October 1, 2015

Outline of the Laboratory,

Graduate School of Pharmaceutical Science, Kyushu University

Clinical Pharmacokinetics

Teaching staff	Professor Ichiro Ieiri, Ph.D. Assistant Professor Takeshi Hirota, Ph.D.
Research	Individualized pharmacotherapy is of critical importance when medical practitioners attempt to promote appropriate use of drugs and to reduce the number of serious adverse events. Pharmacogenomics, the study of variation in patient responses to drugs due to hereditary traits, has been suggested as the area of genetics with the most potential to rapidly provide public health benefits. Determining individual patients' profiles of drug-metabolizing enzymes and drug transporters is now becoming more feasible for clinical practice, at least for certain well-described genetic variations. However, pharmacogenetic knowledge is not sufficient for personalized pharmacotherapy. Therefore, we are estimating the contribution of single nucleotide polymorphisms (SNPs) to the responses to drugs by clinical study together with using NONMEM computer program, and investigating novel mechanisms caused the inter-individual variability as well as SNPs. For example, epigenetic mechanisms, such as methylation and histone acetylation, are well known genetic modifications which influence gene expression without change in DNA sequence. Recently, miRNA is also interesting. We investigate an in vivo role of these epigenetics on pharmacokinetics and pharmacodynamics of clinically useful drugs through clinical trials involving healthy volunteers and patients.

Pharmaceutics

Teaching staff	Professor Shigehiro Ohdo, Ph.D. Associate Professor Satoru Koyanagi, Ph.D. Assistant Professor Naoya Matsunaga, Ph.D.
Research	The study on the individualization of pharmacotherapy has been carried out aiming at further improvement of pharmacotherapy. However, intraindividual variability as well as interindividual variability should be considered to aim at further improvement of rational pharmacotherapy. Because many drugs vary in potency and/or toxicity associated with the rhythmicity of biochemical, physiological and behavioral processes. One approach to increasing the efficiency of pharmacotherapy is the administration of drugs at times at which they are most effective and/or best tolerated. The application of biological rhythm to pharmacotherapy may be accomplished by the appropriate timing of conventionally formulated tabletes and capsules, and the special drug delivery system to synchronize drug concentrations to rhythms in disease activity. In all living organisms, circadian pacemaker resides in the paired suprachiasmatic nuclei (SCN). Clock genes are the genes that control the circadian rhythms in physiology and behavior. The knowledge of clock genes may be important for the clinical practice. Therefore, we aim at the development of new chronotherapy based on the following strategy: to monitor a rhythmic marker for selecting dosing time, to overcome the alteration of the clock function, a new concept of adverse effects, by devising a dosing schedule and to produce new rhythmicity by manipulating the conditions of living organs by using rhythmic administration of altered feeding schedules or several drugs.

Molecular and System Pharmacology

Teaching staff	Professor Kazuhide Inoue, Ph.D. （Expected retirement at the end of March , 2016.）
Research	1. Studies on the mechanisms of the development and maintaining of neuropathic pain Neuropathic pain is often a consequence of nerve injury through surgery, bone compression, diabetes or infection. This type of pain can be so severe that even light touching can be intensely painful; unfortunately, this state is generally resistant to currently available treatments. Recently, we found that the expression of P2X4 receptors in the spinal cord is enhanced in spinal microglia after peripheral nerve injury, and blocking pharmacologically and suppressing molecularly P2X4 receptors produce a reduction of the neuropathic pain behaviour. Understanding the key roles of ATP receptors including P2X4 receptors may lead to new strategies for the management of neuropathic pain.

	2. Studies on the mechanism of brain protection via ATP receptors aiming to development of new drugs The neurons of brain are always receiving many dangerous stimulation, i.e. oxidative stress, mechanical stress, and excitotoxicants. Recently, it was reported that astrocyte and microglia have a role for neuro-protection through ATP receptors. We aim to understand the mechanism of this protection and find seeds of new drugs for the brain protection.

