and/or by the simple mono-exponential model.[1,3)] Furthermore, we have been surprised that the pharmacokinetics of carvedilol in routinely treated patients with heart failure is significantly different from that in healthy subjects, and the precise mechanism has remained to be resolved.[4)]

Indeed, the pharmacokinetics of drugs in pediatric, elderly, and also middle-aged patients with disease is often and unexpectedly different from that in young healthy volunteers. We think that the pharmacokinetic evaluations for the patient population will be indispensable at least in the near future, and that we therefore can not help developing the limited sampling design and analysis method for each target drug.

References

1) Ishida, K., Kayano, Y., Taguchi, M., and Hashimoto, Y. : Simulation for clinical repeated-dose pharmacokinetic trials applying a peak-and-trough sampling design to estimate oral clearance. *Biol. Pharm. Bull.*, 30 : 2159-2162 (2007).

2) Taguchi, M., Nozawa, T., Kameyama, T., Inoue, H., Takesono, C., Mizukami, A., and Hashimoto, Y. : Effect of *CYP2D6*10* on pharmacokinetic variability of routinely a dministered metoprolol in middle-aged and elderly Japanese patients. *Eur. J. Clin. Pharmacol.*, 59 : 385-388 (2003).

3) Takaai, M., Kayano, Y., Shimizu, T., Taguchi, M., and Hashimoto, Y. : Additional notes on clinical repeated-dose pharmacokinetic trials applying a peak-and-trough sampling design to estimate oral clearance. *Drug Meab. Pharmacokinet.*, 23 : 128-133 (2008).

4) Horiuchi, I., Nozawa, T., Fujii, N., Inoue, H., Honda, M., Shimizu, T., Taguchi, M., and Hashimoto, Y. : Pharmacokinetics of R- and S-carvedilol in routinely treated Japanese patients with heart failure. *Biol. Pharm. Bull.*, 31 : 976-980 (2008).

Laboratory of Pharmaceutical Therapy and Neuropharmacology

Professor NITTA Atsumi, Ph.D.
Assistant Professor IZUO Naotaka, Ph.D.
Assistant Professor ASANO Takashi, Ph.D.

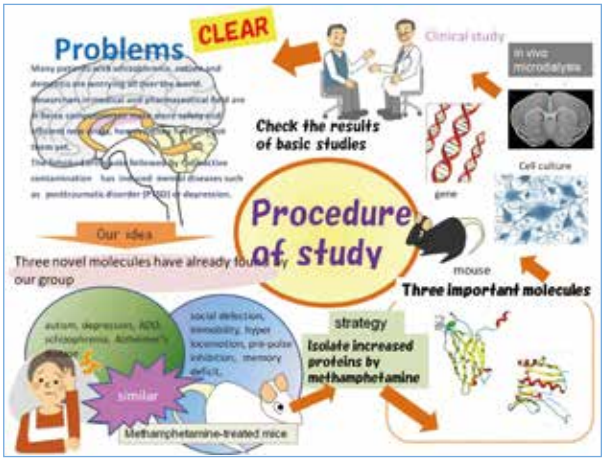
We attempt to clarify the cause of various kinds of mental diseases, such as addiction, schizophrenia, autism, depression, Alzheimer's disease and Parkinson disease. Our final goal of our research projects is establishments of new pharmaceutical treatments for these diseases. Our main projects are shown as below;

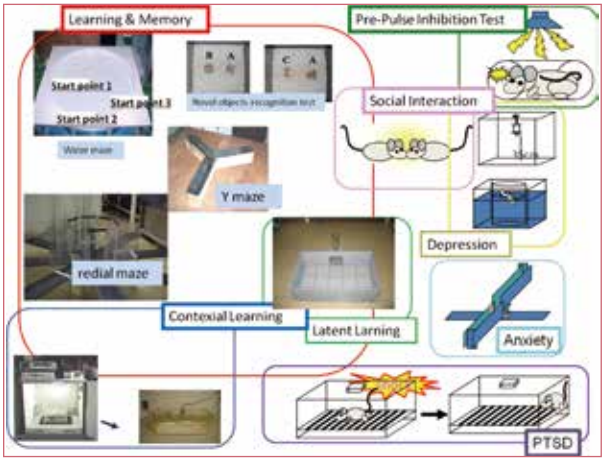
1. Clarify the roles of novel molecules-related psychiatric diseases and drug addiction
   We found novel molecules using by cDNA subtraction methods from the nucleus accumbens of psychostimulant-treated mice. We investigate the physiological activities and roles of the novel molecules using behavioral pharmacological, electrophysiological, and molecular biological methods.
2. Clarify the mechanisms of establishment of nicotine, methamphetamine and THC addiction
   Drug addiction is severe problems over the world. We attempt to clarify the mechanism of establishment of nicotine, methamphetamine and THC to find new prevention and treatment methods.
3. Development of a neuropsychiatric disorder model animal and a cell model, and development of curative medicine.
   To make a new medicine, the animal models of mental diseases are indispensable. However, it is so difficult to create the neuropsychiatric disorder model because we cannot hear the feeling of an animal. Then, we pursued about the genetic factor and environmental factor of neuropsychiatric disorder, and aims at creation of a model animal, and creation of the curative medicine.
4. Pharmaceutical studies
   We propose new systems to supply best pharmaceutical services and education.

We use behavioral, biochemical and molecular methods for the studies for making the diseases' animal models. We expected to rescue the patient from psychiatric and neurological diseases by our research results.

Recent publications

1. Tokutake et al., Cannabinoid type 1 receptors in the basolateral amygdala regulate ACPA-Induced place preference and anxiolytic-like behaviors. ***Neurochemical Res***. 47 (9) 2899-2908 (2022)
2. Kusui et al., Knockdown of Piccolo in the nucleus accumbens suppresses methamphetamine-induced hyperlocomotion and conditioned place preference in mice. ***Neurochemical Res***. 47 (9) 2856-2864 (2022)
3. Chino K et al., Shati/Nat8l overexpression improves cognitive decline by upregulating neuronal trophic factor in Alzheimer's disease model mice. ***Neurochemical Res***. 47 (9) 2805-2814 (2022)
4. Miyanishi H et al., *N*-Acetyl transferase, Shati/Nat8l, in the dorsal hippocampus suppresses aging-induced impairment of cognitive function in mice. ***Neurochemical Res***. 47 (9) 2703-2714 (2022)
5. Miyanishi H, Muramatsu SI, Nitta A. Striatal Shati/Nat8l-BDNF pathways determine the sensitivity to social defeat stress in mice through epigenetic regulation. ***Neuropsychopharmacology***. 46 (9) 1594-1605 10.1038/s41386-021-01033-2 (2021)
6. Nitta A, Izuo N, Hamatani K, Inagaki R, Kusui Y, Fu K, Asano T, Torii Y, Habuchi C, Sekiguchi H, Iritani S, Muramatsu SI, Ozaki N, Miyamoto Y. Schizophrenia-like behavioral impairments in mice with suppressed expression of piccolo in the medial prefrontal cortex. ***J. Pers Med***. 11(7) doi: 10.3390/jpm11070607. (2021)
7. Yuka K, Nishizawa D, Hasegawa J, Uno K, Miyanishi H, Ujike H, Ozaki N, Inada T, Iwata N, Sora I, Iyo M, Yamada M, Kondo N, Won MJ, Naruse N, Uehara-Aoyama K, Ikeda K, and Nitta A. A single medical marker for diagnosis of methamphetamine addiction–DNA methylation of SHATI/NAT8L promoter sites from patient blood. ***Curr Pharm Des***, 26, 1-5; doi: 10.2174/1381612826666200110111703 (2020)



