

2022

PHARMACEUTICAL SCIENCES

KYUSHU UNIVERSITY



PHARMACEUTICAL SCIENCES CONTRIBUTE TO HUMAN HEALTH

Pharmaceutical sciences contribute to human health

What should be done by pharmaceutical scientists?

Pharmaceutical sciences affect both life sciences and physical sciences, and focus on the study of human health and diseases. Pharmaceutical sciences aim to develop new medicines to improve health and encourage the correct use of drugs. Pharmaceutical sciences also contribute to the creation of new knowledge and technology that contribute to the improvement in human health and welfare.

In recent years, novel findings and discoveries have been reported in many areas of the life sciences. The pharmaceutical sciences have contributed to such advances. For example, the success of human genome project has prompted us to investigate the function of each gene and its products. Regarding human diseases, gene therapy has been applied to a number of disorders, and tissue engineering, including stem cell technology, is expected to be of major benefit in the treatment of many complex disorders. Tailor-made treatments are no longer simply a dream. Analyses of the DNA polymorphisms of each person will make such therapy possible in the future. Advances in chemistry as well as bioinformatics and computer science have allowed us to design and synthesize drugs which interact with important bioactive molecules such as enzymes and receptors. These new advances are expected to lead to the development of new treatments for a number of presently incurable diseases. Thus, the pharmaceutical sciences are very important and essential for the future of human health and welfare.

Pharmaceutical Sciences in Kyushu University: subject and goal

Students in the undergraduate school are supposed to study pharmaceutical sciences so that they become highly educated scholars in these fields related to medicine and patient care. They are also expected to become responsible members of society with a highly developed morality. Students are encouraged to learn to develop a creative approach to the pharmaceutical sciences. They are also encouraged to study a wider range of scientific disciplines since the pharmaceutical sciences address many issues including the mechanisms governing life itself, environmental factors affecting health, advanced technology associated with the production of new medicines, and strategies for the safe usage of medicines. What is medicine? What is life? How to use medical drugs? To answer these questions, students are supposed to learn the importance of pharmaceuticals and the role of drugs in treatment by studying general sciences. This approach encourages the students to consider various important issues such as the risk posed by drugs to human life.

The graduate school of pharmaceutical sciences educates students so that they become experts or researchers in this field. The school also expects that the students should become scholars with a social responsibility at an international level. Therefore, the students are supposed to be trained not only in the pharmaceutical sciences but also in general science.

For foreign students

To the students who are planning to study in Graduate School of Pharmaceutical Sciences, Kyushu University, you need to follow the steps as described below before you apply to Graduate Course.

Before you apply to Graduate School of Pharmaceutical Sciences, you must contact one of professors who is working on the field that you are interested in, and obtain the agreement from the professor. This agreement is essential for applying to Graduate School of Pharmaceutical Sciences.

After you obtain the agreement from the professor, you have two options.

Option A:

Before you take an examination for entering Graduate course, you can spend a time for preparing the examination and getting familiar with laboratory as a research student. Almost all students take this option A. The information of research student is found in home page of Graduate School of Pharmaceutical Sciences (<http://www.phar.kyushu-u.ac.jp/>). The application as a research student should be approved by faculty council. Whole procedure from receiving the document by the office to approving it by the council will take 2-3 months. Therefore, you should consider the period of processing time before you start the life in Kyushu University as a research student.

Go to the following site in Home Page of Graduate School of Pharmaceutical Sciences for application of research student:

<http://www.phar.kyushu-u.ac.jp/>

This site also includes information of schedule of the entrance examination for Graduate Course.

Option B:

You can directly take an examination for entering Graduate Course without spending as a research student in professor's laboratory.

The following sites are also helpful for the students who are interested in studying in Graduate School of Pharmaceutical Sciences, Kyushu University.

The site of International Affairs Department includes the information of accommodation, immigration procedures, and others.

1. International Affairs Department, Kyushu University

Go to the following web site,

<http://www.isc.kyushu-u.ac.jp/intlweb/>

The information of scholarship is often changed. Please check the newest information at the following site.

2. For Scholarship, go to the following web site,

<http://www.isc.kyushu-u.ac.jp/intlweb/scholarship/view/list.php>

Clinical Pharmacokinetics

Professor: Naoya Matsunaga, Ph.D.
 Assistant professor: Yuya Yoshida, Ph.D.



