Graduate School of Medicine and Pharmaceutical Sciences
for Education (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.

The Major of Pharmaceutical Sciences

Master's course (2-year)

The aim of this course is to cultivate creative investigators who are able to expend research work in academic institutes, pharmaceutical and related industries, and also to work as specialist personnel in government offices. The program of master's course is consisted of Drug Design and Medicinal Chemistry, Pharmacology and Biopharmaceutics, Biochemistry and Molecular Biology, Natural Medicine and Clinical Medicine. The students study individual research projects based on the fields described above in our laboratories. They are able to acquire leading-edge knowledge and technique in 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 for Education in University of Toyama (Pharmaceutical Sciences)

Hideki Sakai, Ph.D.

Dean, Graduate School of Medicine and Pharmaceutical Sciences for Research, University of Toyama
Vice Dean, Graduate School of Medicine and Pharmaceutical Sciences for Education
Dean, Faculty of Pharmacy and Pharmaceutical Sciences

The Graduate School of Medicine and Pharmaceutical Sciences for Education 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.

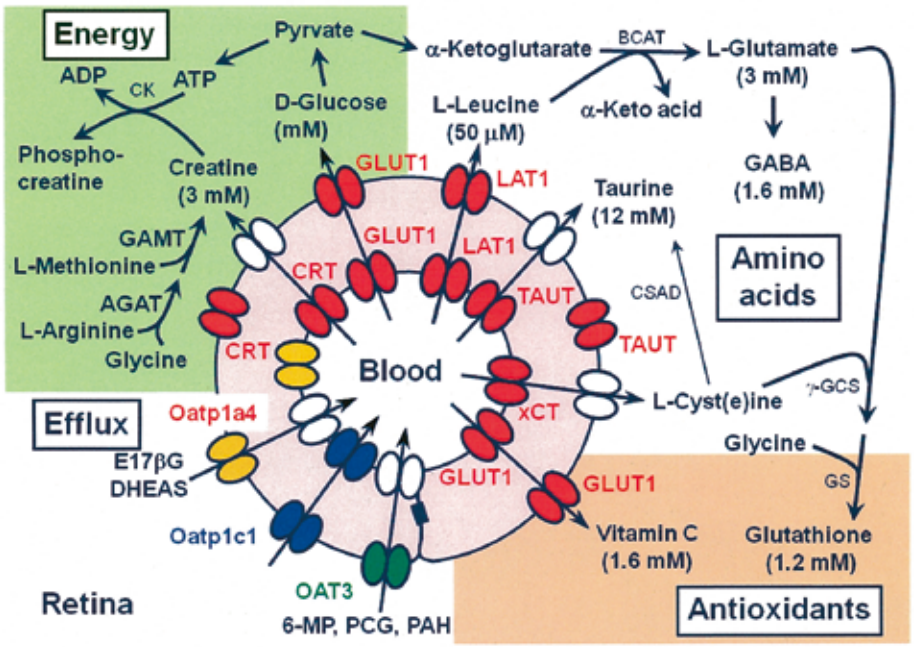
In the 21st century of Japan, also worldwide, better medical care should be achieved for the aging society. Therefore, we need a lot of excellent professionals who can promote an active part in the cutting-edge of the Pharmaceutical Sciences. I do hope that highly motivated students will enter our Graduate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

Contents

Laboratory of Biopharmaceutics

Professor Ken-ichi Hosoya, Ph.D.
Associate Professor Yoshiyuki Kubo, Ph.D.
Assistant Professor Shin-ichi Akanuma, 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 deliver to the retina.



Blood-Retinal Barrier Transporters

Publications

1) Usui et al., Histamine elimination from the cerebrospinal fluid across the blood-cerebrospinal fluid barrier: involvement of plasma membrane monoamine transporter (PMAT/SLC29A4). **J. Neurochem.**, 139, 408-418 (2016)

2) Kubo et al., Retina-to-blood transport of 1-methyl-4-phenylpyridinium involves carrier-mediated process at the blood-retinal barrier. **J. Pharm. Sci.**, 106, 2583-2591 (2017)

3) Akanuma et al., Expression and function of connexin 43 protein in mouse and human retinal pigment epithelial cells as hemichannels and gap junction proteins. **Exp. Eye Res.**, 168, 128-137 (2018)

4) Kubo et al., Blood-to-retina transport of fluorescence-labeled verapamil at the blood-retinal barrier. **Pharm. Res.**, 35:93 (2018)

5) Kubo et al, Recent advances in drug and nutrient transport across the blood-retinal barrier. **Expert Opin. Drug Metab. Toxicol.**, 14, 513-531 (2018)

Laboratory of Applied Pharmacology

Professor Toshiaki Kume, Ph.D.
Associate Professor Tsugunobu Andoh, Ph.D.
Assistant Professor Daisuke Uta, 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 were 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. Therefore, neurodegenerative disease, brain disorders, pain and itch are main research subjects of our laboratory. We have developed many animal models of these diseases including pain and itch, which are used to reveal the mechanisms of target diseases. They are also used to assess the efficacies of analgesics/adjuvant analgesics and anti-pruritic drugs and to elucidate the mechanisms of analgesic and anti-pruritic actions of agents. Two examples of animal models which we are using are as follows :

PAIN : herpes zoster (see photo 1), post-herpetic neuralgia, cancer pain, neuropathic pain induced by anti-neoplastic agents, neuropathy induced by surgical injury to afferent nerve
ITCH : atopic dermatitis (see photo 2), mosquito allergy, xerosis, dermatophyte infection, pollen allergy

Photo 1 :
Mouse model of herpes zoster

Photo 2 :
Mouse model of atopic dermatitis

With regard to natural medicines, we are now investigating the effects of several natural products on oxidative stress or pain of peripheral neuropathy induced by anti-neoplastic agents such as paclitaxel and oxaliplatin. We are also studying the effects of several natural medicines on itch of atopic dermatitis.

Laboratory of Biorecognition Chemistry

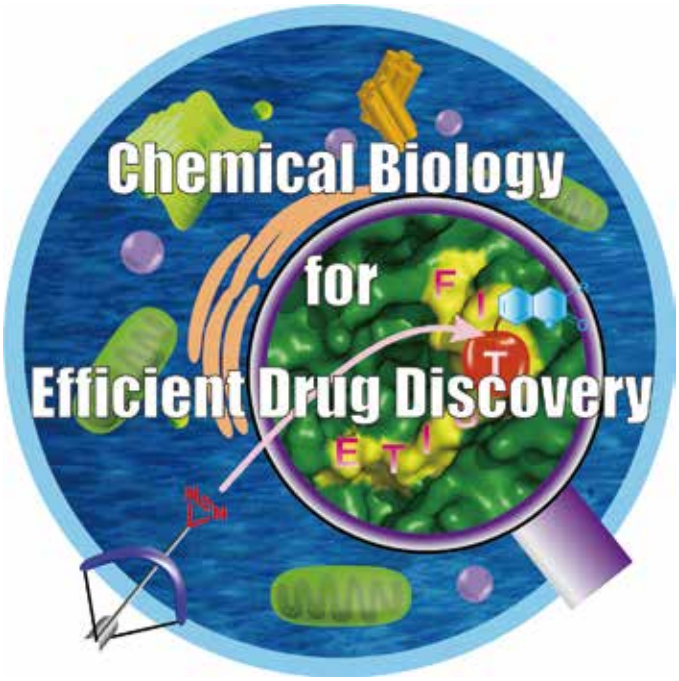
Professor Takenori Tomohiro, Ph.D.
Assistant Professor Junya Chiba, Ph.D.

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) Development of high-throughput approach for imaging and specifying drug targets, and elucidating its binding site within protein by using pro-tag installed multifunctional photoprobes.
2) Self-organizing molecule for create stimuli-responsive macromolecular suits.
3) Rational drug discovery by affinity-based lead optimization.



Laboratory of Cancer Cell Biology

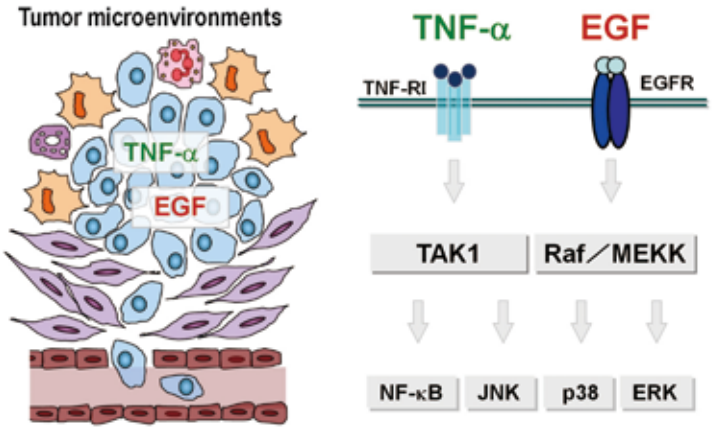
Professor Hiroaki Sakurai, Ph.D.

Research Interests

In tumor microenvironments, multiple cytokines and growth factors are expressed and coordinately regulate the pathogenic alterations. TNF-α and EGF are typical of these secreted ligands and their pathological functions have been extensively studied. Attention has recently been focused on the role of TNF-α in carcinogenesis, tumor angiogenesis and metastasis. On the other hand, overexpression, amplification and mutations of EGFR are involved in carcinogenesis and the progression of several types of cancer. Anti-TNF-α and anti-EGFR agents have already been developed, and are clinically effective against these diseases. Cross talk between different signaling pathways is likely to be important for diverse cellular functions. Therefore, we have investigated the functional interactions of the TNF-α signal and EGFR signal to elucidate new biological processes.