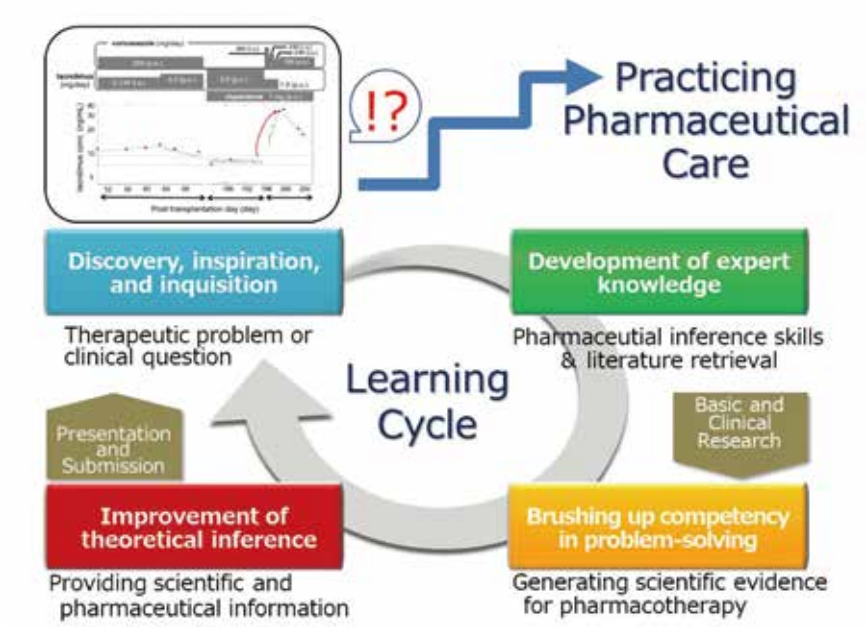


Laboratory of Pharmacy Practice and Sciences

Professor TAGUCHI Masato, Ph.D.

Brushing up clinical inference skills for practicing knowledge and theory-based pharmaceutical care

Pharmacy practice integrates the pharmaceutical sciences with the professional roles of pharmacists. We are mainly focusing on solving the pharmacotherapy-related problems encountered by pharmacists through a pharmacokinetic approach. It includes clinical research in pediatric and elderly patients. Clinical pharmacokinetic study with less blood sampling design and/or modeling and simulation analysis helps compensate for missing clinical evidence to improve the quality of pharmaceutical care for these populations. We also focus on educational research including recurrent programs aiming at fostering special pharmacist in terms of both clinical inference skills and ability to get things done. It will support providing pharmaceutical care service and research activities by local pharmacists.



Research Topics

1) Optimization of drug therapy in pediatric and/or elderly patients based on the development of predictive model for patient's physiological function.
2) Mechanisms of the pharmacokinetic variability in children with congenital heart disease.
3) Exploration of community pharmacy-based drug monitoring and its use for preventing drug-related morbidity.

Publications

1. Mito A. et al.: Effects of concomitant administration of PXR ligand drugs on the anticoagulant effects of warfarin. Biol Pharm Bull. 45: 703-708, 2022.
2. Taguchi M. et al.: Pharmacokinetic variability of caffeine in routinely treated preterm infants: preliminary considerations on developmental changes of systemic clearance. Biol Pharm Bull 44: 69-74, 2021.
3. Tamura R. et al.: Evaluation of the effects of ontogenetic or maturation functions and chronic heart failure on the model analysis for the dose-response relationship of warfarin in Japanese children. Eur J Clin Pharmacol 75: 913-920, 2019.

Laboratory of Integrative Pharmacology

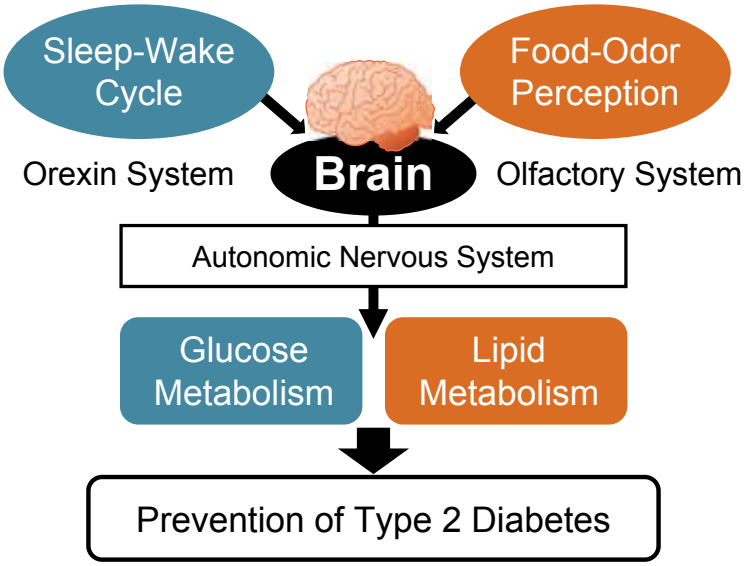
Professor TSUNEKI Hiroshi, Ph.D.

Research Interests:

Glucose and lipid metabolism are regulated by both hormonal and neuronal systems, and the brain plays an important role in the integration of those regulations. Accumulating evidence indicates that the central regulation contributes to prevention of the development of type 2 diabetes and associated disorders. However, no intervention has yet been established, because it is difficult to control the brain functions from outside the body. Therefore, the aim of the research in our laboratory is to develop a new way of promotion of the brain functions to maintain glucose and lipid homeostasis, by focusing on lifestyle improvement. We have already found that daily sleep-wake cycle has the key to strengthen the central regulation of glucose metabolism (particularly through the hypothalamic orexin system), and that food-odor exposure during fasting promotes the central regulation of lipid metabolism in mice. Currently, we are trying to find many more approaches to optimize metabolic functions through the brain and inter-organ network, that can enhance the effect of pharmacotherapy against type 2 diabetes and diabetic complications, including nonalcoholic steatohepatitis, cancer, Alzheimer's disease, and depression.

Recent Publications:

1. Tsuneki et al., Food odor perception promotes systemic lipid utilization. **Nature Metabolism**, 2022;4:1514-1531.
2. Tsuneki et al., Hypothalamic orexin prevents non-alcoholic steatohepatitis and hepatocellular carcinoma in obesity. **Cell Reports**, 2022;41:111497.