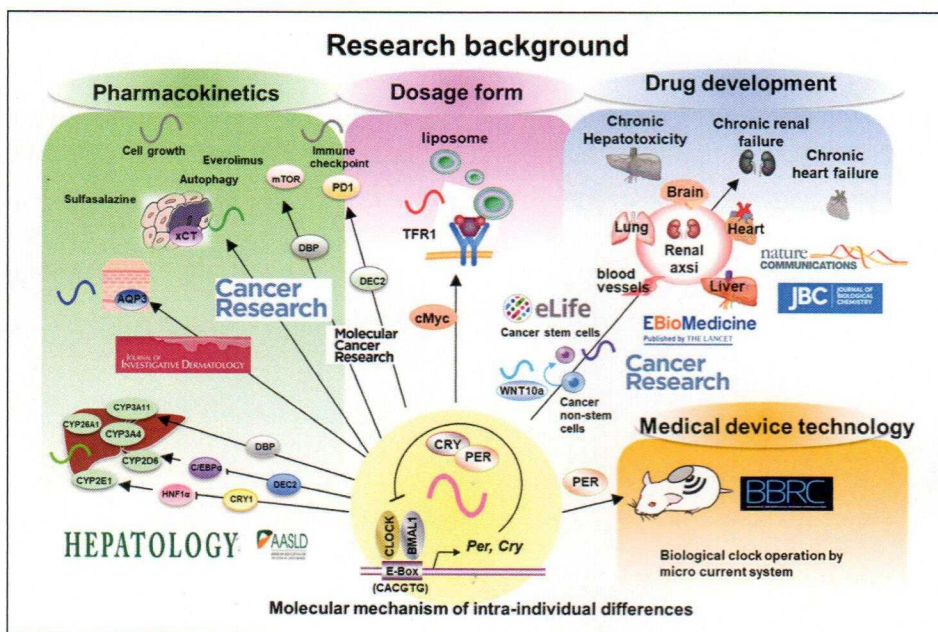
Prof. Matsunaga



Assistant Prof. Yoshida

Research

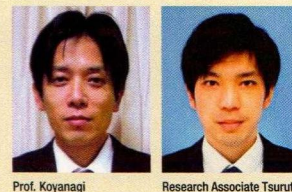
The circadian rhythm, which regulates various body functions, is transcriptionally controlled by a series of clock gene clusters. Clock genes encoding transcription factors that regulate circadian rhythms may inform chronomodulated drug therapy, where time-dependent dose alterations might affect drug efficacy and reduce side effects. We investigate the mechanism of circadian rhythms in drug metabolism and excretion. On the other hand, the clock genes are related to the pathology of various kinds of diseases, cancer, chronic kidney disease (CKD), hepatotoxicity. We investigate the role of cancer stem cells (CSC), chronic kidney disease (CKD), hepatotoxicity and cognitive dysfunction based on the circadian clock. Aging in humans is a worldwide problem; it induces sleep disorders and disruption of the circadian rhythm. We develop a simple method for the synchronization of drug metabolism and clock genes in the body is required.



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Contact Naoya Matsunaga
 TEL: 092-642-6656 FAX: 092-642-6660
 E-mail: matunaga@phar.kyushu-u.ac.jp



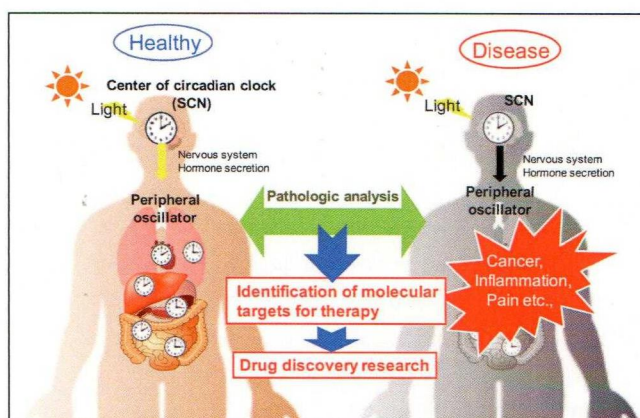
Research

The major objective of our research is to understand the molecular mechanisms for day-night changes in the pathological events and the impact of circadian rhythms on the onset of diseases. Based on these mechanism, we attempt to identify new therapeutic target and to develop novel strategy for treatment of diseases.

Molecular mechanism of circadian clock

The circadian clock is a timekeeping system that allows organisms to adapt their physiological and behavioral functions to anticipatory changes in their environment. In mammals, the circadian clock system is hierarchically organized, consisting of a light-responsive central clock in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus and subsidiary clocks in other brain regions and peripheral tissues. The SCN entrains and synchronizes subsidiary clocks with the environmental light-dark cycle, whereas subsidiary clocks in periphery regulate tissue-specific functions for sustaining homeostasis and our health.

Central and peripheral clocks are both governed by a molecular oscillator driven by transcriptional-translational feedback loop consisting of "circadian clock genes".



Chronopharmacotherapy and identification of new therapeutic target

Recent developments in our understanding of circadian biology and the availability of tools to characterize this oscillation system indicate that the choosing appropriate dosing time have consequences for the efficacy and safety of new and existing therapeutic drugs (Chronopharmacotherapy). Progression of this research field also suggests that many pathological conditions are under the control of the circadian clock. These notions reveal opportunities for new therapeutic strategies. Now novel therapeutic approaches are facilitated by development of chemical probes and synthetic ligands targeted to an increasing number of the key proteins that causing circadian exacerbation of pathological events.

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Department of Molecular and System Pharmacology

Professor: Makoto Tsuda, Ph.D.
 Associate Professor: Takahiro Masuda, Ph.D.
 Assistant Professor: Yuta Kohro, Ph.D.
 Assistant Professor: Miho Shiratori-Hayashi, Ph.D.
 Assistant Professor: Risako Fujikawa, Ph.D.
 Assistant Professor: Mami Kato, Ph.D.



Prof. Tsuda



Associate Prof. Masuda



Assistant Prof. Kohro



Assistant Prof. Shiratori-Hayashi



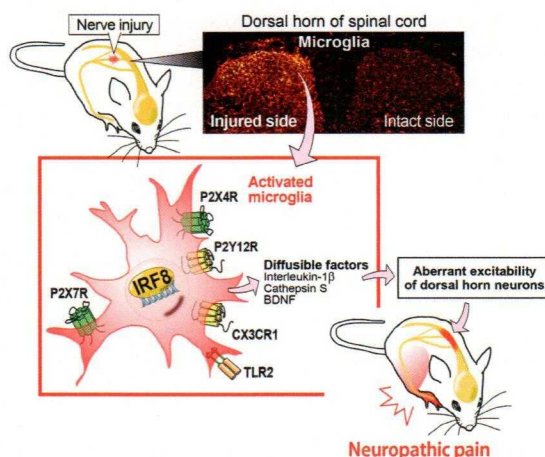
Assistant Prof. Fujikawa



Assistant Prof. Kato

Research

Although it was long believed that glial cells in the nervous system were merely physical and nutrient supports for neurons, an increasing body of evidence has dramatically changed this classical view and indicates that neuron–glia interactions play a key role in central nervous system (CNS) functions under physiological and pathological conditions, including chronic pain and itch. Chronic pain (especially neuropathic pain, pain that occurs after nerve damage that can be induced by bone compression in cancer, diabetes, infection or physical injury) and chronic itch (such as atopic and contact dermatitis and systemic diseases) are both highly debilitating conditions and increasingly being recognized as a consequence of disordered functioning of the nervous system. Optimally treating chronic pain and itch is a major clinical challenge because the underlying mechanisms remain unclear and currently available treatments are frequently ineffective. Work in my laboratory is primarily directed to elucidating glia–neuron interactions in the spinal cord and brain and to understanding the cellular and molecular mechanisms of pathological chronic pain and itch with the goal of counteracting these mechanisms in order to devise strategies for new types of pain- and itch-relieving medications.