Publications

1. 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.
2. Kawasaki Y. et al.: Feedback control of ErbB2 via ERK-mediated phosphorylation of a conserved threonine in the juxtamembrane domain. *Sci. Rep.*, 6: 31502, 2016.
3. Zhou Y. et al. : Crucial roles of RSK in cell motility by catalysing serine phosphorylation of EphA2. *Nat. Commun.*, 6 : 7679, 2015.
4. Sakurai H. : Targeting of TAK1 in inflammatory disorders and cancer. *Trends Pharmacol. Sci.*, 30 : 522-530, 2012.
5. Nishimura M. et al. : TAK1-mediated serine/threonine phosphorylation of epidermal growth factor receptor via p38/extracellular signal-regulated kinase: NF-κB-independent survival pathways in tumor necrosis factor alpha signaling. *Mol. Cell. Biol.*, 29 : 5529-5539, 2009.



Laboratory of Chemical Biology

Professor Masahiko Inouye, Ph.D.
Assistant Professor Yuki Ohishi, 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 :

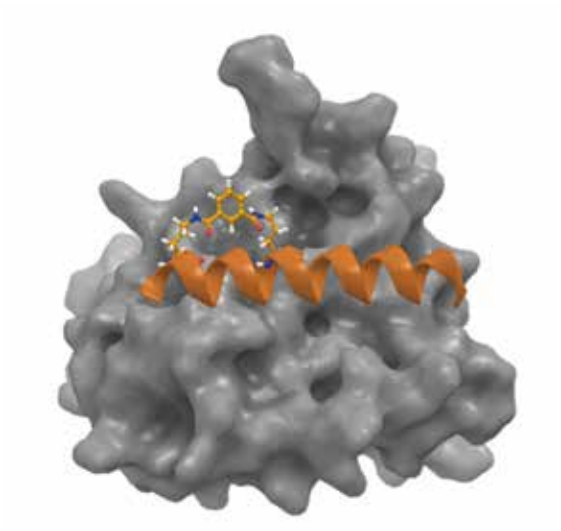
We create a new class of DNA-like oligomers made exclusively of nonnatural nucleosides with four types of nonnatural bases attached to a deoxyribose through *C*-glycoside bond. The artificial DNAs might be applied to a future extracellular genetic system with information storage and amplifiable abilities.

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 :

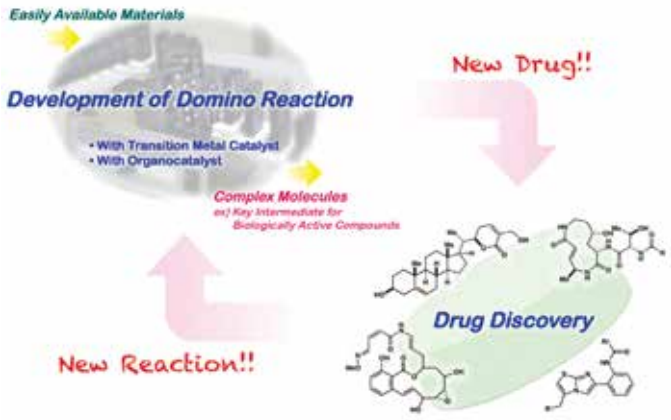
Various ethynylpyridine-based polymers and oligomers were designed and synthesized as conceptually new host molecules for saccharide recognition. We also apply the host molecules to mediators and catalysts for new reactions of saccharides and to materials of biological and industrial interest.



Laboratory of Synthetic and Medicinal Chemistry

Professor Yuji Matsuya, Ph.D.
Associate Professor Kenji Sugimoto, Ph.D.
Assistant Professor Aki Kohyama, 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 Akiko Tabuchi, Ph.D.
Assistant Professor Daisuke Ihara, 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.

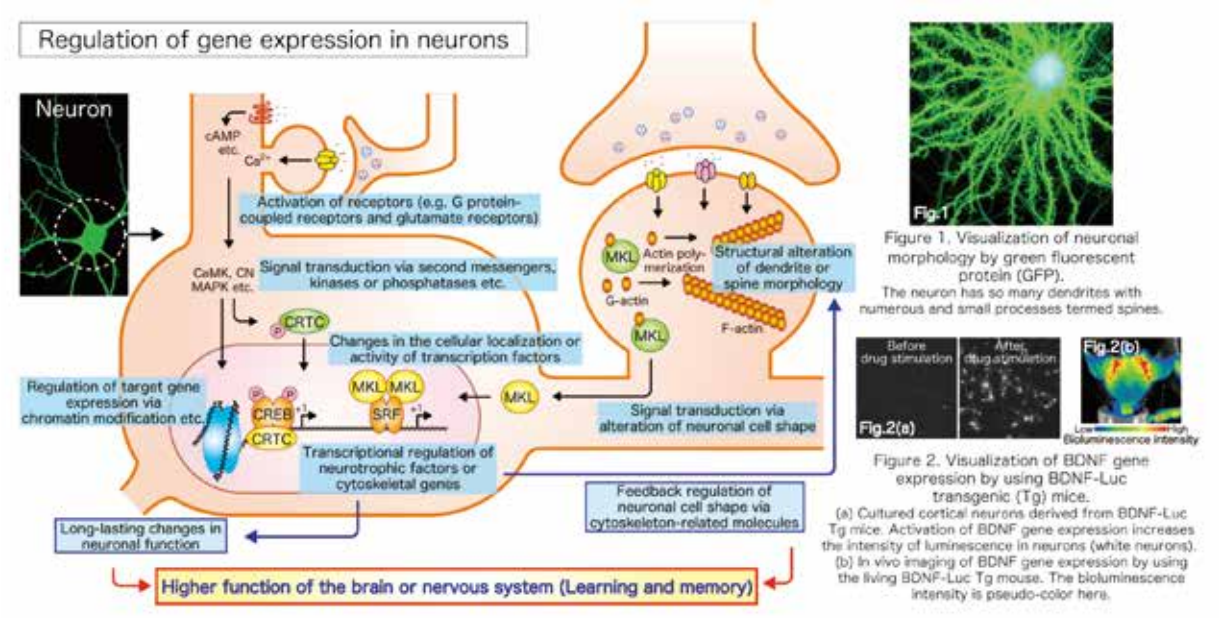


Figure 1. Visualization of neuronal morphology by green fluorescent protein (GFP).
The neuron has so many dendrites with numerous and small processes termed spines.

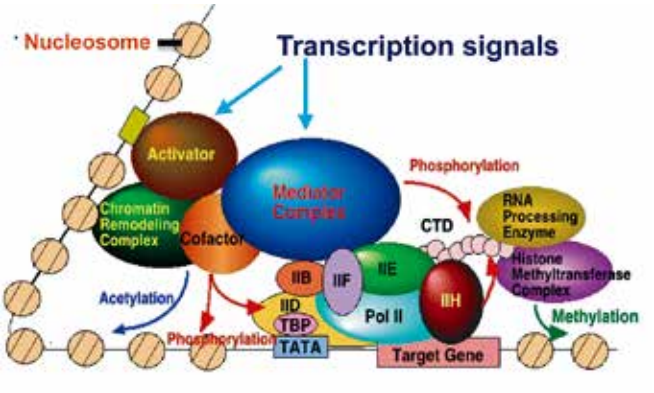
Figure 2. Visualization of BDNF gene expression by using BDNF-Luc transgenic (Tg) mice.
(a) Cultured cortical neurons derived from BDNF-Luc Tg mice. Activation of BDNF gene expression increases the intensity of luminescence in neurons (white neurons). (b) In vivo imaging of BDNF gene expression by using the living BDNF-Luc Tg mouse. The bioluminescence intensity is pseudo-color here.

Publications (selected):

Kaneda *et al.*, Sci Rep. (2018)
Kikuchi *et al.*, BBRC (2017)
Fukuchi *et al.*, J Neurosci. (2015)
Ishikawa *et al.*, Neuro Report (2014)
Ihara *et al.*, Neuropharmacology (2012)
Tabuchi, Biol. Pharm. Bull. (2008)
Shiota *et al.*, J Neurochem. (2006)
Ihara *et al.*, Cell Struct Funct. (2017)
Fukuchi *et al.*, Sci Rep. (2017)
Fukuchi *et al.*, J Biol Chem. (2015)
Ishikawa *et al.*, FEBS Open Bio (2013)
Ishikawa *et al.*, J Biol Chem. (2010)
Yasuda *et al.*, J Neurochem. (2007)
Tabuchi *et al.*, J Neurochem. (2005)

Laboratory of Gene Regulation

Associate Professor Yutaka Hirose, Ph.D.
Assistant Professor Aki Tanaka, Ph.D.



After accomplishment of the human genome project, it has become obvious that we cannot understand the mechanisms of living activities by simply reading the whole gene sequences. For example, the body size and the extent of brain development of humans are quite different from those of mice although they both have almost identical 23,000 genes. Recently, it was also discovered with surprize that four certain transcription factors can induce differentiated cells to pluripotent stem cells. It has become obvious that these phenomena are caused by coordinative regulations of trascription and its closely related nuclear events. Our objectives are to elucidate the specific regulatory mechanisms that control such events, especially "the switch mechanisms of changing between transcription activation and repression" by using molecular biological, biochemical, and genetical approaches.

Main research projects :

1. Studies on molecular mechanisms of transcription of eukaryotic genetic information

We are studying the transcriptional regulation mechanisms of RNA polymerase II (Pol II) by the general transcription factors and how the nuclear signals are transduced to Pol II via the Mediator complex and are proceeded to transcription initiation, elongation and posttranscriptional regulations like RNA processing.

2. Studies on crosstalks between transcription and chromatin regulation primarily through the Mediator complex

Since the histone remodeling complex SWI/SNF, the transcriptional repressor polycomb complex, and the histone methylation enzymes were isolated as the Mediator interacting factors, we are studying the regulation mechenisms.

3. Studies on molecular mechanisms for the coordination of gene expression processes via the C-terminal domain of the RNA polymerase II largest subunit

The C-terminal domain of the Pol II largest subunit (CTD) is composed of tandem repeats of heptapeptide YSPTSPS and subjected to reversible phosphorylation during transcription cycle. The phosphorylated CTD plays critical roles in coordinating multiple nuclear processes by serving as a scaffold to recruit various proteins involved in transcription, chromatin modification, and RNA processing. We are studying on the molecular mechanisms for the coordination of gene expression processes by examining the roles of CTD kinases, phosphatases, and phosphorylated CTD binding factors in gene regulation.