Department of Hospital Pharmacy

Professor KATO Atsushi, Ph.D.
Assistant Professor SHINZAWA Kenta, Ph.D.

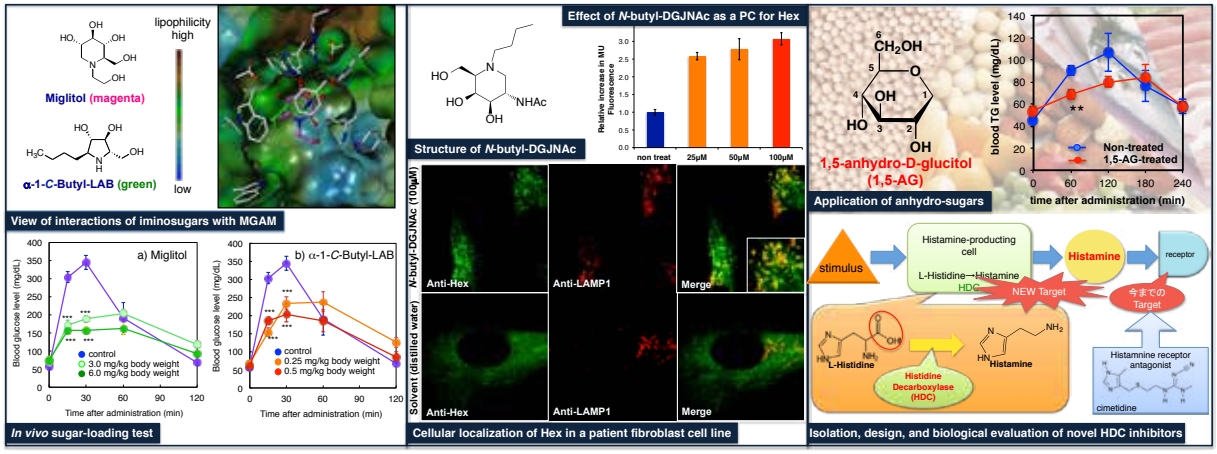
Examples of current projects

1) Iminosugars as potential therapeutic agents

Glycosidases are involved in several important anabolic and catabolic process, such as intestinal digestion, lysosomal catabolism, and post-translational modification, which are closely related to the endoplasmic reticulum (ER) quality control and ER-associated degradation of glycoproteins. Thus, glycosidase-inhibiting iminosugars could have enormous potential applications as biochemical tools and therapeutic agents. These iminosugars can inhibit various glycosidases because of a structural resemblance to their sugar moiety to natural substrates. For example, *N*-hydroxyetheyl-1-deoxynojirimycin (Glyset^{TM}), which corresponds to an α-D-glucose configuration, has been approved as a second-generation α-glucosidase inhibitor to treat type-2 diabetes. *N*-Butyl-1-deoxynojirimycin (Zavesca^{TM}) is an inhibitor of ceramide-specific glucosyltransferase and has been approved for the oral treatment of substrate reduction therapy in type-1 Gaucher disease. The iminosugar derivatives, α-6-*C*-nonylisofagomine, α-1-*C*-nonyl-1, 5-dodeoxy-1, 5-iminoxylitol, and α-1-*C*-octyl-1-deoxynojirimycin are candidates as oral agents of pharmacological chaperone therapy in type-1 Gaucher disease. Our laboratory provides a unique opportunity to find a range of new medicines for different therapeutic areas from compounds of a defined chemical class.

2) Isolation of water-soluble bioactive components from medicinal plants

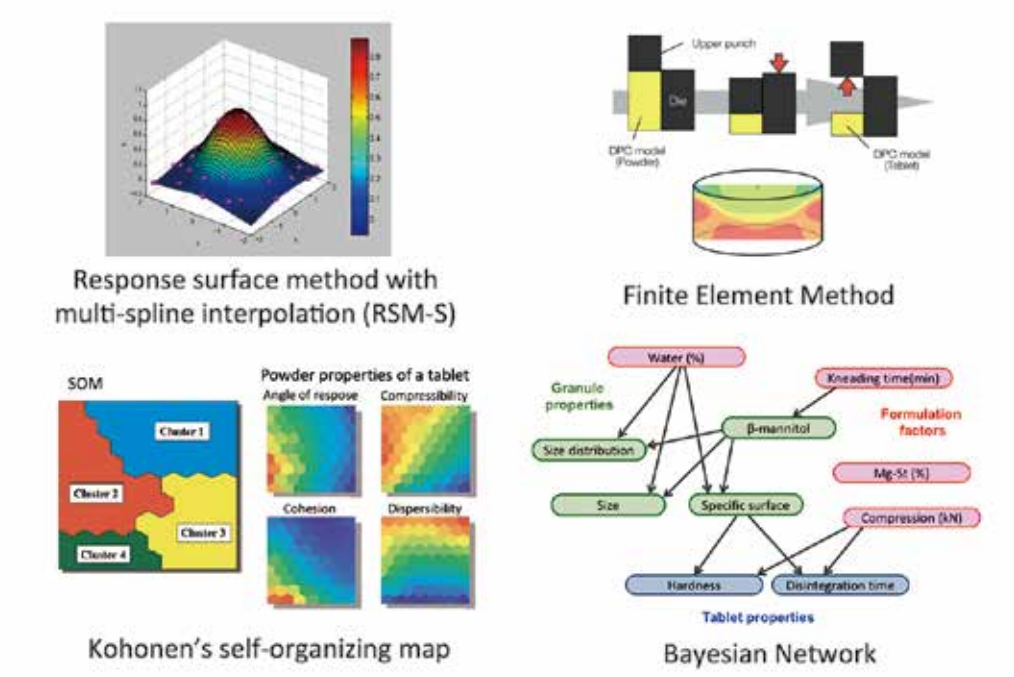
Herbal medicines were often traditionally prepared in water but active compounds soluble in water are often hidden by high concentrations of primary metabolites. Our laboratory has a unique experience and track record in identifying novel bioactive compounds in plant water-soluble fractions that can often fully explain the claimed activities of the plants. We believe that the elusive active components of many herbal medicines reside in the water-soluble extractable material; the failure to understand these components may well explain the variable results obtained for many herbal preparations. The water-soluble components of many food plants and products have also been found by our research to contain novel functional components.



Laboratory of Pharmaceutical Technology

Professor ONUKI Yoshinori, Ph.D.

Pharmaceuticals are supposed to be designed by considering various characteristics (e.g., safety, efficacy and quality). In general, their characteristics are affected by many formulation factors (e.g., physicochemical properties of drug, formulation, and process parameters) in complicated manner. For the development of pharmaceuticals, it is crucial to understand fully the complicated relationships between formulation factors and characteristics and then to optimize their formulations and process parameters. The aim of our lab is to promote the further development of the pharmaceutical technology through the outstanding pharmaceutical researches. Especially, our lab is focusing on establishment of novel technologies for the development of pharmaceuticals based on statistics and computer simulation. Furthermore, our lab is investigating physical properties of pharmaceuticals using cutting-edge technologies including molecular imaging techniques.