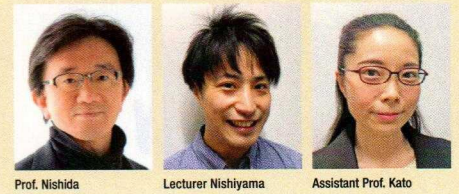
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Contact Makoto Tsuda
 TEL: 092-642-6628
 E-mail: tsuda@phar.kyushu-u.ac.jp
 URL: <http://life-innov.phar.kyushu-u.ac.jp/index.html>

Department of Physiology

Professor: Motohiro Nishida, Ph.D.
 Lecturer: Kazuhiro Nishiyama, Ph.D.
 Assistant Professor: Yuri Kato, Ph.D.

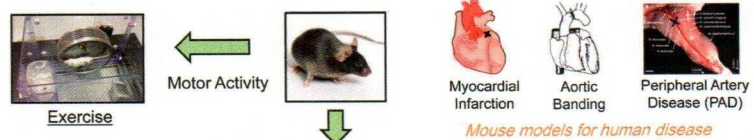


Research

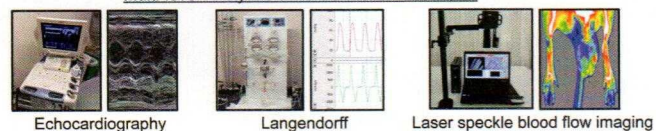
Our cardiocirculatory function is mainly controlled by muscular organs composed of striated muscles (heart and skeletal muscles) and smooth muscle (blood vessels). We aim to elucidate the molecular mechanisms underlying transition of these muscles from adaptation to maladaptation against environmental stress (mainly hemodynamic load) multi-level techniques to evaluate cardiovascular functions (in vivo and in vitro), and work toward practical application (e.g., drug discovery and repurposing (Echo-pharma)). We also investigate the mechanism of muscle repair and regeneration, and aim to develop a novel therapeutic strategy for refractory diseases. In addition, we address the inclusive research to elucidate the mechanism underlying maintenance and transfiguration of cardiocirculatory homeostasis via multi-organ interactions by combining non-invasive measuring methodologies of motor functions and those cardiovascular functions.

Our laboratory has various techniques and equipments to drive the above researches.

1. Non-invasive measurements of muscular functions : Echo-cardiography (mouse and rat), Laser Doppler flowmetry (mouse), Measuring devices of motor activity (mouse), Tail-cuff (mouse and rat), blood pressure telemetry (mouse)

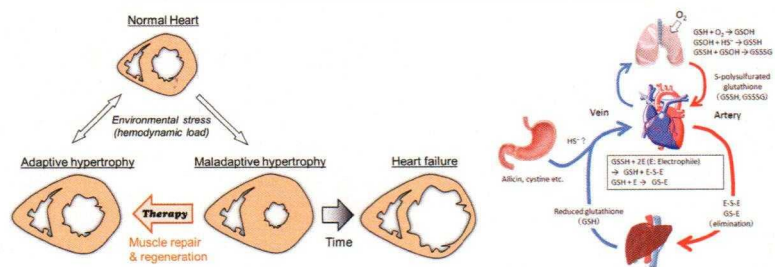


2. Invasive measurements of cardiovascular functions : Langendorff perfusion system (mouse and rat), Mouse millar catheter (for P-V loop measurement)



3. Isolation of primary-cultured cells and experiments : mechanical stretching machine, Ca²⁺ imaging, FRET imaging, Confocal laser microscopy, Patch-clamp recording, Plate reader (BRET assay, post-translational modification analyses)

Elucidation of Multi-level interactions based on the cardiocirculatory system and molecular mechanisms of cardiovascular diseases



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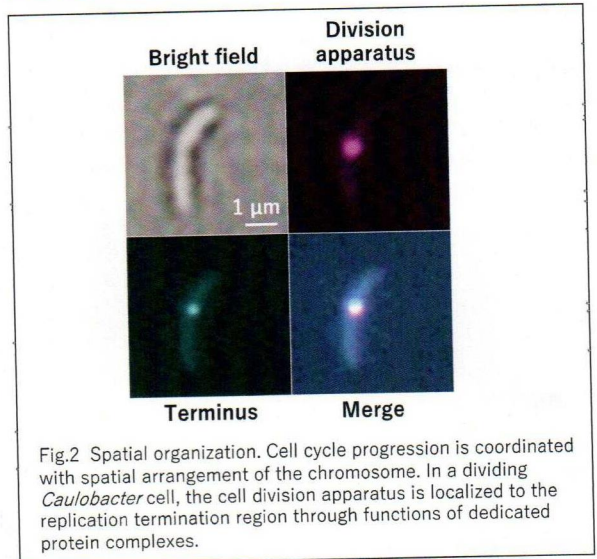
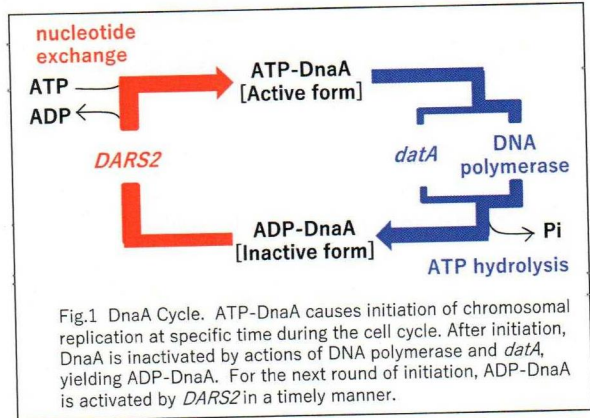
Molecular Biology

Professor: Tsutomu Katayama, Ph.D.
 Associate Professor: Shogo Ozaki, Ph.D.
 Assistant Professor: Kazutoshi Kasho, Ph.D.