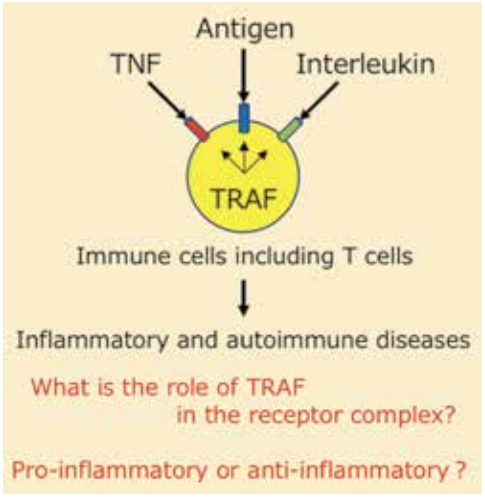
Laboratory of Molecular Cell Biology

Professor Takanori So, Ph.D.
Associate Professor Masashi Morita, Ph.D.
Assistant Professor Kosuke Kawaguchi, Ph.D.

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.

Novel cytokine receptor signaling mechanisms in immune cells that are regulated by TRAF and TNF-related 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 recently that intracellular TRAFs which associate with many different 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 pro-inflammatory activity in $CD4^+$ T cells.

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

Understanding of 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 projects

1. Regulation of pro-inflammatory cytokine signaling by TRAF family molecules
2. Regulation of T cells by TNF-related family molecules
3. Analysis of structure and function of ABC protein subfamily D
4. Elucidation of molecular pathology of X-linked adrenoleukodystrophy and development of therapeutic agents

Laboratory of Medicinal Bioresources

Professor Fumiya Kurosaki, Ph.D.
Associate Professor Futoshi Taura, Ph.D.
Assistant Professor Jung-Bum Lee, 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

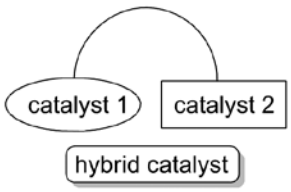
Professor Takayuki Yakura, Ph.D.
Associate Professor Hisanori Nambu, Ph.D.
Assistant Professor Tomoya Fujiwara, Ph.D.

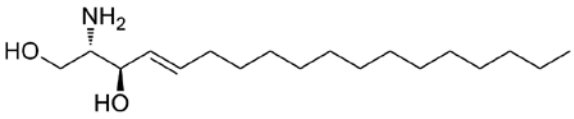
Research Interests

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. Moreover we have been pursuing the organofluorine chemistry.

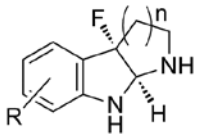
Emphasis is presently placed on the following four research projects.

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.
4) Design, synthesis, and biological evaluation of organofluorine compounds as novel drug candidates.





sphingosine

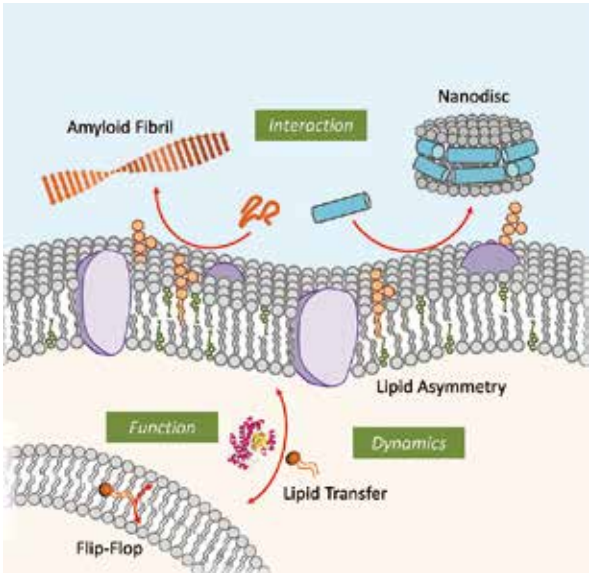


organofluorine compound

Laboratory of Biointerface Chemistry

Professor Minoru Nakano, Ph.D.
Associate Professor Keisuke Ikeda, Ph.D.
Assistant Professor Horoyuki Nakao, 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, such as biogenesis of lipoproteins and protein-mediated lipid transfer. In addition, we are developing new pharmaceuticals using lipid assemblies, such as liposomes, emulsions, cubosomes, and nanodiscs. Our current research projects are listed below.



Membrane-protein interaction and dynamics of membrane lipids

High-density lipoprotein (HDL) is a target for the development of new drugs for arteriosclerosis because of negative correlation between circulating levels of HDL and a risk of cardiovascular disease. However, the molecular mechanism by which HDL is formed is less well understood. We aim to elucidate this mechanism by physicochemical approaches with model lipid membranes. So far, we clarified that several changes in membrane environment facilitate spontaneous reconstitution of discoidal HDLs (nanodiscs) on the interaction with apolipoprotein A-I. We also developed a method to detect interbilayer and transbilayer transfers of phospholipids by means of time-resolved small-angle neutron scattering and revealed that nanodiscs represents a 20-fold higher lipid transfer than liposomes. We are now focusing on the quantitative analysis of protein-mediated lipid transport such as lipid transfer proteins and flippases, which are biologically important.

New lipid colloidal particulates

Lipid emulsion is used as a model compound of a plasma lipoprotein particle and it is applied to the drug delivery system. We found for the first time that emulsion binds apolipoproteins about 10-fold more than liposome. In consequence, the systemic catabolism of the particulates and their interaction with the cultured cell change remarkably. In addition, the colloidal particles having bicontinuous cubic structure (cubosome) and inverted hexagonal structure (hexosome) have been successfully prepared for the first time. Accordingly, we now focus on clarifying physical properties of the nonlamellar phases and their biophysical function. The development of their application for drug is also in progress.

Laboratory of Structural Biology

Professor Mineyuki Mizuguchi, Ph.D.
Associate Professor Takayuki Obita, Ph.D.
Assistant Professor Takeshi Yokoyama, 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 Hideki Sakai, Ph.D.
Associate Professor Takahiro Shimizu, Ph.D.
Assistant Professor Takuto Fujii, Ph.D.

In the Department 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 TRP-related channels.

Our recent publications on these topics are as follows:

Structure and function of transportsome in gastrointestinal cells

1. Positive regulation of the enzymatic activity of gastric H^+,K^+-ATPase by sialylation of its β-subunit. (2016) *Biochim. Biophys. Acta* 1858 : 1228-1235.
2. Proton-Potassium (H^+/K^+) ATPases: Properties and Roles in Health and Diseases. (2016) *Met. Ions Life Sci.* 16 : 459-483.
3. Inhibition of gastric H^+,K^+-ATPase by 4-(2-butyl-6,7-dichloro-2-cyclopentylindan-1-on-5-yl)oxybutyric acid (DCPIB), an inhibitor of volume-regulated anion channel. (2015) *Eur. J. Pharmacol.* 765 : 34-41.
4. Functional coupling of chloride-proton exchanger ClC-5 to gastric H^+,K^+-ATPase. (2014) *Biol. Open* 3 : 12-21
5. Modulation of H^+,K^+-ATPase activity by the molecular chaperone ERp57 highly expressed in gastric parietal cells. (2013) *FEBS Lett.* 587 : 3898-3905

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

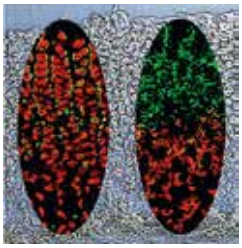
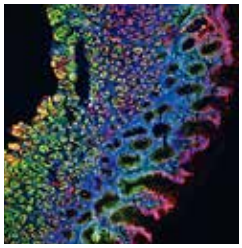
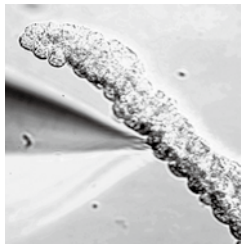
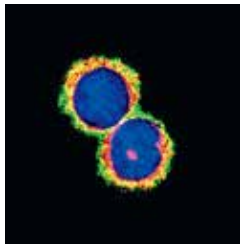
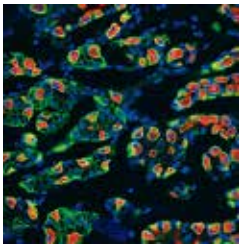
1. Up-regulation of Kv7.1 channels in thromboxane A_2-induced colonic cancer cell proliferation. (2014) *Pflügers Arch.* 466 : 541-548
2. Inhibition of ecto-ATPase activity by curcumin in hepatocellular carcinoma HepG2 cells. (2012) *J. Physiol. Sci.* 62 : 53-58

Molecular candidates for volume-sensitive anion channels

1. Volume-sensitive outwardly rectifying Cl^- channels contribute to butyrate-triggered apoptosis of murine colonic epithelial MCE301 cells. (2015) *J Physiol Sci.* 65 : 151-157.
2. TMEM16F is a component of a Ca^{2+}-activated Cl^- channel but not a volume-sensitive outwardly rectifying Cl^- channel. (2013) *Am. J. Physiol. Cell Physiol.* 304 : C748-C759

Physiological properties of TRP-related channels

1. 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
2. Gating modulation by heat of the polycystin transient receptor potential channel PKD2L1 (TRPP3). (2014) *Pflügers Arch.* 466 : 1933-1940
3. Bimodal effect of alkalization on the polycystin transient receptor potential channel, PKD2L1. (2011) *Pflügers Arch.* 461 : 507-513

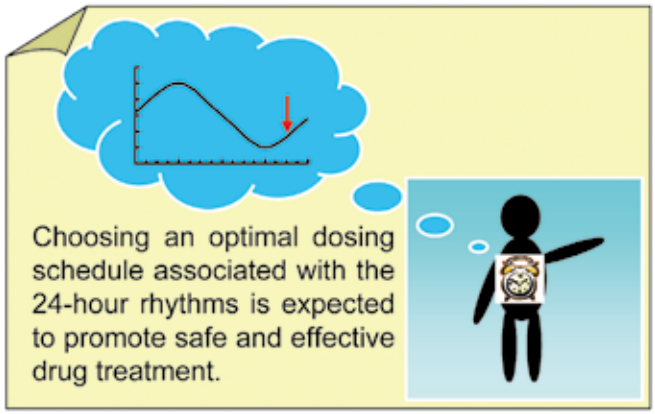






Laboratory of Medical Pharmaceutics

Professor Hideto To, Ph.D.
Associate Professor Yasuhiro Tsuji, Ph.D.
Asistant Professor Fumiyasu Okazaki, 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
- Emerging Infections, Pharmacokinetics and Pharmacodynamics
- Evaluation of clinical effective and safety range based on pharmacokinetics of an antimicrobial agents
- Special population pharmacokinetics and pharmacodynamics of antimicrobial and antifungals

Laboratory of Plant Resource Sciences

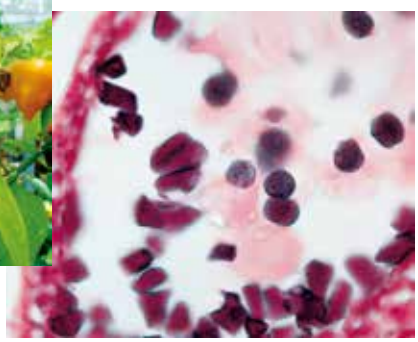
Professor Fumiya Kurosaki, Ph.D. (concurrent post)
Assistant Professor Yoshimi Yamamura, Ph.D.