Optimization techniques for designing pharmaceutical formulations and manufacturing processes

Research Topics

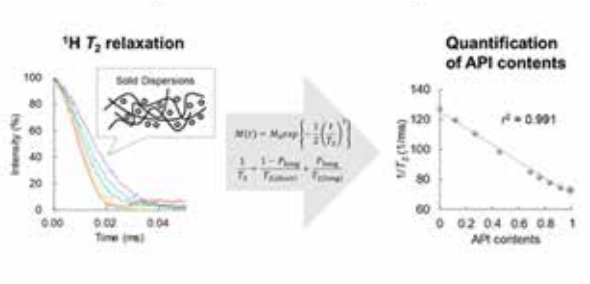
1. Development of optimization techniques for designing pharmaceutical formulations and manufacturing processes
2. Studies on pharmaceutical characteristics using molecular imaging techniques

Laboratory of Pharmaceutical Technology

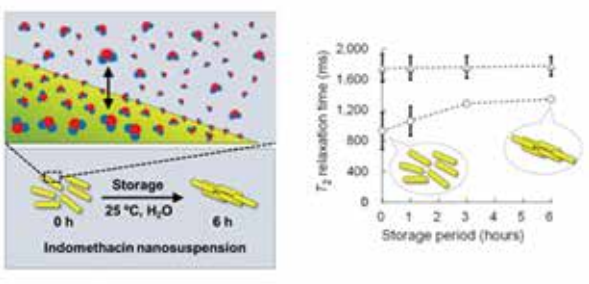
Specially Appointed Associate Professor OKADA Kotaro, Ph.D.

From the viewpoint of assuring the efficacy and safety of pharmaceuticals, it is essential to correctly evaluate the physical properties of the active pharmaceutical ingredients in pharmaceutics. In our laboratory, we are engaged in research on pharmaceutical engineering, which investigates drug formulations from an engineering aspect. In particular, we are researching the physical properties of active pharmaceutical ingredients using relaxation phenomena in nuclear magnetic resonance (NMR). Our previous studies demonstrated that T_1 and T_2 relaxation measurements using a low-field NMR system could evaluate crystalline state in solid dosage form and agglomeration of drug particles in nanosuspension. Bench-top low-field NMR system is specialized for relaxation measurements, which can be completed in a short time, and is expected to be applied to process analytical techniques in pharmaceutical manufacturing.

The crystallinity of an active pharmaceutical ingredient in solid dosage form



Dispersibility in drug nanosuspension



Research Topics

Development of methods for evaluating the physical properties of pharmaceutical products using nuclear magnetic resonance relaxation

1. The crystallinity of an active pharmaceutical ingredient in solid dosage form
2. Dispersibility in drug nanosuspension
3. Miscibility of molecular to nano size in amorphous solid dispersion

Section of Natural Products & Drug Discovery

Professor MORITA Hiroyuki, Ph.D. Associate Professor Suresh Awale, Ph.D.
Assistant Professor KODAMA Takeshi, Ph.D. Assistant Professor NAKASHIMA Yu, Ph.D.

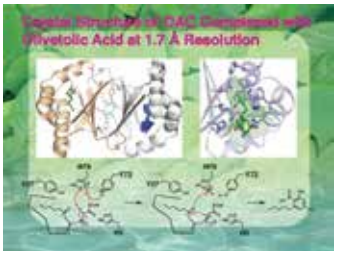
https://www.inm.u-toyama.ac.jp/en/research/natural/

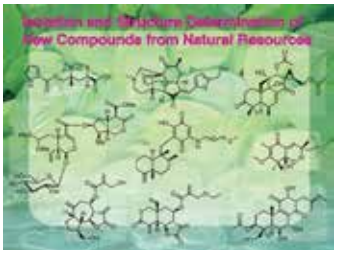
Outline of the research

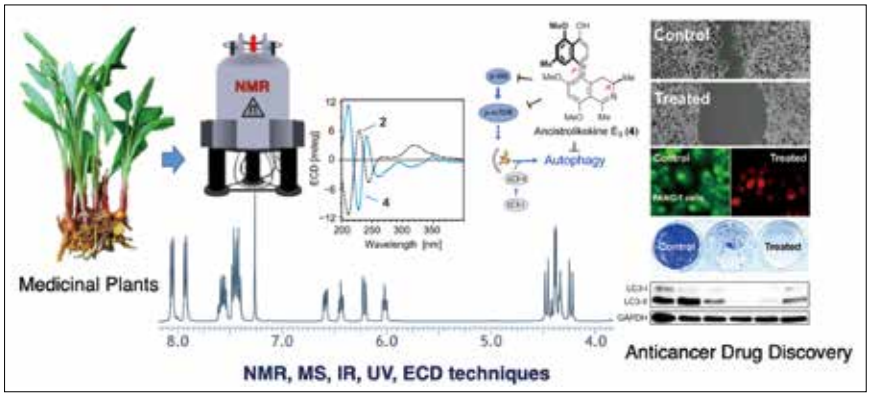
This field consists of two independent units with a research focus on advanced natural products and attendant drug discovery. We utilize the cutting-edge technologies, such as enzyme engineering, x-ray crystallography, NMR spectroscopy, etc. to understand the fundamentals of natural product biosynthesis, the discovery of bioactive compounds, and clarify their molecular mechanism for drug development against various diseases, as mentioned in the primary research focus of each unit.

Research Projects

- Studies on biosynthesis of naturally occurring bioactive compounds
- Structural basis for secondary metabolite enzymes
- Enzyme engineering for novel drug development
- Isolation of bioactive compounds from plants, microorganisms, and marine organisms
- Investigation of Asia's natural resources not fully utilized
- Discovery of natural anticancer agents from medicinal plant resources by employing a novel antiausterity screening strategy
- Chemical investigation of medicinal plants and search for novel bioactive secondary metabolites
- Investigation of the structure-activity relationship of the active natural compounds and their mechanism of action against cancer cell survival pathways
- Discovery of metabolomic biomarkers associated with cancer cells by utilizing FT-NMR and MS strategy







【Keywords】 Natural resources not fully utilized, Medicinal Plants, Marine organism, Microorganism, Active secondary metabolite, Drug discovery and development research, Traditional medicine, Nuclear Magnetic Resonance (NMR), FT-MS, Structure analysis of natural products, Biosynthesis, Enzyme engineering, Structure analysis of proteins, Cancer research, Antiausterity strategy, Mechanism of action, Cancer metabolomics, Biomarker discovery

Section of Neuromedical Science

Professor TOHDA Chihiro, Ph.D. Associate Professor TOHDA Michihisa, Ph.D.
Assistant Professor YANG Ximeng, B.S. Assistant Professor INADA Yuna, Ph.D.