Research

In the cell cycle progression, chromosomal DNA is replicated only once at a specific time by the carefully controlled molecular switch for replicational initiation. In addition, the replicated chromosomes are translocated in cells for equipartition. If these regulations are interfered with, various cell defects occur, such as abnormal chromosomes, and inhibitions in cell division and growth of abnormal cells. Thus, study on these regulatory mechanisms is of significance as a basis for the developments of antibiotics and anticancer drugs. We have shown that DnaA protein initiating *E. coli* chromosomal replication is activated in a timely manner by forming a specific complex on a non-coding DNA region termed *DARS2* (Fig. 1). After initiation, DnaA is inactivated in a timely manner by two different regulatory systems: one is coupled with loading of DNA polymerase on DNA and the other depends on a non-coding DNA region termed *datA* (Fig. 1). In addition, we have revealed fundamental structure and dynamics in DnaA complexes formed on the replication origin (*oriC*) which are essential for DNA duplex unwinding for initiating replication. Moreover, we found specific protein complexes which regulate migration of the chromosomes in *Caulobacter crescentus* by mediating the replication termination region and the cell division apparatus (Fig. 2). These studies provide a substantial contribution to our knowledge on molecular biology and bacterial chromosome dynamics, which opens various opportunities to advance basic and applied pharmaceutical biochemistry.



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Contact Tsutomu Katayama
 TEL: 092-642-6641 FAX: 092-642-6646
 E-mail: katayama@phar.kyushu-u.ac.jp
 URL: <http://bunsei.phar.kyushu-u.ac.jp/>

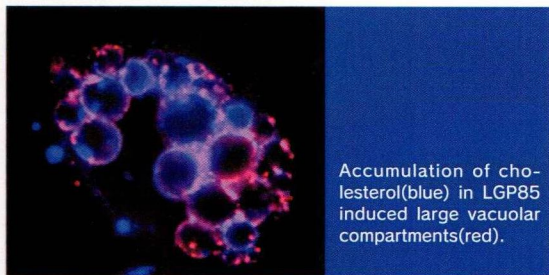
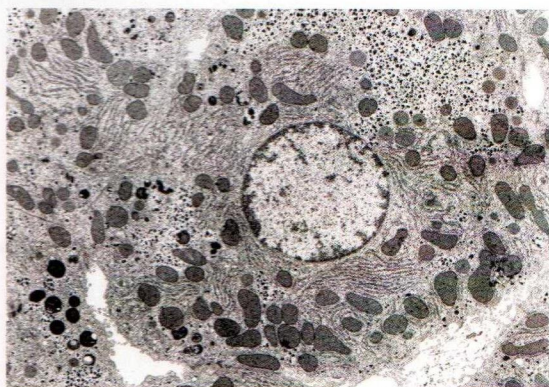
Pharmaceutical Cell Biology

Professor: Yoshitaka Tanaka, Ph.D.
Associate Professor: Yuji Ishii, Ph.D.
Assistant Professor: Yuko Hirota, Ph.D.
Assistant Professor: Keiko Fujimoto, Ph.D.



Research

This laboratory focuses on lysosomes because they exhibit a number of important basic functions (digesting proteins, lipids, carbohydrates and organelles and supplying acid hydrolases for programmed cell death) as well as having a highly specialized organization and functions in specialized cells (melanosomes in melanocytes, lytic granules in lymphocytes)(Project 1). We want to understand the molecular basis of lysosomal membrane proteins and how they contribute to cell physiology. Our initial approach was to study the function of specific lysosomal membrane proteins. We have prepared and used knockout mice to understand their physiological significance and found that LAMP2 function plays a role in a number of human diseases. We subsequently showed that LGP85 responds to membrane traffic to lysosomes via the cell expression system. An important goal is to identify the protein machinery that regulates membrane traffic to lysosomes. Using specific probes and materials (antibodies, ligands and cDNAs), we have been studying the molecular mechanism of membrane traffic to lysosomes and successfully identified several molecules which regulate membrane traffic to lysosomes. Our research has implications for some neurodegenerative diseases, since lysosome dysfunction is directly linked to many human diseases. Lysosomal biogenesis has relevance to virus budding, and thus our research also has many potential implications for viral pathogenesis.



Accumulation of cholesterol(blue) in LGP85 induced large vacuolar compartments(red).

This laboratory is also involved in the following toxicological areas: the molecular mechanism of dioxin toxicity (Project 2); and functional cooperation of phase I and II drug metabolizing enzymes (Project 3).

In the Project 2, our main interest is focused on the molecular mechanism whereby dioxins produce their reproductive and developmental toxicity. Accumulating evidence we provided suggests that dioxin-mediated damage to fetal gonadotropins imprints defects which are continued until adult ages. The methodology how we can combat with TCDD-produced damage to next generations is also being investigated.

We are trying to establish a new concept in the Project 3. It is well known that drug-metabolizing enzymes play an important role in the detoxification and activation of foreign chemicals. Although different sorts of drug-metabolizing enzymes have long been considered to work separately, our recent studies have demonstrated that cytochrome P450 (representative phase I enzyme) binds to phase II enzymes such as UDP-glucuronosyltransferase. This association is functional interaction resulting in a change in the function of both enzymes. It is one possibility that such interaction explains the inter-individual difference in drug sensitivity.

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Contact

Yoshitaka Tanaka
TEL: 092-642-6618 FAX: 092-642-6619
E-mail: ytanaka@phar.kyushu-u.ac.jp
URL: <http://saisei.phar.kyushu-u.ac.jp/>
URL: <http://eisei.phar.kyushu-u.ac.jp/>

Pharmacognosy

Professor: Satoshi Morimoto, Ph.D.
 Associate Professor: Seiichi Sakamoto, Ph.D.
 Assistant Professor: Naoya Shindo, Ph.D.



Prof. Morimoto



Associate Prof. Sakamoto



Assistant Prof. Shindo

Research

1. Three enzymes (THCA-, CBDA-, CBCA-synthases) which catalyze biosynthesis of marijuana compounds (cannabinoides) were purified from *Cannabis* leaves, and their enzymatic properties were extensively investigated in our laboratory. We have now attempted molecular cloning, expression and crystallization of these synthases. Among them, we succeed in determination of the crystal structure of THCA synthase, and based on these data, the mechanism of THCA-synthase reaction has been examined. Recently, we also focused on allelopathy of *Cannabis* leaves.
2. We found that morphine is metabolized to bismorphine in response to stress in opium poppy. This bismorphine specifically binds to pectin in the cell wall of opium poppy, resulting in resistance to hydrolysis by pectinase.
3. We have developed immunochemical analyses for quantitative determination of natural products using monoclonal antibody, such as an enzyme-linked immunosorbent assay, immunochromatography and Eastern blotting. These were confirmed as a highly reliable methods with sufficient accuracy to be useful for quality control of crude drugs.