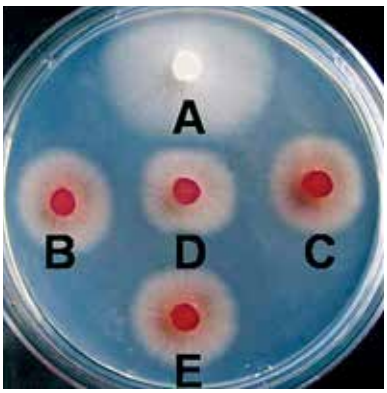
It is widely recognized that higher plant cells are rich sources of a variety of natural products for medicinal use. Numerous attempts have been made to secure and/or stimulate the productivities of these important secondary metabolites of plant cells; such as enhancement of the activities of biosynthetic 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.

Our research interests are

1) Molecular biology of secondary metabolites biosyntheses in medicinal plants
2) Evaluation and screening of plant strains with high-productivities of valuable natural compounds, and breeding new varieties
3) Characterization of virulence mechanism in pathogenic fungi and establishment of the molecular basis for plant defense mechanism

These approaches should allow the improvement of the quality of higher plants as the useful medicinal sources.





Left, Red pepper fruits with high-producing activity of capsaicin ; **Center**, *In situ* hybridization analysis of the expression of a biosynthetic enzyme gene of capsaicin ; **Right**, Plant pathogen *Fusarium verticillioides.* (A, wild-type ; B-E, pathogenic gene-deletion mutants)

Laboratory of Clinical Pharmacology

Professor Toshiyasu Sasaoka, M.D., Ph.D.
Associate Professor Hiroshi Tsuneki, Ph.D.
Lecturer Tsutomu Wada, 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 :

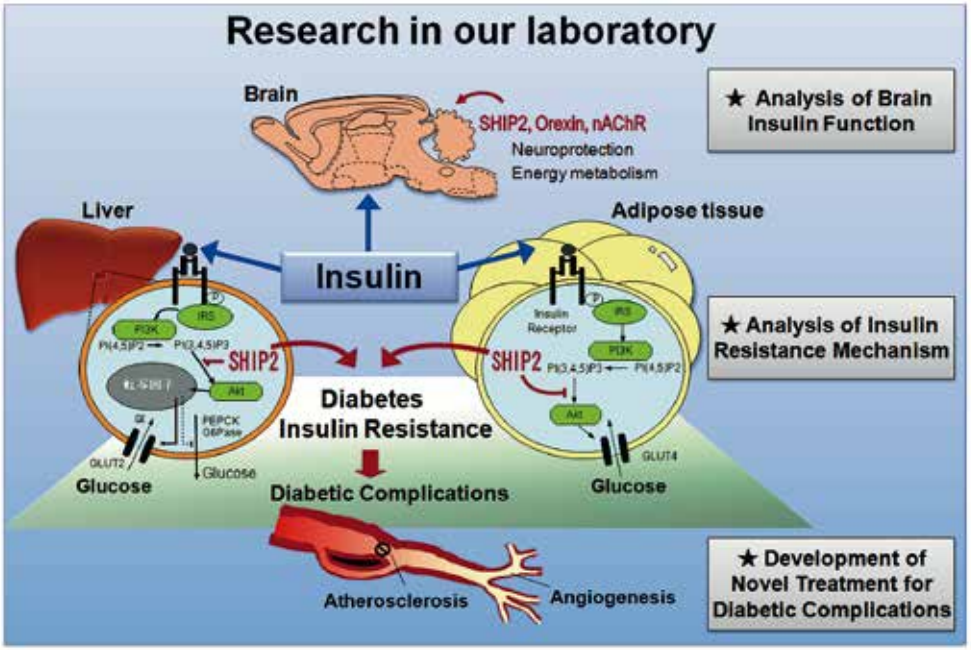
Our laboratory studies the impacts of protein and lipid phosphatases, including SHIP2 that we identified, and adrenal and sex steroid hormones on the development of insulin resistance.

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 Yukiya Hashimoto, Ph.D.
Associate Professor Masato Taguchi, 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.

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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).
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Laboratory of Pharmaceutical Therapy and Neuropharmacology

Professor Atsumi Nitta, Ph.D.
Associate Professor Yoshiaki Miyamoto, Ph.D.
Assistant Professor Kyosuke Uno, Ph.D.

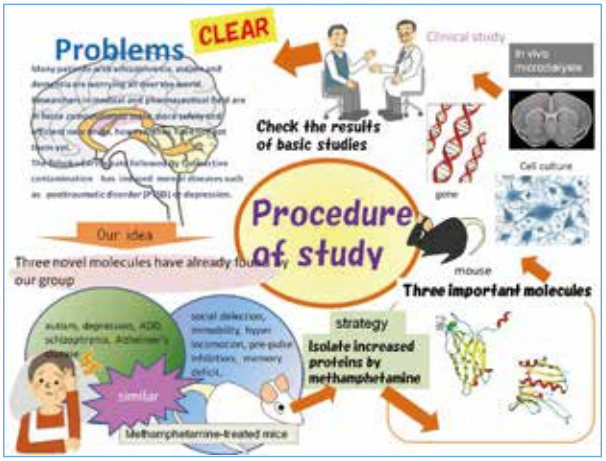
We attempt to clarify the cause of various kinds of mental diseases, such as addiction, schizophrenia, autism, depression, Alzheimer's disease and Parkinson disease. Our final goal of our research projects is establishments of new pharmaceutical treatments for these diseases. Our main projects are shown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

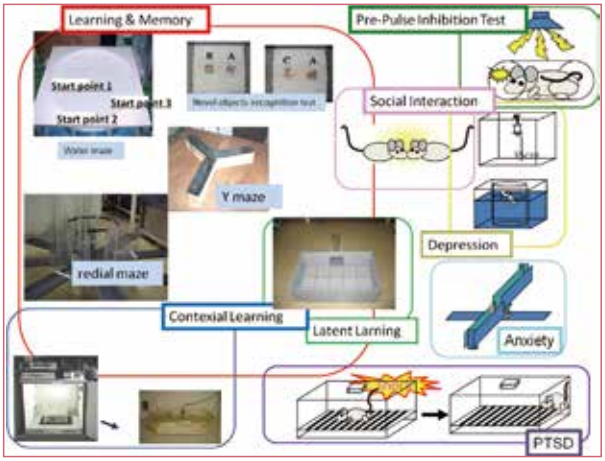
1. Clarify the roles of novel molecules-related psychiatric diseases and drug addiction
   We found novel molecules using by cDNA subtraction methods from the nucleus accumbens of psychostimulant-treated mice. We investigate the physiological activities and roles of the novel molecules using behavioral 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. Sumi K, Uno K, Noike H, Tomohiro T, Hatanaka Y, Furukawa-Hibi Y, Nabeshima T. Miyamoto Y, Nitta A. Behavioral impairment in SHATI/NAT8L knockout mice via dysfunction of myelineation development. **Sci Rep**, 7; 16872 (2017)
2. Fu K, Miyamoto Y,, Otake K, Sumi K, Saika E, Matsumura S, Sato N, Ueno Y, Seo S, Uno K, Muramatsu S, Nitta A, Involvement of the accumbal osteopontin-interacting transmembrane protein 168 in methamphetamine-induced place preference and hyperlocomotion in mice. **Sci Rep**, 7; 13084 (2017)
3. Miyamoto Y, Iegaki N, Fu K, Ishikawa Y, Sumi K, Azuma S, Uno K, Muramatsu S, Nitta A Striatal *N*-acetylaspartate synthetase Shati/Nat8l regulates depression-like behaviors via mGluR3-mediated serotonergic suppression in mice. **Int J. Neuropsychopharmcol**. doi: 10.1093/ijnp/pyx078 (2017)
4. Uno K, Miyazaki T, Sodeyama K, Miyamoto Y, Nitta A. Methamphetamine induces Shati/Nat8L expression in the mouse nucleus accumbens via CREB- and dopamine D1 receptor-dependent mechanism. **PLoS One**. 12; e0174196. doi: 10.1371/journal. pone. (2017)





Department of Hospital Pharmacy

Professor Isao Adachi, Ph.D.
Associate Professor Atsushi Kato, Ph.D.
Assistant Professor Yasuhiko Mimura, 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™), 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™) 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.