Outline of the Research

"Section of Neuromedical Science" including two units progresses researches aiming at overcoming neurodegenerative diseases and age-related diseases from respective viewpoints. Laboratory of Neuromedical Science conducts a wide range of research, from basic research to clinical research, to find epoch-making therapeutic agents for intractable Neurodegenerative diseases and to elucidate the factors controlling disease states. Laboratory of Consilienceology for Wakan-yaku conducts research based on the originality and the theories of Wakan-yaku (Japanese oriental medicines) to discover new therapeutic concepts for functional psychiatric disorders and heart diseases.

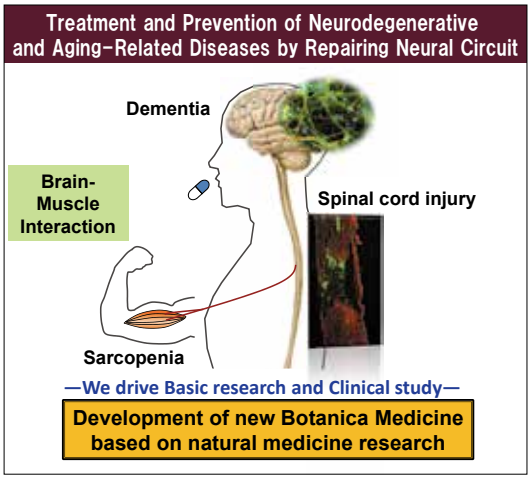
Research Projects

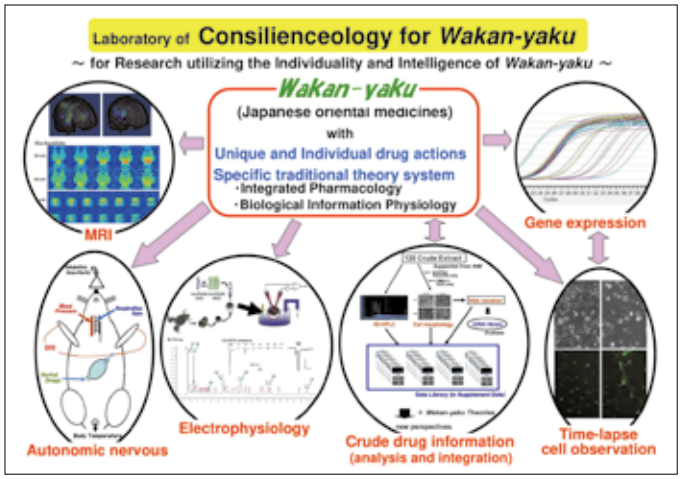
Laboratory of Neuromedical Science
(Professor Chihiro Tohda; Assist. Prof. Ximeng Yang; Assist. Prof. Yuna Inada)

- Elucidation of the molecular mechanism of restoring the neuronal network for homeostasis and/or improvement of neural function.
- Traditional medicine research for developing fundamental therapeutic drugs for Alzheimer's disease, spinal cord injury, cervical spondylosis myelopathy, sarcopenia, and glaucoma.
- Molecular basis of crosstalk between the central nervous system and peripheral organs, which controls neural function.
- Clinical study aiming to develop new botanical drugs and new usage of Kampo formulas.
- Clinical study to analyze factors affecting physical and mental health and to identify biomarkers of well-being.

Laboratory of Consilienceology for Wakan-yaku (Assoc. Prof. Michihisa Tohda)

- Providing evidence for Wakan-yaku theories and supplying new research strategies based on it
- Elucidation of unique effects of Wakan-yaku closely related on physiological reactions and development of ultra-low concentration therapeutic compounds based on the theories
- Novel classification of depression based on the Wakan-yaku theories, elucidation of pathogenic mechanism, and development of new antidepressant drugs
- Development of novel Wakan-yaku prescriptions to prevent "heart failure due to the side effects by anti-cancer drugs" and "fatal recurrent myocardial infarction"





Section of Host Defences

Professor HAYAKAWA Yoshihiro, Ph.D.
Associate Professor WATANABE Shiro, Ph.D.
Assistant Professor SUSUKIDA Takeshi, Ph.D.
Assistant Professor SASAKI So-ichiro, Ph.D.

https://www.inm.u-toyama.ac.jp/en/research/host-defences/

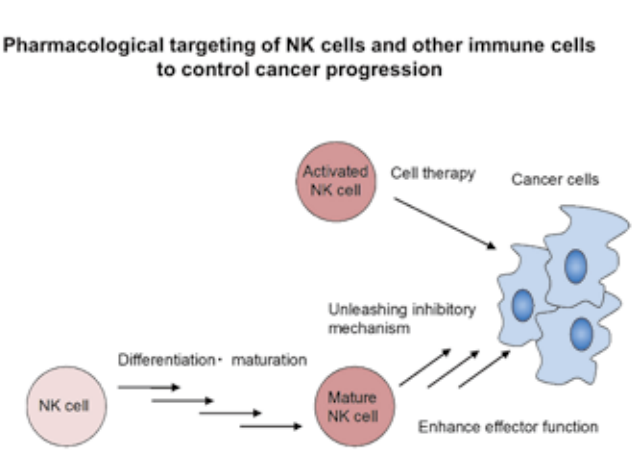
Outline of the research

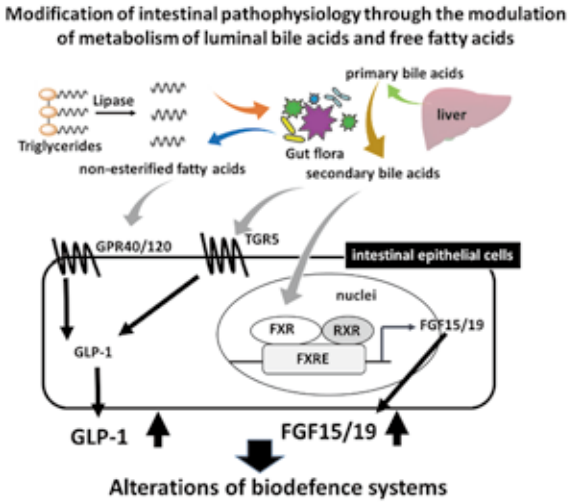
Our research focuses on understanding the biological defence system including immune response, inflammation, and cellular metabolism, and its role in pathological diseases. We mainly study the role of the biological defence system in the protection or progression of diseases, and the effects of natural medicines including Kampo medicines on the biological defence system.