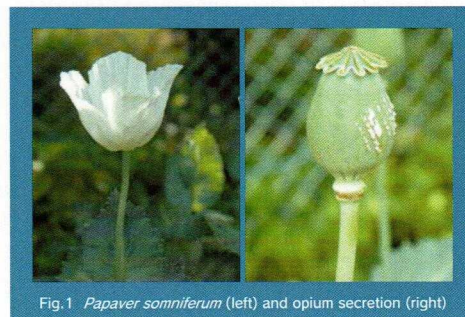


Fig.1 *Papaver somniferum* (left) and opium secretion (right)

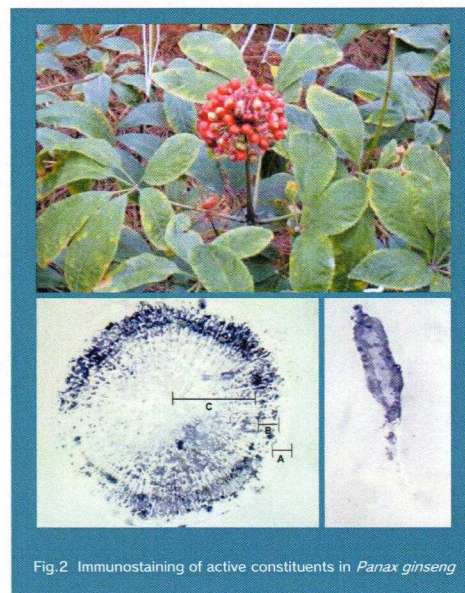


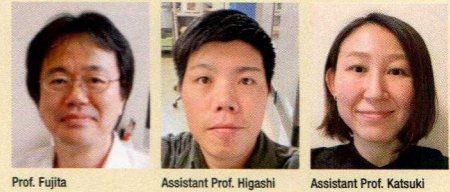
Fig.2 Immunostaining of active constituents in *Panax ginseng*

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Contact Satoshi Morimoto
 TEL/FAX: 092-642-6580
 E-mail: morimoto@phar.kyushu-u.ac.jp
 URL: <http://seigyo.phar.kyushu-u.ac.jp/>

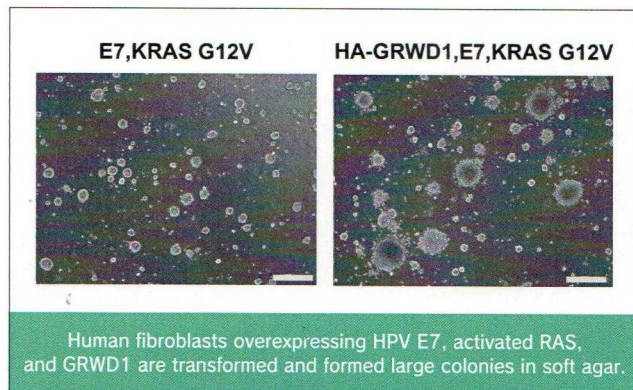
Professor: Masatoshi Fujita, M.D., Ph.D.
Assistant Professor: Torahiko Higashi, Ph.D.
Assistant Professor: Yoko Katsuki, Ph.D.



Research

We have been clarifying molecular mechanisms of chromosomal DNA regulations, deregulation of which would lead to chromosomal instability and eventually cancer. Actually, we recently revealed that GRWD1, a Cdt1-binding protein, act as an oncogene. Now, we have been especially focusing on:

1. Functions and cell cycle regulations of DNA replication initiation proteins, ORC, CDC6, Cdt1, MCM, and related factors.
2. Involvement of the replication initiation proteins in telomere homeostasis.
3. Molecular mechanisms for ATM- and ATR-mediated cellular responses to chromosomal stress and involvement of the replication initiation proteins in such processes.
4. Relationship between chromatin regulations (by chromatin remodeler and histone chaperone) and replication/telomere/checkpoint regulations.
5. Novel MCM8/9 inhibitors that selectively hypersensitize cancer cells to platinum compounds and PARP inhibitors.



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Professor: Jose Caaveiro, Ph.D.

Assistant Professor: Tomohiro Yamashita, Ph.D.



Research

In the laboratory of Global Healthcare we address topics relevant to universal public health. (1) We seek to elucidate the molecular basis of diseases of global reach such as cancer, infectious diseases (AIDS, Influenza, and MRSA) and neurodegenerative diseases. (2) We apply state of the art screening technologies to find novel compounds to fight disease, and also to ameliorate those suffering from chronic and neuropathic pain. And (3) we develop technologies for a more efficient use of antibodies and other immunological proteins by employing rational design methodologies. With strong support from the recently created Green-Pharma Research Center, and relying on a large network of collaborators, we aim to make decisive contributions to improve human well-being. We also hope to augment the international presence of the School of Pharmaceutical Sciences, and to catalyze the emergence of leadership students with a deeper understanding of global issues.

<p>Drug Discovery</p>	<p>Drug Discovery Research systems</p>	
<p>Antibodies</p>	<p>Functional Drug Screening System</p>	<p>Imaging Cytometer</p> <p>Fluorescent imaging in automatic microscope</p>
	<p>Reagent Dispenser</p> <p>pipetting, dilution, dispensing</p>	<p>We support discovery of new drug targets or seeds from "drug ideas" in academia.</p>