Protein structure, function and design

Teaching staff	Professor Tadashi Ueda, Ph.D. Associate Professor Yoshito Abe, Ph.D. Assistant Professor Mitsunori Shiroishi, Ph.D.
Research	Our group is involved in Structural Biology and Protein Engineering. 1.Analyses of protein structures and functions 2. Protein Engineering for pharmaceutical sciences. 3.Analysis of protein folding mechanism 4.Development of retarded methods for protein aggregation or amyloid fibrillations based on their mechanisms

Pathophysiology

Teaching staff	Associate Professor Mami Noda, Ph.D.
Research	In the Pathophysiology laboratory, we are investigating the cellular mechanism of neurodegenerative diseases and psychiatric disorders. The main topics of our research are as follows: ● Neuron-glia interaction and the role of glial cells in neurological diseases. Glial cells (astrocytes, microglial, and oligodendrocytes) play important roles in various neurological diseases. We focus on microglial and astrocytes and try to clarify the followings: 1) Receptors and ion channels in glial cells. 2) The role of glial cells in inflammation and trauma. 3) The role of glial cells in brain metastases of cancer cells. 4) The role of glial cells in neurodegenerative and psychological diseases. ● Functional analyses of genes responsible for Parkinson's disease. Loss-of-function mutations of some genes related to ubiquitin-proteasome system cause an autosomal recessive juvenile-onset form of Parkinson's disease (AR-JP). We are trying to investigate physiological functions, especially in the nervous system, of those genes. ● Anti-oxidative stress in model animals of neurodegenertion. We are trying to find evidences for the benefits of taking anti-oxidants using Parkinson's disease model mice. We already observed that molecular hydrogen has protective effects on animal model of Parkinson's disease and now we are trying to clarify the molecular basis.

Molecular Biology

Teaching staff	Professor Tsutomu Katayama, Ph.D. Assistant Professor Hironori Kawakami, 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. If this regulation is interfered with, various cell defects occur, such as abnormal chromosomes, inhibition of cell division, and growth of abnormal cells. Thus, a study on this regulatory mechanism is of significance as a basis for the developments of antibiotics and anticancer drugs. We have shown that a protein (DnaA) initiating E. coli chromosomal replication is inactivated by timely and direct interaction with a subunit of chromosomal replicase (DNA polymerase III holoenzyme). This interaction depends on loading the subunit onto DNA. This conformational change occurs for the nucleotide-polymerizing action of the replicase after the initiation reaction by DnaA. Thus, during the cell cycle, the initiation protein is most likely inactivated just after initiation of chromosomal replication in this manner. We have termed this regulatory system RIDA (Regulatory

	inactivation of DnaA). Reactivation of DnaA will occur before the next round of the replication cycle. We are investigating the molecular mechanisms in this DnaA-activity cycle including timely inactivation and activation.

Molecular Life Sciences

Teaching staff	Professor Hideyuki Yamada, Ph.D. Associate Professor Yuji Ishii, Ph.D. Assistant Professor Tomoki Takeda, Ph.D.
Research	This laboratory is involved in the following toxicological areas: the molecular mechanism of dioxin toxicity (Project 1); and functional cooperation of phase I and II drug metabolizing enzymes (Project 2). In the Project 1, 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 2. 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.

Bio-analytical Chemistry

Teaching staff	Professor Akio Ojida, Ph.D. Assistant Professor Manabu Nakazono, Ph.D. Assistant Professor Syouhei Uchinomiya, Ph.D.
Research	1) Development of Fluorescent Probe Development of fluorescent probes capable of sensitive detection of biological molecules is a critical issue in biological analyses. We have been developing small molecular-type fluorescent probes for various molecules of biological significance, and applying them to cell function analysis, enzyme assay, and drug screening, etc. 2) Development of New Methods for Protein Functional Analysis Proteins play significant roles in biological systems. We have been developing a new protein labeling method, which allows to selective introduction of various functional molecular probes into a target protein. We have also been trying to create functional molecular probes available in the protein labeling. The labeling method employing the designer probes should facilitate protein function analyses in cellar systems.