Research Projects

- **Cancer Biology and Immunology**: Our research unit studies the control of immunological diseases (cancer, inflammation, allergy) focusing on innate immune cells, which are important for the biological defense system. In particular, we study the biology of natural killer (NK) cells and their importance in the control of immunological diseases. Furthermore, we study the role of the immune response in cancer progression using annimal models and in vivo imaging, and the effects of traditional medicines n the control of immunological diseases.
- **Nutritional Biochemistry**: Our recent investigations using experimental animals have revealed that the administration of Wakanyaku influenced many aspects of intestinal pathophysiology. Intraluminal bile acids (BA) and non-esterified fatty acids (NEFA) are the potent ligands for the receptors eliciting the formation of peptide hormones in the intestinal epithelial cells, which are involved in the control of biodefense systems. Thus, we hypothesized that the above-mentioned actions of Wakanyaku are mediated by the modulation of the metabolism of BA and NEFA in the intestinal lumen. We are aiming to elucidate a novel mechanism of action of Wakanyaku through the comprehensive analysis of intraluminal BA and FFA and relating signaling responses in the intestinal epithelial cells.

【Keywords】Host defence, Immunology, Cancer, Inflammation, Lipid metabolism





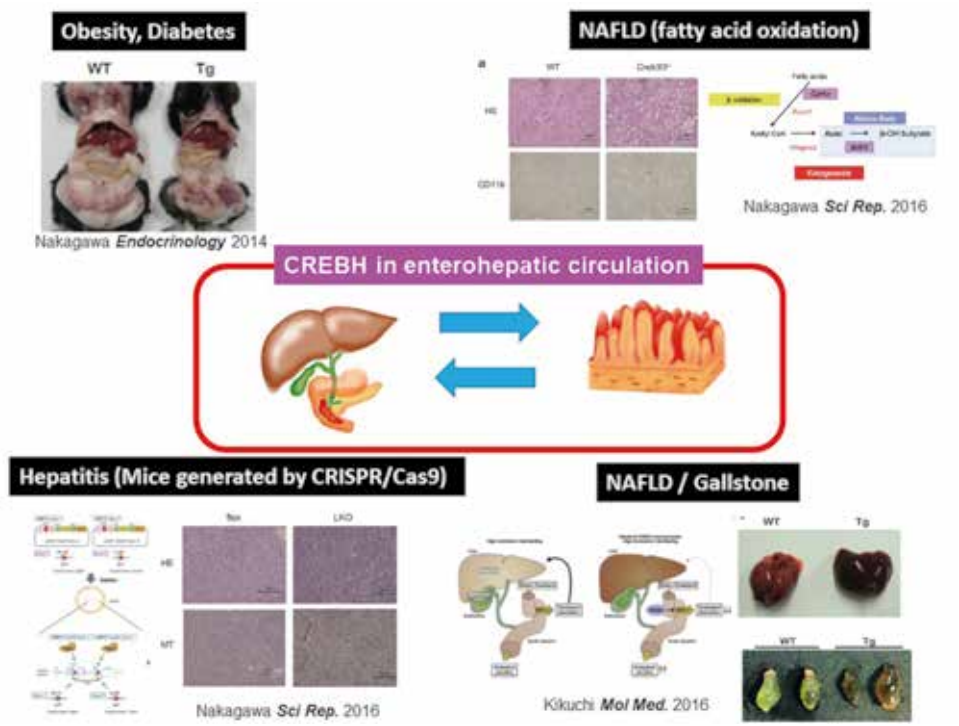
Division of Complex Biosystem Research

Professor NAKAGAWA Yoshimi, Ph.D.
Associate Professor KIM Jundal, Ph.D.

We have analyzed the function of a membrane-bound transcription factor, CREBH, localizing in the endoplasmic reticulum. CREBH is expressed in the small intestine and the liver. Thus, although CREBH is thought to govern the nutrient homeostasis, it remains unknown.

We found that CREBH controls carbohydrate and lipid metabolism regulating gene expression of enzymes related to these metabolisms. Especially, Hepatic CREBH regulates FGF21, a novel hormone from the liver to control systemic energy homeostasis[1,2], and PPARα, a transcription factor which is a target molecule for the drugs to ameliorate hyperlipidemia[1,3,4]. Intestinal CREBH controls lipid absorption from the small intestine regulating NPC1L1, a cholesterol transporter5. Thus, these regulations by CREBH ameliorate lifestyle-related disease[5].

Now, we are trying to elucidate the mechanism of CREBH functioning in the liver, small intestine, the linkage of two tissues (enterohepatic circulation) to the nutritional metabolism, and the influence on CREBH on other peripheral tissues (see Figure). Then, we are analyzing the molecular level in pathogenesis of lifestyle-related disease such as nonalcoholic fatty liver, liver cancer, and atherosclerosis using in vitro, in vivo, in silico analysis systems.



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1 Nakagawa, Y. et al. Endocrinology 155, 4706-4719 (2014).
2 Satoh, A. et al. iScience 23, 100930 (2020).
3 Nakagawa, Y. et al. Sci Rep 6, 39182 (2016).
4 Nakagawa, Y. et al. Sci Rep 6, 27857 (2016).
5 Kikuchi, T. et al. Mol Metab 5, 1092-1102 (2016).

Division of Presymptomatic Disease

Professor KOIZUMI Keiichi, Ph.D.
Assistant Professor YAMAMOTO Takeshi, Ph.D.
Assistant Professor HAYASHI Shusaku, Ph.D.
Specially Appointed Associate Professor OKU Makito, Ph.D.

https://www.inm.u-toyama.ac.jp/en/research/presymptomatic-disease/

Outline of the research

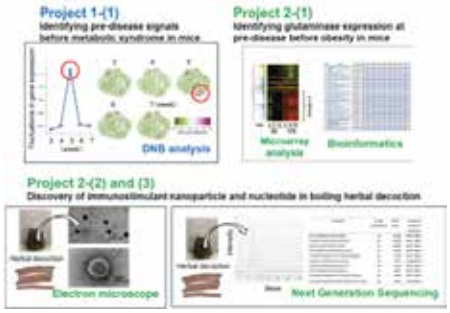
The pre-disease state, which is known as *Mibyou* in traditional Japanese medicine (Kampo medicine), is an Oriental medical concept and has not yet been scientifically understood. In collaboration with our division and Research Center for Pre-Disease Science, University of Toyama, we are conducting research to scientifically detect the *Mibyou* state by analyzing the fluctuation and expression change of biometric information such as genes, proteins, and behavior during the onset process, and to clarify the biological meaning of this state. There have been marked increases in the incidence of complex diseases, such as metabolic syndrome, and it is hard to treat them using only modern medical drugs. In contrast to the symptomatic treatments offered by modern medical drugs at the disease state, drugs targeting *Mibyou* may have great potential advantages as preventive and preemptive medicine. Therefore, we will work on the development of the drug treatment for *Mibyou*, and consequently the novel medical strategies.

Research Projects

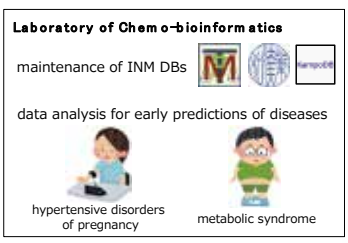
1. Deepening of biology for the pre-disease state (*Mibyou*).
   1) Understanding of the fluctuation of biometric information and its medical applications.
2. Drug development for the pre-disease state (*Mibyou*).
   1) Development of the glutaminase inhibitor and its medical applications.
   2),3) Elucidation of the function of immunostimulatory nanoparticles (Nanosome) and nucleotide degradant (BIND) discovered by traditional Japanese medicine (Kampo formula) and their medical applications.
   4) Elucidation of the pathological mechanism and the search for new seeds of medicine for medical applications in enteric immune diseases.