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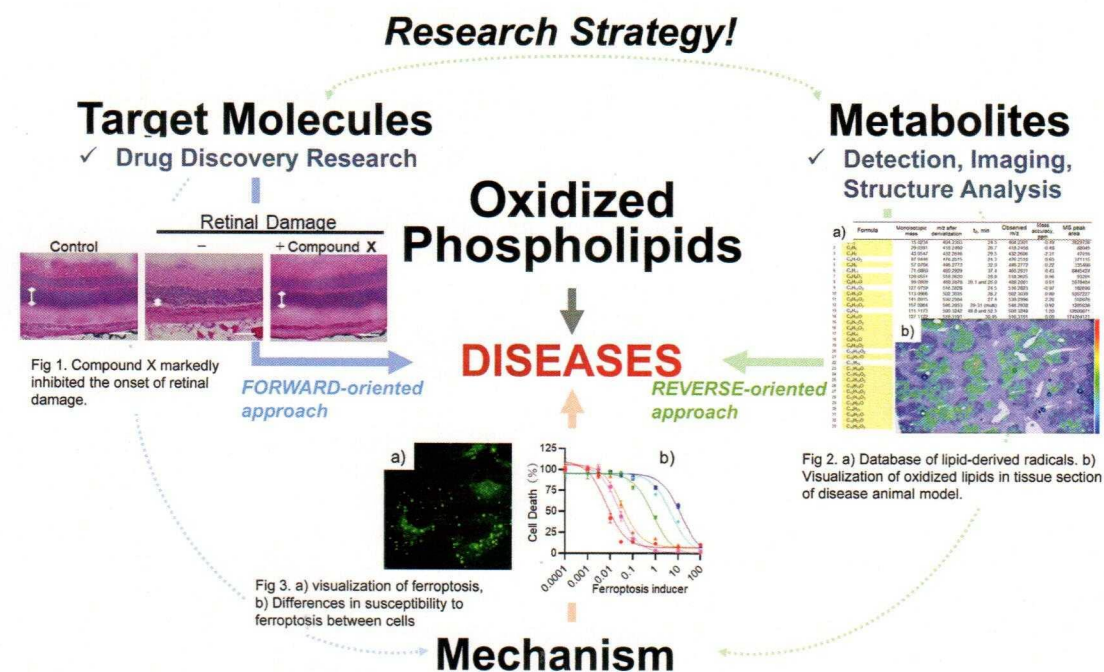
Contact Jose Caaveiro
 TEL: 092-642-6617
 E-mail: jose@phar.kyushu-u.ac.jp
 URL: <https://global.phar.kyushu-u.ac.jp/>



Research

Lipids and their metabolites are easily oxidized in chain reactions initiated by lipid radicals, forming lipid peroxidation products including the electrophiles 4-hydroxynonenal and malondialdehyde. These products can bind cellular macromolecules, causing inflammation, apoptosis and other damage. Methods to detect and neutralize the initiating radicals/oxidized lipids would provide insights into disease mechanisms and new therapeutic approaches. In our laboratory, several research projects are in progress:

1. Drug discovery research targeting oxidized lipids
2. Detection, structural analysis, and visualization of oxidized lipids
3. Mechanism of how oxidized lipids are involved in disease development

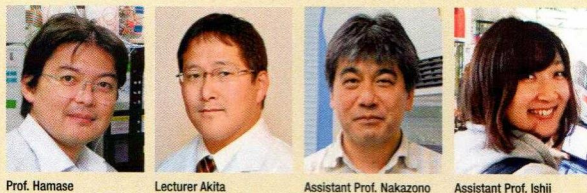


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Drug Discovery and Evolution

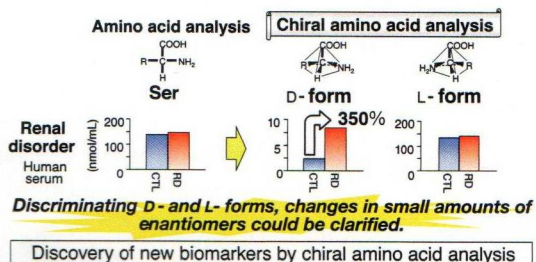
Professor: Kenji Hamase, Ph.D.
Lecturer: Takeyuki Akita, Ph.D.
Assistant Professor: Manabu Nakazono, Ph.D.
Assistant Professor: Chiharu Ishii, Ph.D.



Drug Discovery and Evolution is a department dedicated to the researches on industry, university and government collaboration. We have developed and expanded the "only one" innovative analytical technology in the world focusing on chiral amino acids and related compounds. Using the methods, we are investigating new biologically active substances for drug discovery, and also investigating new biomarkers for early diagnosis of various diseases. New functional foods, beverages and cosmetics are also designed and produced.

Research

- 1) Drug discovery and diagnosis using enantioselective metabolomics
Trace levels of chiral amino acids, hydroxy acids and peptides are found in mammals including humans. We have established highly sensitive and selective analytical methods for the enantioselective metabolomics studies resulting in the discovery of novel physiologically active molecules and early diagnostic markers.



- 2) Anti-aging research focusing on isomerization of proteins
Analysis of D-amino acid residues in proteins is normally difficult due to the racemization during hydrolysis. We have established a novel method for the screening of D-amino acids in proteins, and anti-aging researches are carried out focusing on the isomerization of amino acids in proteins.



Analysis of D-amino acids in aged proteins

- 3) Development of new analytical reagents, materials and instruments
Development of high-performance analytical methods is the key to progress all researches. For the sensitive analysis of D-amino acids in complicated biological matrices, we designed and practically realized various analytical reagents, materials and instruments.



Commercially available collaboration products



Multi-dimensional HPLC system

- 4) Development of novel functional foods, beverages and cosmetics including D-amino acids
By the discovery of physiologically active D-amino acids, novel functional foods, beverages and cosmetics could be designed. We have developed various products by the industrial - academic - government cooperation researches.

Publications

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Contact

Kenji Hamase
TEL/FAX: 092-642-6598
E-mail: hamase@phar.kyushu-u.ac.jp
URL: <http://soyaku.phar.kyushu-u.ac.jp/>

Medicinal Chemistry & Chemical Biology

Professor: Akio Ojida, Ph.D.
 Assistant Professor: Shohei Uchinomiya, Ph.D.