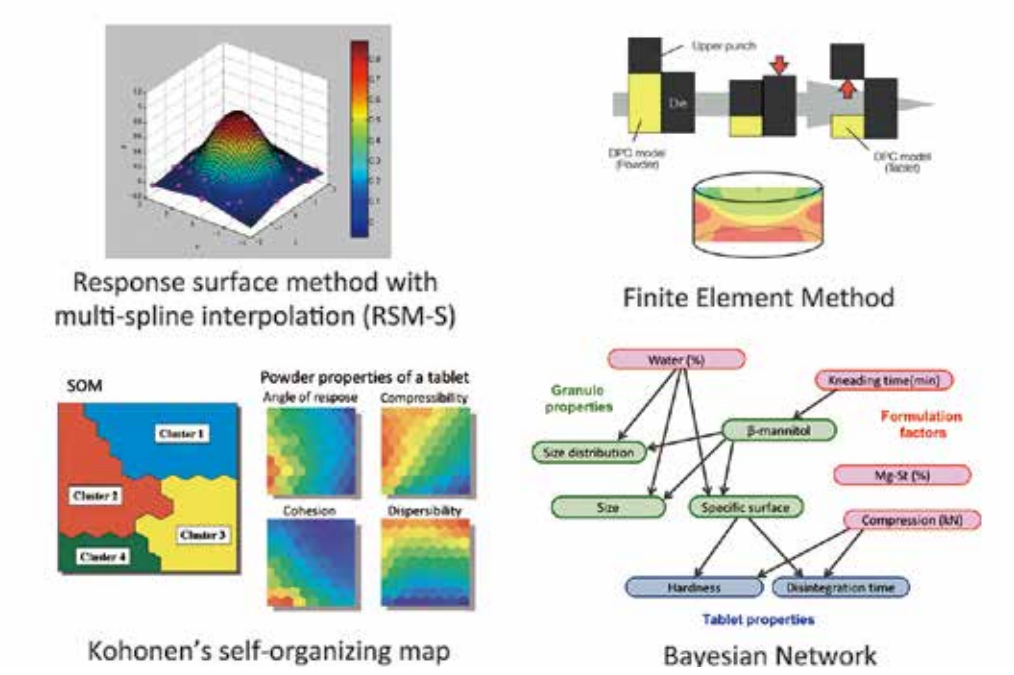
2) Isolation of water-soluble bioactive components from medicinal plants

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.

Department of Pharmaceutical Technology

Professor Yoshinori Onuki, Ph.D.
Assistant Professor Yoshihiro Hayashi, Ph.D.

Pharmaceuticals are 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 department is to promote the further development of the pharmaceutical technology through the outstanding pharmaceutical researches. Especially, we are focusing on establishment of novel technologies for the development of pharmaceuticals based on statistics and computer simulation. Furthermore, we are investigating physical properties of pharmaceuticals using cutting-edge technologies including molecular imaging techniques.



Optimization techniques for designing pharmaceutical formulations and manufacturing processes

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

Division of Pharmacognosy

Professor Katsuko Komatsu, Ph.D.
Associate Professor Kazufumi Toume, Ph.D.
Assistant Professor Shu Zhu, Ph.D.

Purpose of Research

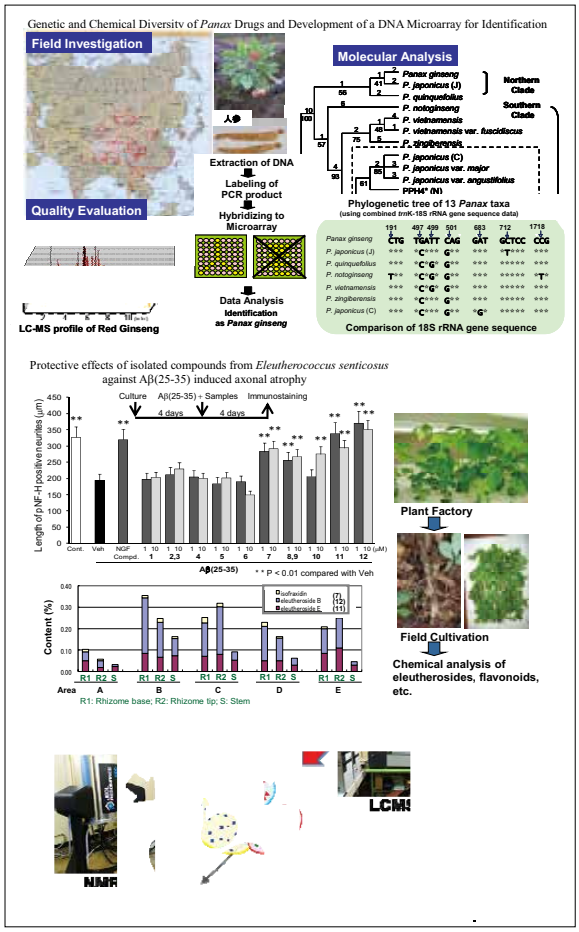
Aim to develop a strategy for the sustainable use of herbal drug resources, comprehensive studies have been conducted in the division of Pharmacognosy, including field investigation on medicinal plants and traditional medicines, molecular systematic, pharmacognostical, chemical and pharmacological analyses on various herbal drugs.

The main targets of medicinal plants and herbal drugs are Ginseng drugs-Genus *Panax*, Rhei Rhizoma-Genus *Rheum*, Curcuma drugs-Genus *Curcuma*, Acanthopanacis Radix-Genus *Acanthopanax* & Genus *Eleutherococcus*, Paeoniae Radix-Genus *Paeonia*, Gentiana drugs-Genus *Gentiana*, etc.

The contents of researches are as follows.

Research Outline

1) Field investigation on herbal drug resources around Asian countries (such as China, Mongolia, Thailand, Indonesia, Vietnam, Myanmar, etc.) and analysis on genetic and chemical diversity of the medicinal plants.
2) Authentication and quality evaluation on various herbal drugs for the purpose of selecting proper species for cultivation.
3) Analyzing genetic polymorphisms of medicinal plants and developing convenient molecular method as well as DNA microarray for identification of herbal drugs.
4) Chemometric profiling of multiple components in crude drugs and Kampo formula using NMR and LC-MS.
5) Search and structure elucidation of bioactive compounds for treatment of dementia, cancer, and allodynia.



Welcome to join our group

★ Field work and laboratorial research are performed together
★ Enjoy talking with foreign researchers and experience other cultures
★ Study natural medicines in the Museum of Materia Medica

Division of Natural Products Chemistry, Department of Medicinal Resources

Professor Hiroyuki Morita, Ph.D.
Assistant Professor Chin Piow Wong, Ph.D.

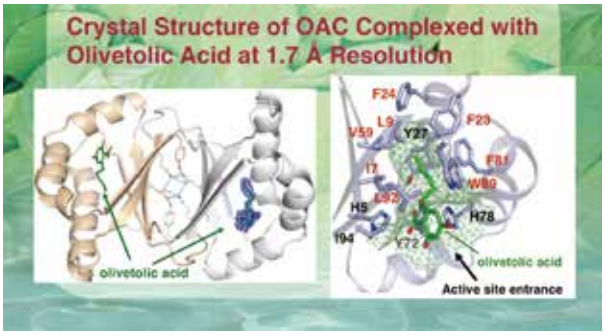
The major aim in our division is to clarify the detailed inhibition mechanism of the naturally occurring bioactive substances in natural medicines with the crystal and solution NMR structure analyses of the target proteins complexed with the substances, and to discover novel bioactive substances from natural medicines. Further, to elucidate the biosynthesis of the bioactive substances from natural medicines, and to produce novel bioactive substances, we also focus on the functional analysis and engineering of novel biosynthetic enzymes. Multidisciplinary methods such as synthesis of the enzyme substrates, analysis/isolation/structure elucidation of the bioactive substances from natural medicines and enzyme reaction products with HPLC, NMR and MS/MS etc, molecular cloning of the biosynthetic enzymes, expression/purification/crystallization of the enzymes, and crystal and solution NMR structure analyses of the enzymes are employed for our researches.

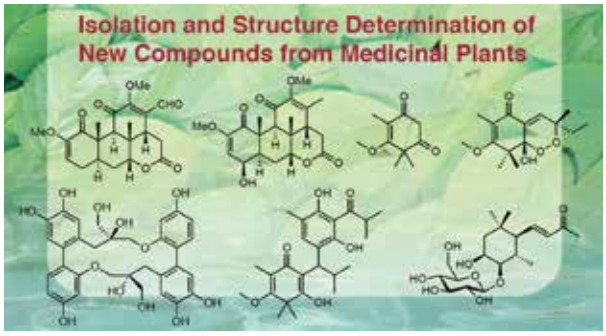
Basic research for naturally occurring bioactive substances in traditional natural medicines

1) Discovery of naturally occurring anti-HIV agents that inhibit HIV-1 Vpr protein from plants, microorganisms, and marine organisms and analysis of their inhibition mechanisms.
2) Studies on antibacterial agents from plants, microorganisms, and marine organisms based on the FtsZ's inhibitory activity.
3) Discovery of novel anticancer agents from plants, microorganisms, and marine organisms and synthesis of their derivatives.
4) Complex structure analyses between protein and natural product for developing novel medicines.
5) Investigation of Asia's natural resources not fully utilized.

Studies on biosynthesis of bioactive substances in traditional natural medicines

1) Crystal structure analyses of secondary metabolite enzymes.
2) Structure-based engineering of secondary metabolite enzymes to produce new compounds.
3) Heterologous expression and functional analysis of novel enzymes involved in the biosynthesis of bioactive substances.





【keywords】 Natural resources not fully utilized, Medicinal plant, Marine organism, Microorganism, Active secondary metabolite, Structure analysis of natural products, Anti-cancer, Anti-microbe, Anti-virus, Biosynthesis, Enzyme engineering, Genetic engineering, Structure analysis of Proteins

Division of Medicinal Pharmacology

Professor Kinzo Matsumoto, Ph.D.
Associate Professor Michihisa Tohda, Ph.D.
Assistant Professor Hironori Fujiwara, Ph.D.

In this laboratory, we investigate pharmacological effects and underlying mechanisms of traditional medicines which particularly target cognitive and neuropsychiatric disorders. Our studies aim 1) to clarify pathophysiology and onset mechanisms underlying cognitive and neuropsychiatric disorders, 2) to elucidate quantitatively the pharmacological effects of traditional medicines using model systems for the disorders, and 3) to identify active components of traditional medicines, molecular mechanisms of their actions, and endogenous factors mediating the actions.