【Keywords】Pre-disease, Fluctuation, Kampo, Enteric immune diseases, Mucosal immune system

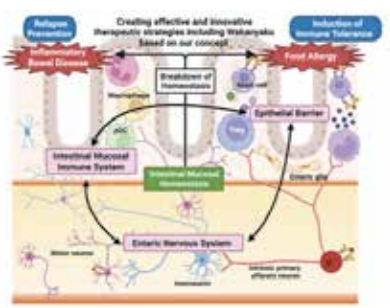
Laboratory of Drug Discovery and Development for Pre-disease
Project 1-(1) and 2-(1)～(3)



Laboratory of Chemo-bioinformatics
Project 1-(1)



Laboratory of Gastrointestinal
Project 2-(4).



Section of Kampo Diagnostics

Professor SHIBAHARA Naotoshi, M.D., Ph.D.

Recently, the traditional Japanese Medicine (kampo) prescriptions have been widely used to treat various diseases, and there are great expectations to treat and prevent in the chronic and refractory diseases. On the other hand, it has been criticized that kampo medicine is not scientific but experimental, and the accumulation of scientific evidences with the basic and clinical researches is required. For the accumulation of scientific evidences, it is necessary to externalize the concepts of kampo medicine and 'sho', which is judged comprehensively by a complex of subjective and objective symptoms at a certain point of patients, and to clarify the efficacies and the mechanisms of kampo prescriptions. For that reason, this Section aims to establish new kampo medicine by the basic and clinical researches on the concepts of kampo medicine and kampo prescriptions.

The main theme of research

(1) Basic researches on pharmacological effects of kampo prescriptions and crude drugs (1) Effect on edema and pain, 2) Influence of modified kampo prescriptions on pharmacological effect, 3) Influence of quality of crude drugs on pharmacological effect), (2) Clinical researches on the concepts of kampo medicine and 'sho' (1) Digitalization of the concepts of kampo medicine, 2) Effects of kampo prescriptions on stress, 3) Clinical effects of kampo prescriptions on various diseases), (3) Researches of medical training program in kampo medical and pharmacology (1) Educational effect of medical training program, 2) Development of medical training program)

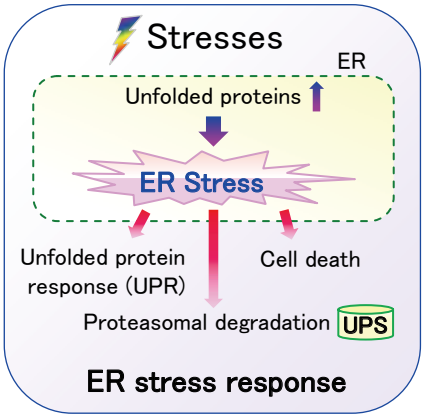
Molecular Genetics Research Laboratory, Life Science Research Center

Professor TABUCHI Yoshiaki, Ph.D.
Assistant Professor HIRANO Tetsushi, Ph.D.

In order to adapt stressful conditions, cells have developed cellular stress response systems. One of these is endoplasmic reticulum (ER) stress which is defined as accumulation of unfolded proteins. ER stress induces a coordinated cytoprotective program called unfolded protein response (UPR), and is vital to the protein quality control and the proteasome plays a key role in it. If the stress is beyond capacity of the adaptive machinery, cells undergo cell death. We are currently studying the molecular mechanisms underlying cellular responses to ER stress, heat stress, mechanical stress, etc. using recombinant genetic engineering and bioinformatics technologies.

Theme of research :

1) Mechanical control of cell differentiation.
2) Elucidation of molecular mechanism of cellular stress response.



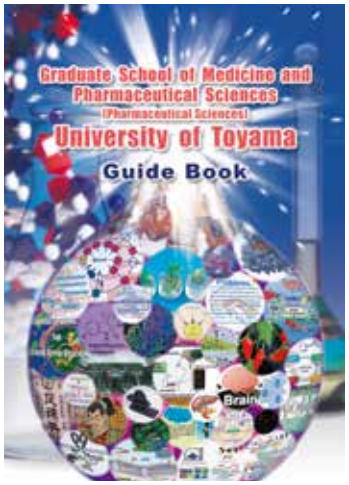
Recent publications :

1) Tabuchi Y *et al.*: HIKESHI silencing can enhance mild hyperthermia sensitivity in human oral squamous cell carcinoma HSC-3 cells. *Int J Mol Med* **46**: 58-66 (2020)
2) Hirano T *et al.*: Aging-related changes in the sensitivity of behavioral effects of the neonicotinoid pesticide clothianidin in male mice. *Toxicol Lett* **342**: 95-103 (2021)
3) Tabuchi Y *et al.*: Genetic response to low-intensity ultrasound on mouse ST2 bone marrow stromal cells. *Mol Med Rep* **23**: 173 (2021)
4) Hirano T *et al.*: Neurotoxicity of a pyrethroid pesticide deltamethrin is associated with the imbalance in proteolytic systems caused by mitophagy activation and proteasome inhibition. *Toxicol Appl Pharmacol* **430**: 115723 (2021)
5) Suzuki N *et al.*: Hydroxylated benzo[c]phenanthrene metabolites cause osteoblast apoptosis and skeletal abnormalities in fish. *Ecotoxicol Environ Saf* **234**: 113401 (2022)

Please visit our website at http://www.lsrc.u-toyama.ac.jp/mgrc/html/laboratory.html.
E-mail: ytabu@cts.u-toyama.ac.jp (YT); thirano@cts.u-toyama.ac.jp (TH)

薬 & 薬

Toyama is proud of the Tateyama mountain range, which includes magnificent 3,000- meter peaks. Among them is Yakushidake peak, on top of which is located a small shrine dedicated to a Bhêchadjaguru, the healing Budda. With a medicine pot in his left hand, he has been the subject of mountain worship as a god of medicine for centuries. A grand view of Yakushidake can be appreciated from the top roof of our School building. Seeing the peak from there, I can't help but be inspired about my pharmaceutical work.