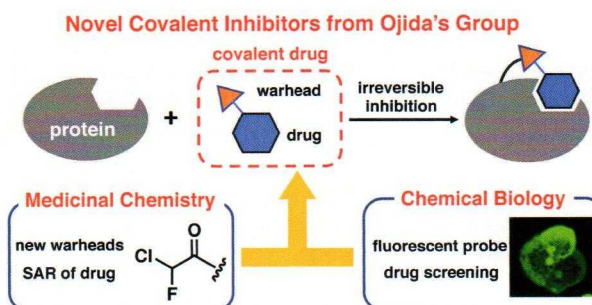
Prof. Ojida



Assistant Prof. Uchinomiya

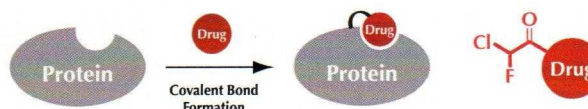
Research

Advantages of covalent drug can be found in strong and long-duration of biological effect, which are often difficult to be achieved by usual reversible drugs. Our goal is to develop novel covalent drugs through combination of medicinal chemistry and chemical biology approaches.



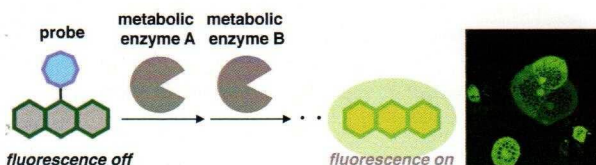
1) Development of novel warheads for covalent drug ^{1), 2)}

Development of covalent drugs with sufficient reactivity for target proteins while minimizing off-target reactivity is not an easy task. We have tried to develop the target-specific covalent drugs by exploiting new reaction chemistry suitable for covalent drug. We have successfully developed novel warheads such as chlorofluoro acetamide (CFA) and bicyclobutane (BCB)-amide. These warheads were applied to develop the targeted covalent inhibitors (TCI) for cancer and infectious disease treatments with low toxic effects.



2) Development of fluorescent probes ^{3), 4)}

Development of fluorescent probes capable of sensitive and selective detection of biological event is still challenging issue in biological analyses. We have reported small molecular-type fluorescent probes for various signaling biomolecules, such as H₂S (hydrogen sulfide) and histamine. We also develop novel fluorescent probes detectable of activity of metabolic pathways, which has been regarded as a challenging task in the field of fluorescence biological analysis. We have successfully developed the fluorescence probe for fatty acid beta oxidation (FAO) pathway in live cells. We applied this probe to discovery of a new covalent inhibitor that disturbs FAO pathway.

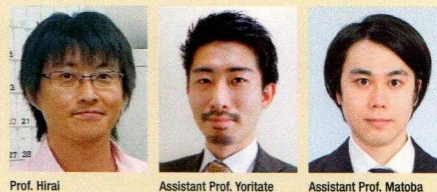


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Contact Akio Ojida
 TEL: 092-642-6596 FAX: 092-642-6601
 E-mail: ojida@phar.kyushu-u.ac.jp
 URL: <http://bunseki.phar.kyushu-u.ac.jp/>

Professor: Go Hirai, Ph.D.
 Assistant Professor: Makoto Yoritata, Ph.D.
 Assistant Professor: Hiroaki Matoba, Ph.D.

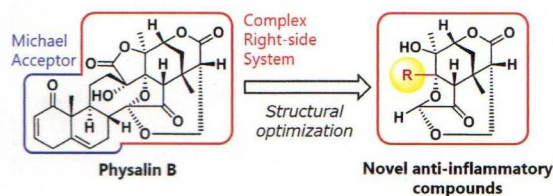


Research

The aim of our research group is to contribute to pharmaceutical and biochemical science by creating “novel molecules”. We design, synthesize, and evaluate them with our own hands by incorporating various chemical and biological knowledge. Here we show our research projects that have been conducted in our group.

(1) Creation of novel bioactive molecules based on natural products including secondary metabolites and biomolecules

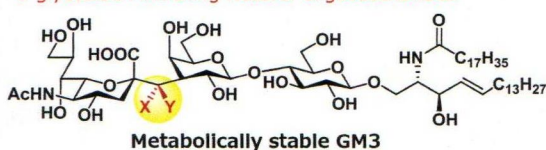
Natural products and biomolecules (proteins, carbohydrates, lipids, etc.) have unique structures and often exhibit unique biological activities. Natural products themselves, however, hardly used for pharmaceutical research and clinical applications due to, for instance, toxicity and physical properties. We have been designing and synthesizing new molecules based on their structures to overcome the drawbacks of natural products and elucidating their functions. For example, we have been developing new molecules with anti-inflammatory activity based on physalin-type natural products, which are oxidized steroids isolated from physalis plants, and also have been working on the synthesis of spectomycin-type antibiotics and their inhibitory activity of SUMOylation on proteins. More recently, we have been working on a research related to cholesterol.



(2) Creation of new functional glycoconjugates to elucidate their functions

Glycoconjugates, in which carbohydrates are bound to proteins, lipids, etc., are thought to play an important function in life activities such as immune response, bacterial/viral infection, cell proliferation and differentiation. However, it is difficult to use them for drug discovery research because glycoconjugates are easily degraded by enzymes expressed in the cells and tissues. We are working on molecular design, synthesis, and elucidation of glycoconjugate analogs, which are not degraded by enzymes and can show the function of the original glycoconjugate. We are also challenging the design and de-

C-glycoside Mimicking Natural Oligosaccharides



velopment of molecules that can contribute to elucidating the role of enzymes that degrade glycoconjugates.

Our laboratory has 24 members (as of April 2022) including undergraduates, graduates, and staff researchers. We try to focus on students’ “autonomy” and “communication and dialogue” within members, and we are trying to promote research activities brightly and positively. We hope you students will develop mentality to challenge the unknown world, do not stay in the existing framework, and become active scientists in various fields, such as drug discovery, chemistry, or pharmacist in the future.



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Green Pharmaceutical Chemistry ✓

Professor: Takashi Ohshima, Ph.D.
 Lecturer: Hiroyuki Morimoto, Ph.D.
 Assistant Professor: Ryo Yazaki, Ph.D.