Ⅰ. Experimental studies on pathophysiology, onset mechanisms, and prevention/therapy of neuropsychiatric disorders in animal models

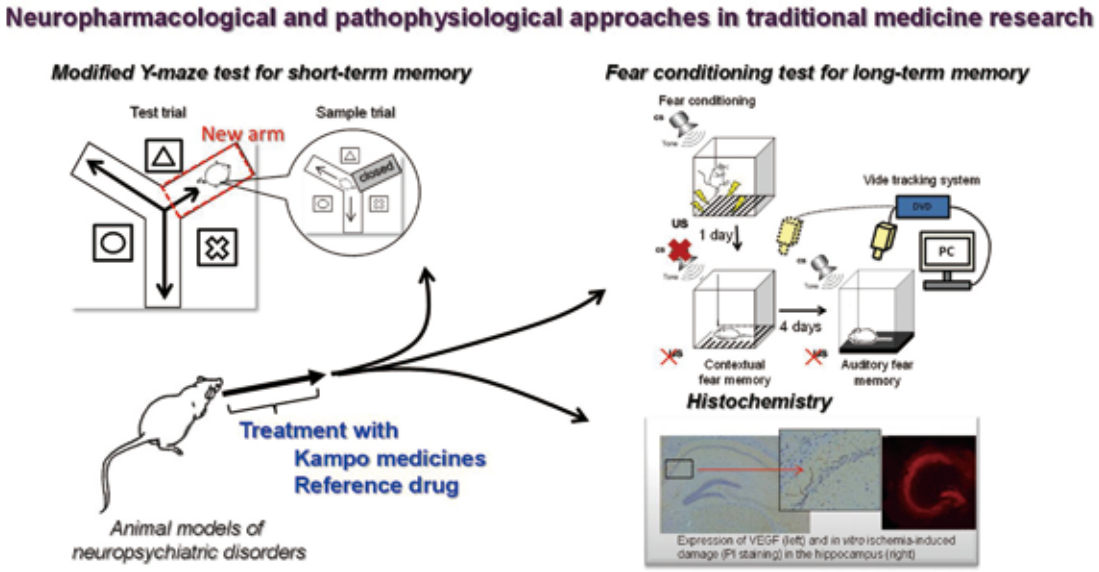
1) Pharmacological and neurobiological analysis of behavioral abnormalities caused in animal models of neuropsychiatric disorders such as social isolation rearing and chronic mild stress.
2) Elucidation of neurobiological activities of traditional medicines with preventive/therapeutic potentials for neuropsychiatric and developmental disorders in the models.

Ⅱ. Neuropharmacological studies on psychotropic actions of natural medicine materials

1) Elucidation of traditional medicine as anti-dementia/neuroprotective drugs, and clarification of the mechanisms underlying their actions.
2) Molecular pharmacological and electrophysiological analysis of the actions of psychotropic drugs using *in vitro* models of neurological disorders.

Ⅲ. Molecular biological studies on the actions of psychotropic drugs and traditional medicines

1) Studies to identify the depression-related intrinsic factors and to develop antidepressants with novel mechanisms, on the basis of the *Wakan-yaku* theories such as Yin-Yang and 5-Elememts.
2) Analysis of endogenous and exogenous factors mediating anti-dementia or anti-stress effects of traditional medicines.



【keywords】Sporadic dementia, Epigenetic neuropsychiatric disorder, Stress, Wakan-yaku theory

Division of Pathogenic Biochemistry

Professor Yoshihiro Hayakawa, Ph.D.
Assistant Professor Satoru Yokoyama, Ph.D.

The Major purposes in our department are to analyze the pathogenesis of various diseases such as cancer metastasis and immunological diseases, and to examine the regulatory effects of traditional medicines and their components and the molecular mechanisms using biochemical and immunological methods. In addition to investigate the isolation and identification of effective components from traditional medicines, it is also important to study the holistic patterns of symptoms and individual pathogenic alterations, so-called "Sho", by which the diagnosis of diseases states and the ways of treatment including prescriptions are determined. We have been studying the "Sho" to elucidate the molecular basis of pathogenic alterations in response to the traditional medicines by advanced technologies of molecular biology and immunology

Major research Projects

Investigation of the role of innate immune responses in cancer/immuno-pathology and its application for drug discovery

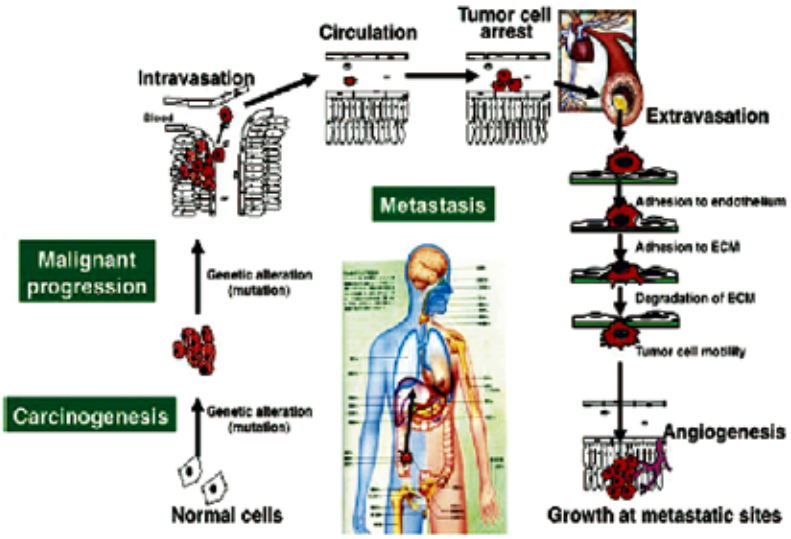
1) NK cell biology and their roles in the immune response to cancer
2) Role of innate immune responses in the cancer progression
3) Real-time in vivo imaging of cancer pathogenesis

Control of tumor growth and metastasis

1) Screening of effective substances in various tumor models
2) Control of tumor invasion and metastasis by various compounds
3) Molecular mechanism for epithelial-mesenchymal transition

Pharmacological and biochemical analysis of natural medicines

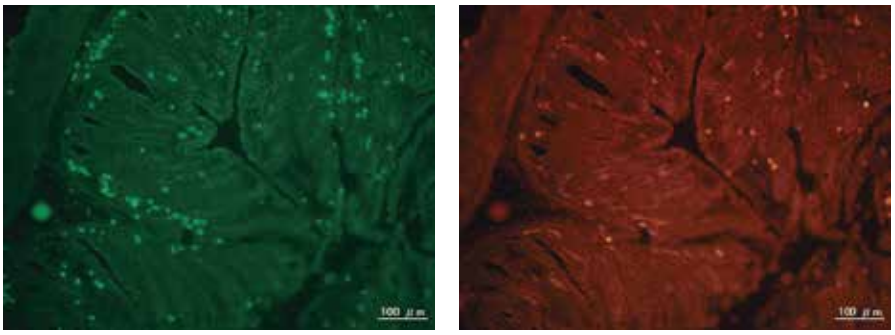
1) Combination therapy of anti-cancer agents and natural medicines
2) Effects of natural medicines on intracellular signalings



Division of Gastrointestinal Pathophysiology

Professor Makoto Kadowaki, Ph.D.
Assistant Professor Takeshi Yamamoto, Ph.D.
Assistant Professor Shusaku Hayashi, Ph.D.

The major aim in our laboratory is to clarify the pathogenesis and mechanisms underlying gastrointestinal disorders, especially enteric immune diseases using molecular biological, pharmacological, pathophysiological, immunological, morphological, and neurological techniques in the experimental models and cultured immune cells. Further, to integrate knowledge from experimental models to human diseases, our laboratory is engaged in the search for new seeds of the therapeutic medicines including Japanese traditional medicine (Kampo medicine) and new concept of the therapeutic mechanisms based on our experiments.



The number of nicotinic acetylcholine receptors (left) and $CD4^+$ helper T lymphocytes (right) are increased in the colon of ulcerative colitis model mouse.

In states of enteric immune diseases, such as ulcerative colitis or food allergy, various features of gut function, including motility, secretion and sensitivity are altered. The recent evidences for various direct nerve innervations of mast cells and other immune cells in the gut mucosa suggest that homeostatic regulation in the gut involves not only conventional neuro-effector functions but also neuro-immune cross-talk. Thus, for the maintenance of homeostasis in the living body, the gut is equipped with the highly organized mucosal intranet of the enteric nervous system and the enteric immune system.

1. Development of experimental models of the enteric immune diseases.

   Our research focus is mainly on the investigation of food allergy and ulcerative colitis. There are few useful experimental models of these diseases and so the pathogenic mechanisms underlying these diseases remain poorly understood.

2. Elucidation of the pathogenesis and mechanism underlying the enteric immune diseases.

   We are investigating the enteric immune diseases mainly from the viewpoint of disruption of "enteric intranet" organized by the enteric immune system, enteric nervous system and enteric endocrine system.