Pharmacology and Toxicology

Teaching staff	Professor Hitoshi Kurose, Ph.D. Asssociate Professor Michio Nakaya, Ph.D. Assistant Professor Akiomi Nagasaka, Ph.D.
Research	The heart works as a pump in the body. When the heart is exposed to stress such as hypertension, the heart compensates its function by increasing the size but not the number of cells. The enlarged heart (hypertrophied heart) develops heart failure when the stress is not removed. Heart failure is also induced by myocardial infarction. Heart failure is defined as a final stage that the heart cannot supply enough blood to peripheral tissues by any kinds of cardiovascular diseases. The five-year survival rate of patients diagnosed as heart failure is about 50%, almost equivalent to survival rate of cancer. In our laboratory, we are working on fibrosis that is developed with heart failure. Fibrosis is defined as excess deposition of collagen into extracellular space. Cardiac fibrosis causes impairment of cardiac functions, especially the diastolic function. As the collagen turnover rate is very low, it is difficult to cure fibrosis. Our focus of research is to manage collagen production. In the body, collagen is produced by at least three kinds of myofibroblasts: differentiation of resident fibroblasts, differentiation of endothelial cells through endothelial-mesenchymal transition (Endo MT), and differentiation of fibrocytes. However, individual functions of these myofibroblasts are largely unknown, and the

	contribution of each myofibroblast to fibrosis is also unknown. We are working on functions of myofibroblasts, mechanisms of differentiation into myofibroblasts and de-differentiation of myofibroblasts. Furthermore, inflammation always occurs at hypertrophy and myocardial infarction. Inflammatory cells such as macrophages and neutrophils infiltrate to the damaged areas, and cause inflammation. These cells are believed to contribute to cardiac fibrosis. However, the exact functions of inflammatory cells on fibrosis and interaction of inflammatory cells with myofibroblasts remain to be determined. We are working on identification of novel target proteins of fibrosis, mechanistic analysis of fibrotic process, and drug development to treat fibrosis. Fibrosis occurs not only in the heart but also other tissues such as lung and liver. It is interesting to test whether the model of cardiac fibrosis that we are going to establish is also applicable to fibrosis of other tissues.

Pharmaceutical Cell Biology

Teaching staff	Professor　Yoshitaka Tanaka, Ph.D. Associate Professor　Yukio Nishimura, Ph.D. Assistant Professor　Keiko Fujimoto, Ph.D. Assistant Professor　Yuko Hirota, 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). 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.

Green Pharmaceutical Chemistry

Teaching staff	Professor　Takashi Ohshima, Ph.D. Assistant Professor　Hiroyuki Morimoto, Ph.D. Assistant Professor　Ryo Yazaki, Ph.D.
Research	The following topics are currently under investigation in our laboratories: 1. Development of New Environmentally Benign Catalytic Processes 2. Development of New Chemoselective Catalyses 3. Synthesis of Biologically Active Natural Products Using One-Pot Multistep Catalysis 4. Development of New Molecularly-Targeted Anticancer Drugs 5. Promotion of ñGreen Pharmaò

Bio-functional Science

Teaching staff	Associate Professor　Ken-ichi Yamada, Ph.D.
Research	Development of detection method for intermediate in lipid metabolism and application to animal models for inflammation and related diseases Research on mechanism of life style related diseases based on a treatment of redox imbalance state Development of imaging probe to detect and analyze the functional molecule from whole body to cells Synthesis of novel contrast agent for MRI and optical imaging and application to theranostics Development of age-related macular degeneration drug

Bioorganic and Synthetic Chemistry

Teaching staff	Professor　Shigeki Sasaki, Ph.D. Associate Professor　Yosuke Taniguchi, Ph.D. Assistant Professor　Yukiko Abe Assistant Professor　Yasufumi Fuchi
Research	The research activities of the laboratory of Bioorganic and Synthetic Chemistry have focused on the following topics: 1. new artificial nucleosides for the formation of　the triplex. 2. reactive oligonucleotides for selective modification of RNA. 3. the new detecting method for the oxidized nucleosides. 4. recognition of highly-ordered DNA structures. 5. cooperation with the DDS group to modify gene expression in cells.