Prof. Ohshima



Lecturer Morimoto

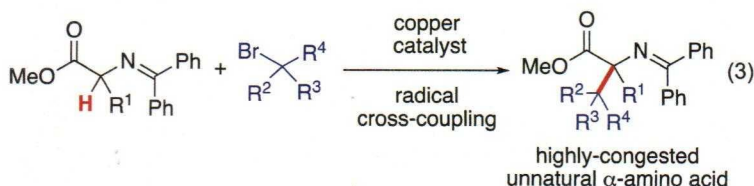
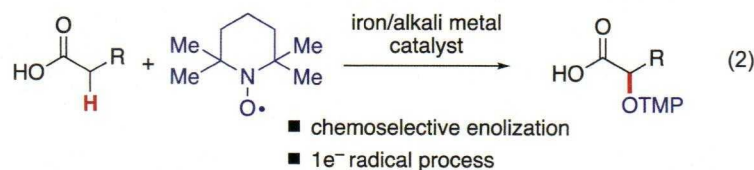
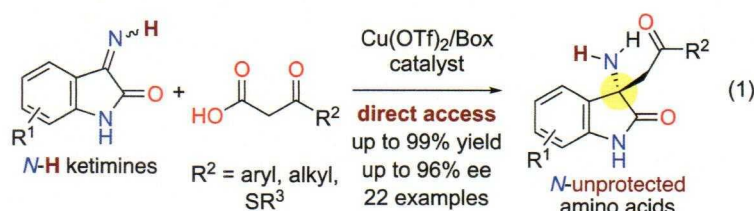


Assistant Prof. Yazaki

Research

In response to the quest for the green and sustainable production of valuable chemicals, such as pharmaceuticals, agrochemicals, and functional materials, this laboratory focuses on the development of environmentally friendly “green” processes based on the newly developed cooperative catalysts and Digitalization-driven Transformative Organic Synthesis (Digi-TOS). Their applications to short-step syntheses of biologically active natural and unnatural products are also studying. The following topics are currently under investigation in our laboratory.

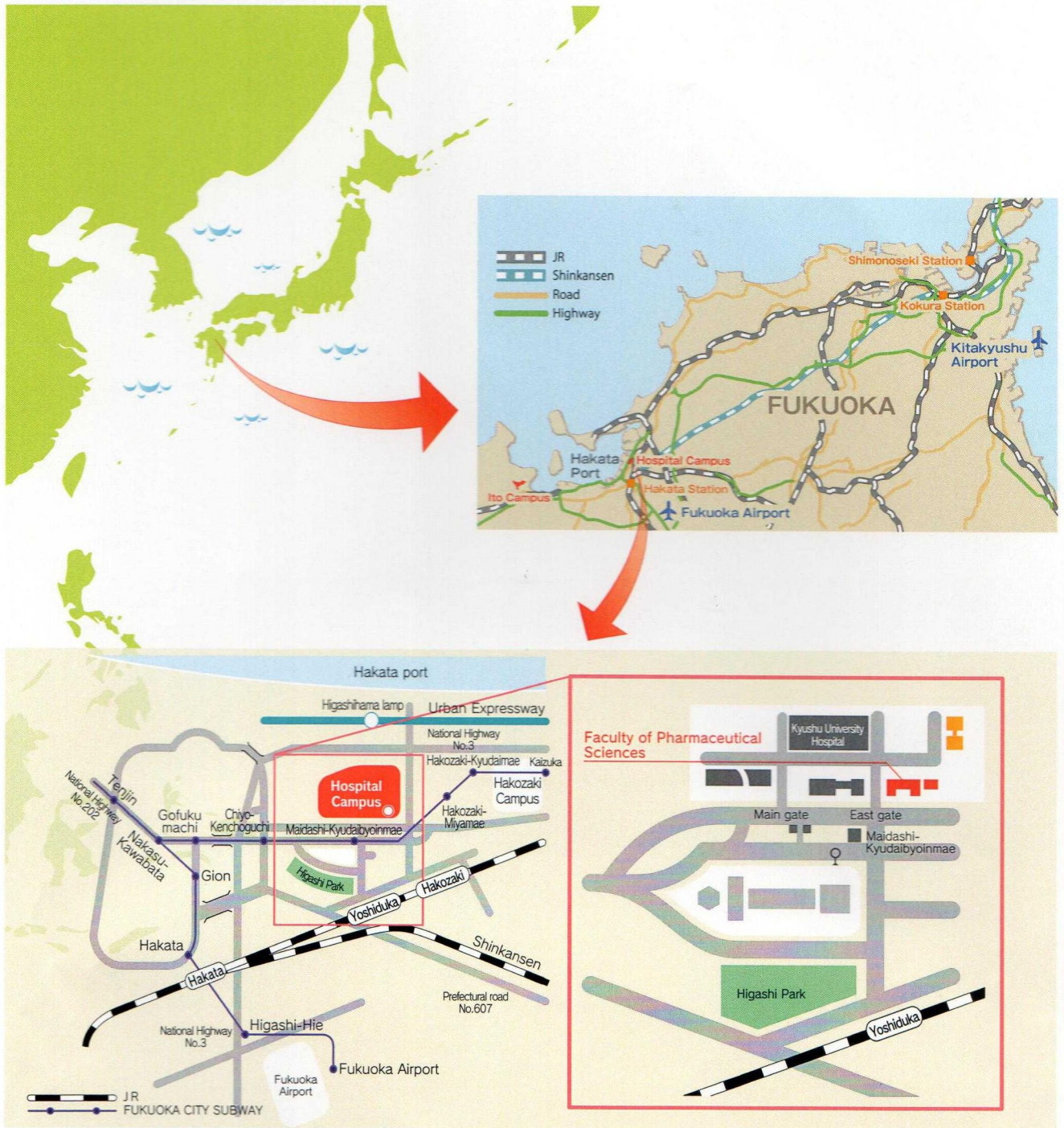
1. Development of Environmentally Benign Processes Based on the Catalytic Activation of Unreactive Functional Groups
2. Synthesis of Biologically Active Natural Products Using One-Pot Multistep Catalysis
3. Drug Discovery Research with the “GreenPharma” Concept



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Contact Takashi Ohshima
 TEL: 092-642-6650
 E-mail: ohshima@phar.kyushu-u.ac.jp
 URL: <https://green.phar.kyushu-u.ac.jp>



Faculty of Pharmaceutical Science,
Kyushu University

Edit and publish

3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

Faculty of Pharmaceutical Science
Kyushu University

International Relations Unit



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School of Pharmaceutical Sciences
Kyushu University