3. Search for new seeds of the therapeutic medicine on the enteric immune diseases.

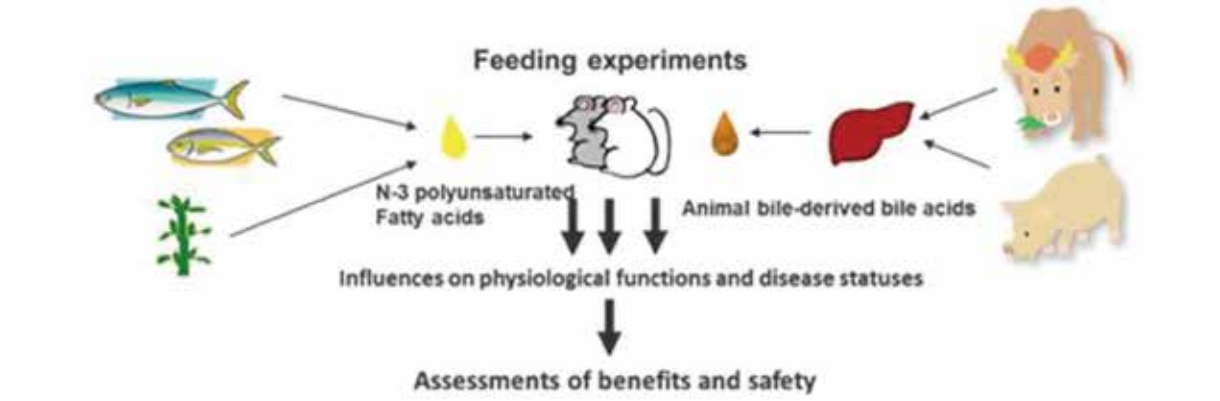
   Until now, there is no useful and selective therapeutic medicine for the enteric immune diseases. To break an innovative medicine, our laboratory is searching for new seeds, particularly from kampo medicines.

Division of Nutritional Biochemistry

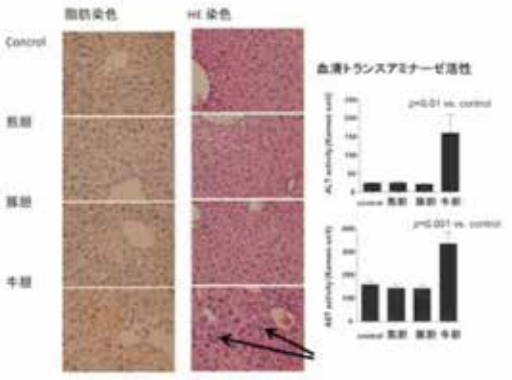
Associate Professor Shiro Watanabe, Ph.D.
Assistant Professor Kyosuke Fujita, Ph.D.

We focus on the novel functions and the assessment of safety of Wakan-yaku from viewpoints of lipid metabolism. Instrumental analysis of lipids and biochemical/molecular biological tests for lipid metabolism are the major techniques used in our research division. Special emphases of our recent research are on the effects of fish- or plant-derived n-3 polyunsaturated fatty acids and animal bile-derived bile acids on lipid metabolism and various diseases in the experimental animals. Followings are ongoing research projects.

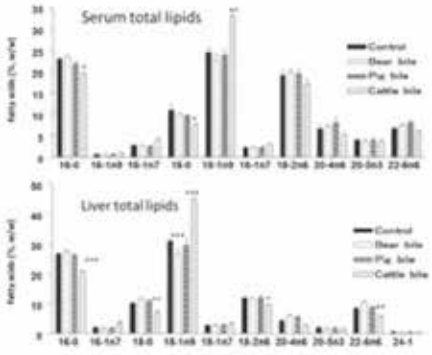
1) Influences of animal bile derived bile acids on lipid metabolism as well as pathophysiology in enterohepatic tissues
2) Detection by lipidomic approaches of novel actions of natural medicines in the modulation of lipid metabolism



Cattle bile induces steatohepatitis in mice



Lipidomic analysis for fatty acid profiling



Division of Kampo Diagnostics

Professor Naotoshi Shibahara, M.D., Ph.D.
Associate Professor Keiichi Koizumi, Ph.D.
Assistant Professor Michiko Jo, 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 division 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 Effect on edema, chronic renal disease and diabetes mellitus, Effect on mucosal immune activity, Effect on mucosal vaccine adjuvant, Analysis of in vivo kinetics, Influence of modified kampo prescriptions on pharmacological effect, Influence of quality of crude drugs on pharmacological effect, (2) Clinical researches on the concepts of kampo medicine and 'sho' Digitalization of the concepts of kampo medicine, Association between autonomic nervous system and the concepts of kampo medicine Effects of kampo prescriptions on stress, Clinical effects of kampo prescriptions on various diseases, (3) Researches of medical training program in kampo medical and pharmacology Educational effect of medical training program, Development of medical training program

Division of Neuromedical Science

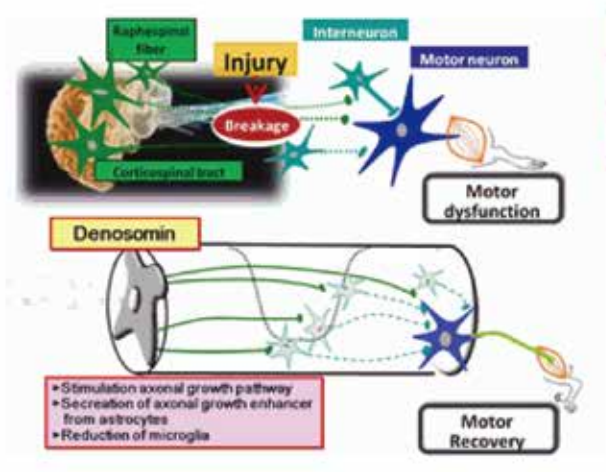
Professor Chihiro Tohda, Ph.D.
Assistant Professor Tomoharu Kuboyama, Ph.D.
Specially Appointed Assistant Professor Ximeng Yang, B.S.

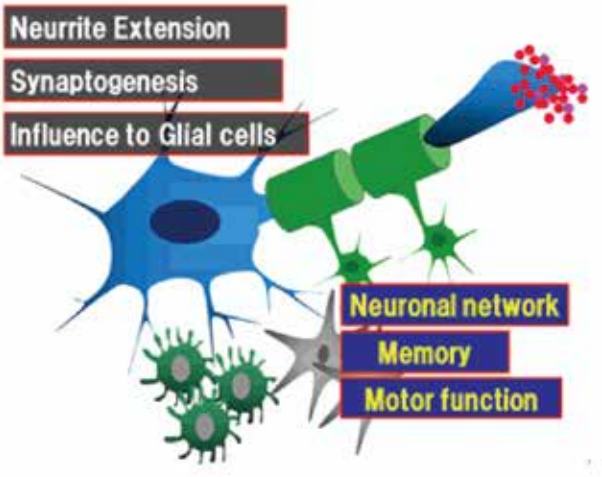
We have progressed studies which aim at overcoming neurodegenerative diseases and aging-related diseases, such as Alzheimer's disease, spinal cord injury and sarcopenia. For developing epoch-making pharmacotherapies and finding critical regulating factors against those diseases, we investigate them by multi-viewpoints such as pharmacological, neuroscientific and traditional medicinal approaches.

In Alzheimer's disease study, we found that several Kampo medicines and herbal drug-derived compounds remarkably improved memory dysfunction in model mice. Those traditional medicines and their ingredients possibly show us novel signaling pathways that elicit reconstruction of the neural network. Spinal cord injury (SCI) study based on traditional medicine has found several effective drugs that have multiple effects at least on neurons, astrocytes, microglia and skeletal muscles, resulting in conversion of their properties toward improvement of motor function. We are challenging to establish tremendous strategies to treat SCI patients in the chronic phase.

Research Projects

1) Integrative elucidation of the molecular mechanism of restoring the neuronal network in the central nervous system.
2) Traditional medicine research seeking fundamental therapeutic drugs for Alzheimer's disease, spinal cord injury or depression.
3) Clarifying the molecular mechanism of recovery from neurodegenerative diseases by focusing the glial cell-neuron interaction.
4) Drug development for skeletal muscle atrophy.
5) Proof of concept in humans aiming to develop new botanical drugs and new Kampo formulas.



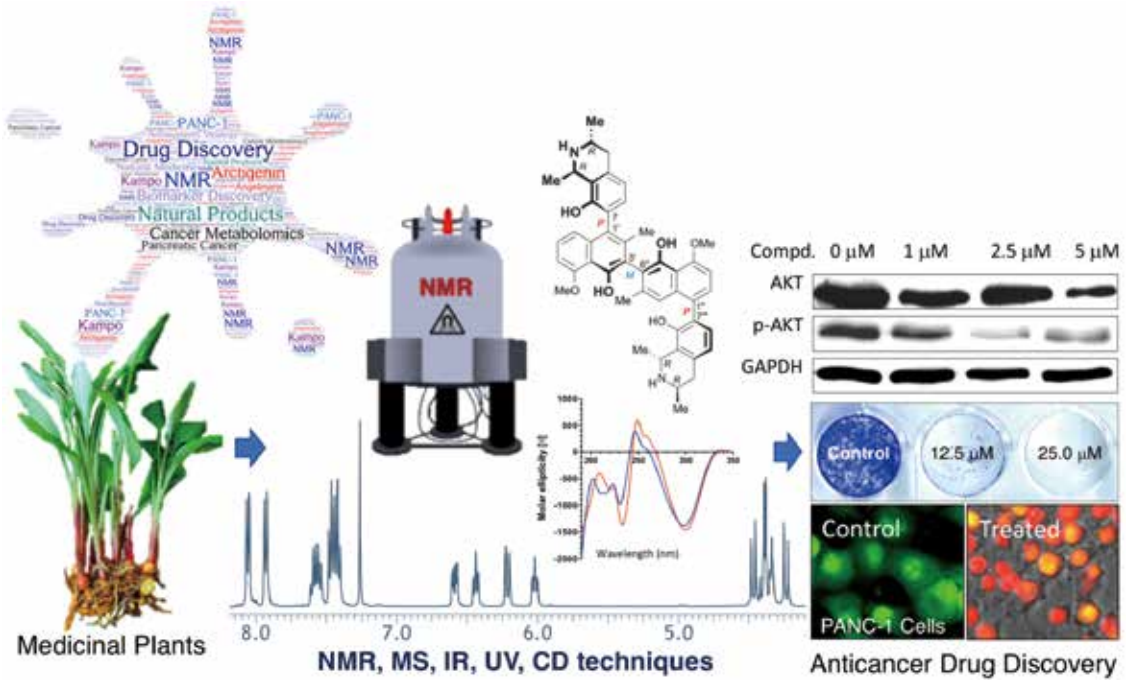


Division of Natural Drug Discovery

Associate Professor Suresh Awale, Ph.D.