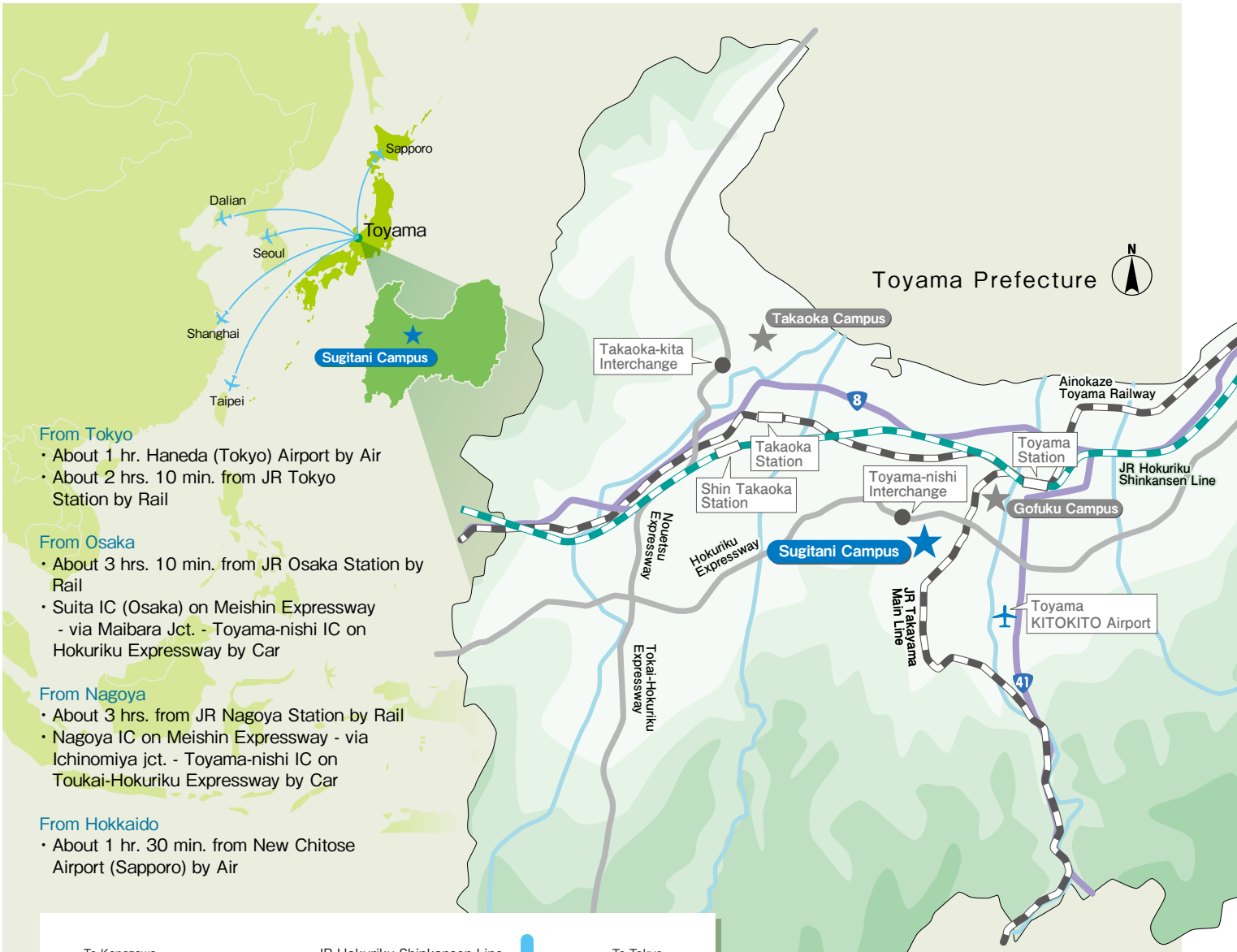


Explanation of the cover

School of Pharmaceutical Sciences, University of Toyama has a long history of 130 years originated from the Kyoritu Toyama Pharmacy School founded in 1893. Concerning the graduate school, the Master's course was established in 1963, and the Ph.D. course was established in 1978. The cover of this guide book is designed in the image of our Graduate School (Pharmaceutical Sciences) continuing to produce a lot of original and excellent results leading the world through our advanced studies based on the history and tradition of "Toyama's pharmaceuticals". In the flask, we put many pictures and figures that symbolize our current studies to express our dynamism in science. In addition to them, "the long history of the pharmaceuticals in Toyama" is shown with the pictures of old instruments for natural medicine used in the Meiji-era※, the Toyama Prefecture School of Pharmacy founded in 1910, the medicine bag of the famous traditional medicine "Han-Gon-Tan"※, and the paper balloons※ and the wood block prints of souvenirs from medicine peddlers in Toyama who is called "Baiyaku-san"※. Why don't you study "the unique pharmaceutical science" in Toyama integrating the traditions and the frontier sciences ?

※ Collection of Toyama Medicine Peddlers Museum

University of Toyama Sugitani Campus Guide Map



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- About 2 hrs. 10 min. from JR Tokyo Station by Rail

From Osaka

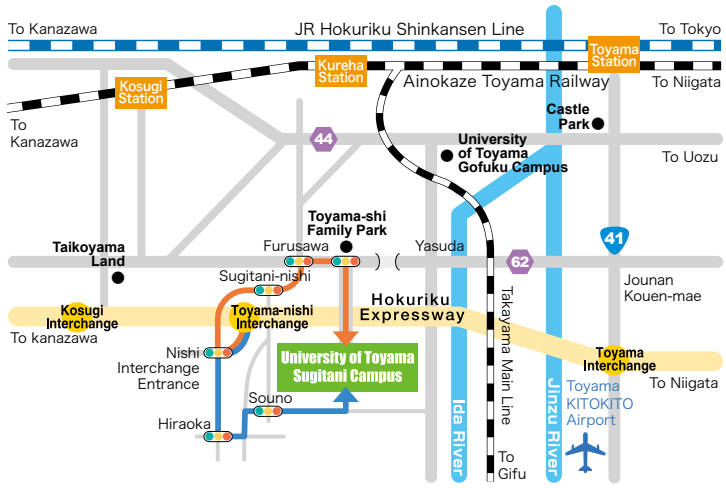
- About 3 hrs. 10 min. from JR Osaka Station by Rail
- Suita IC (Osaka) on Meishin Expressway - via Maibara Jct. - Toyama-nishi IC on Hokuriku Expressway by Car

From Nagoya

- About 3 hrs. from JR Nagoya Station by Rail
- Nagoya IC on Meishin Expressway - via Ichinomiya jct. - Toyama-nishi IC on Toukai-Hokuriku Expressway by Car

From Hokkaido

- About 1 hr. 30 min. from New Chitose Airport (Sapporo) by Air



By Bus

Approximately 20 minutes from Toyama KITOKITO Airport to JR Toyama Station
Approximately 30 minutes from JR Toyama Station to the Sugitani Campus

By Taxi

Approximately 25 minutes from JR Toyama Station to the Sugitani Campus
Approximately 25 minutes from Toyama KITOKITO Airport to the Sugitani Campus

By Car

Approximately 5 minutes from the Hokuriku Expressway Toyama-nishi Interchange to the Sugitani Campus

University of Toyama Sugitani Campus

School of Pharmacy and Pharmaceutical Sciences Bldg. and Institute of Natural Medicine

Graduate School of Medicine and Pharmaceutical Sciences
(Pharmaceutical Sciences)
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