The major research focus of our Division is the discovery of anticancer agents from natural sources by targeting cancer cells' characteristic performance, such as tolerance to nutrient starvation.

We welcome highly motivated students who have a dream to advance natural drug discovery research, and to contribute the better health to our human society. Our lab has an extensive cross-disciplinary scientific collaboration with national and international groups. We have established a unique NMR strategy based chemical biology approach to understand the effect of anticancer agents, cancer cells metabolism, and biomarkers discovery. In particular, we are actively engaged in the following areas.



1) Screening medicinal plants from different origins (e.g., Japanese Kampo, Ayurveda, etc.) for anticancer activity by employing unique anti-austerity strategy developed by our group.
2) Discovering novel anticancer drug candidates by using bioactivity as an index. The active plants are subjected to bioactivity-guided isolation and identification by utilizing state-of-the-art chromatographic techniques (e.g., MPLC, HPLC, etc.) and spectroscopic techniques (e.g., NMR, MS, UV, IR, CD, etc.). The structure-activity relationship of the lead compounds are investigated by studying their effects on the panel of other human cancer cell lines (e.g., PANC-1, MIA Paca-2, KLM-1, NOR-P1, Capan-1, PSN-1, Hela, A549, HepG2, etc.). Potential candidates are evaluated for their *in vivo* anti-tumor activity in xenograft model.
3) Elucidating the mechanism of the novel anticancer agents against the key cancer cell' survival pathway, and quantitative metabolome analysis using FT-NMR and FT-MS.

[Keywords] Drug Discovery and Development Research, Traditional Medicine, Kampo, Natural Products, Nuclear Magnetic Resonance (NMR), FT-MS, Cancer Research, Antiausterity Strategy, Mechanism of Action, Chemical Biology, Cancer Metabolomics, Biomarker Discovery.

WWW Publications Visit us on Facebook

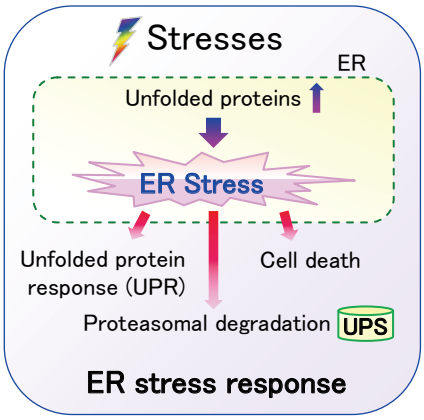
Molecular Genetics Research Laboratory, Life Science Research Center

Professor Yoshiaki Tabuchi, 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) Yunoki *et al.*: Gene networks of basal cell carcinoma of eyelid using gene expression profiles. *Oncol Lett* (in press)
2) Tazaki *et al.*: RANKL, Ephrin-Eph and Wnt10b are key intercellular communication molecules regulating bone remodeling in autologous transplanted goldfish scales. *Comparative Biochemistry and Physiology: Part A: Molecular & Integrative Physiology* (in press)
3) Hanmoto *et al.*: Effects of low-intensity pulsed ultrasound on osteoclasts: Analysis with goldfish scales as a model of bone. *Biomed Res* **38**, 71-77 (2017)

Please visit our website at
http://www.lsrc.u-toyama.ac.jp/mgrc/html/laboratory.html.

E-mail : ytabu@cts.u-toyama.ac.jp

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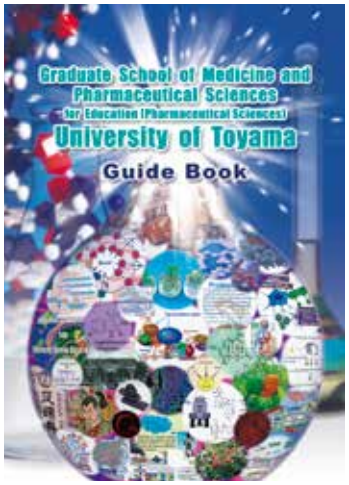
Toyama is proud of the Tateyama mountain range, which includes magnificent 3,000- meter peaks. Among them is Yakushidake peak, on top of which is located a small shrine dedicated to a Bhêchadjaguru, the healing Budda. With a medicine pot in his left hand, he has been the subject of mountain worship as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

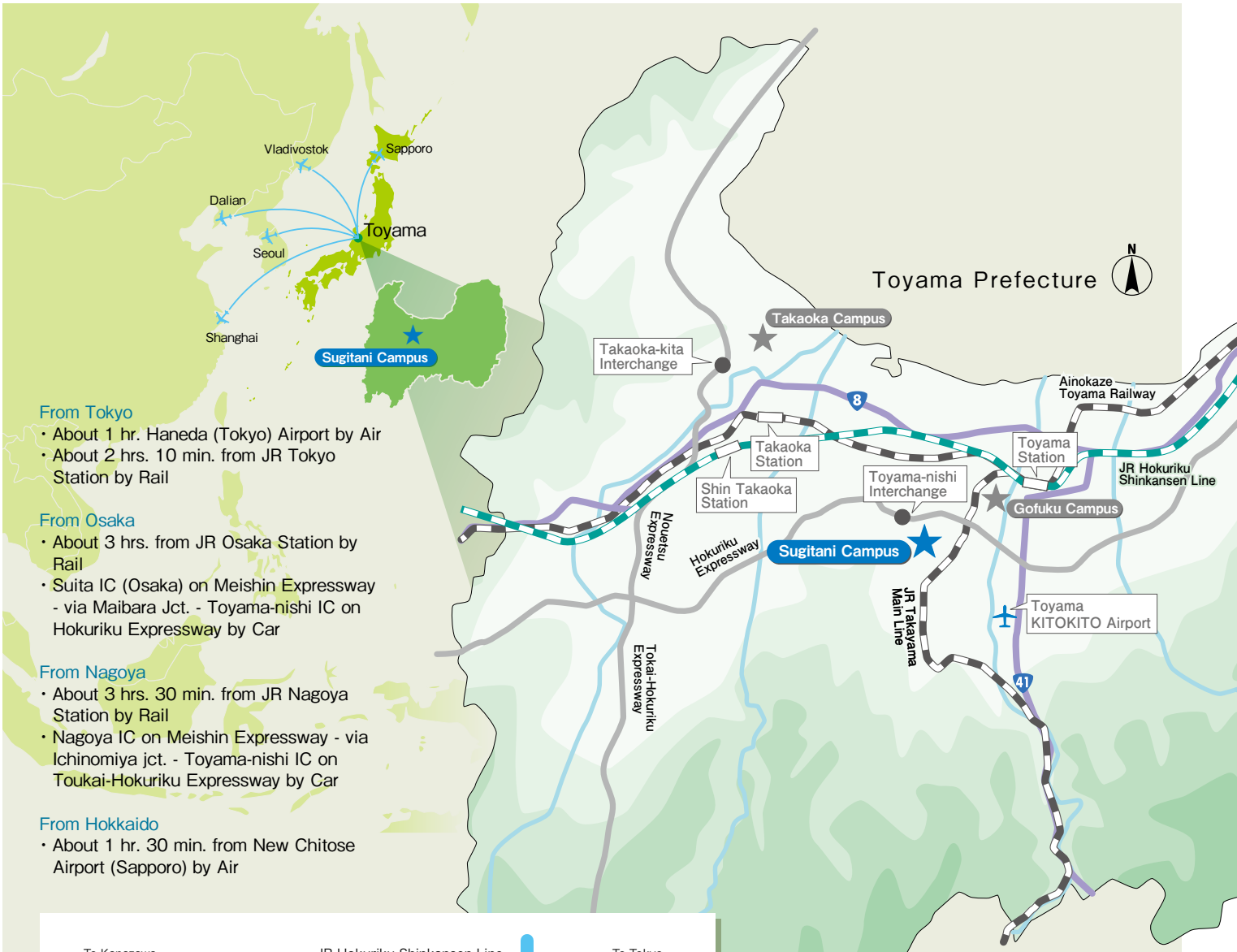


Explanation of the cover

Faculty of Pharmaceutical Sciences, University of Toyama has a long history of 120 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



From Tokyo

- About 1 hr. Haneda (Tokyo) Airport by Air
- About 2 hrs. 10 min. from JR Tokyo Station by Rail

From Osaka

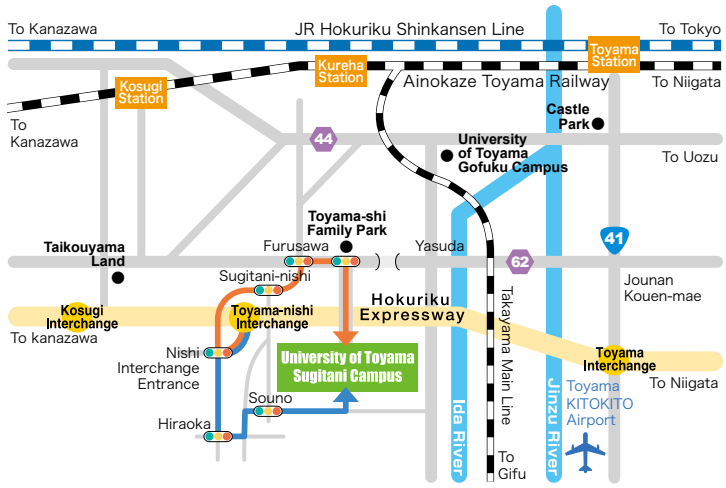
- About 3 hrs. from JR Osaka Station by Rail
- Suita IC (Osaka) on Meishin Expressway - via Maibara Jct. - Toyama-nishi IC on Hokuriku Expressway by Car

From Nagoya

- About 3 hrs. 30 min. 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 20 minutes from JR Toyama Station to the Sugitani Campus
Approximately 20 minutes from Toyama KITOKITO Airport to the Sugitani Campus

By Car

Approximately 4 minutes from the Hokuriku Expressway Toyama-nishi Interchange to the Sugitani Campus

University of Toyama Sugitani Campus

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

Graduate School of Medicine and Pharmaceutical Sciences

for Education (Pharmaceutical Sciences)

University of Toyama

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