Pharmaceutical Synthetic Chemistry

Teaching staff	Professor　Hiroshi Suemune, Ph.D. （Expected retirement at the end of March , 2016.） Associate Professor　Mariko Aso, Ph.D. Assistant Professor　Kazuteru Usui, Ph.D.
Research	In our group, several research projects based on synthetic organic chemistry are in progress: 1. Molecular design of nucleic acids with functions; spin-labeled nucleic acids and amine reactive nucleic acids for studies on protein structures and functions. 2. The development of asymmetric organocatalysts with [n]helicene skeleton. 3. Design of artificial amino acids, and their application to the development of peptides with functions and biological activities. 4. Development of bisphosphonate derivatives with bone specificity and biological activities.

Cellular Biochemistry

Teaching staff	Professor　Masatoshi Fujita, M.D.,Ph.D. Associate Professor　Tomofumi Miyamoto, Ph.D. Assistant Professor　Nozomi Sugimoto, Ph.D. Assistant Professor　Chiaki Tanaka, Ph.D. Assistant Professor　Kazuma Yoshida, Ph.D.
Research	We have been clarifying molecular mechanisms of chromosomal DNA regulations, deregulation of which would lead to chromosomal instability and eventually cancer. Now,we have been especially focusing on: 1. Function and cell cycle regulation 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 process. 4. Relationship between chromatin regulations regulations (by chromatin remodeler and histone chaperone) and replication/telomere/checkpoint regulations. 5. Novel anti-microtubule agents with carbazole and benzohydrazide structures we identified. Search for Cdt1-geminin binding inhibitors that could selectively damage cancer cells by inducing re-replication.

Pharmacognosy

Teaching staff	Professor　Satoshi Morimoto, Ph.D. Associate Professor　Hiroyuki Tanaka, Ph.D. Assistant Professor　Seiichi Sakamoto, Ph.D.
Research	1. Three enzymes (THCA-, CBDA-, CBCA-synthases) which catalyze biosynthesis of marihuana 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. 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.

Functional Molecular Science

Teaching staff	Professor Noboru Koga, Ph.D. （Expected retirement at the end of March , 2016.） Associate Professor Satoru Karasawa, Ph.D. Assistant Professor Takeyuki Akita, Ph.D.
Research	In the molecule-based magnets, we proposed the use of the heterospin systems consisting of 2p spins due to organic radicals and 3d spins of metal ions. The strategy for heterospin systems successfully provided unique molecular magnets by strong magnetic interaction between the organic spin and the metal spin; photoresponsive and monometallic single-molecule magnets (SMM) in nanometer size and 1D-chain showing SMM behavior. The magnetism studies extended to the application to an MRI contrast agent, in which DNA strands and hyperbranched polymers carrying the spins and self-assemblies of small-size molecules with a stable radical were used. We also started to study the emitting materials with external-stimuli responsiveness.

Clinical pharmacy and Pharmaceutical care

Teaching staff	Associate Professor Takao Shimazoe, Ph.D. Associate Professor Toshio Kubota, Ph.D. Assistant Professor Daisuke Kobayashi, Ph.D.
Research	● Establishment of pharmaceutical education system. ● Study of prevention and treatment for various diseases with drugs, herbs, foods, and so on. ● Establishment of evaluation method for patient education on various diseases. ● Study on circadian rhythms. ● Molecular biological, basic and clinical study on prevention and treatment for side effects of drugs.

Drug Discovery and Evolution

Teaching staff	Associate Professor Kenji Hamase, Ph.D.
Research	Drug discovery and diagnosis using chiral amino acid metabolomics. Anti-aging research focusing on isomerization of proteins. Industrial-academic-government cooperation research on heart and renal disorders. Development of analytical reagents, materials and instruments. Development of novel functional foods, beverages and cosmetics including D-amino acids.

Life Innovation

Teaching staff	Professor Makoto Tsuda, Ph.D. Associate Professor Hidetoshi Saitoh, Ph.D. Assistant Professor Yuta Kohro, Ph.D.
Research	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 pain and itch signaling (in particular 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.

Translational Pharmaceutical Sciences II

Teaching staff	Professor Motohiro Nishida, Ph.D. (Concurrent Post) Assistant Professor Shigekazu Tabata, Ph.D. .
Research	Identification of muscular mechano-activated molecular targets to mimick kinesitherapy and its therapeutic application. Development of orphan drugs to maintain mitochondrial quality control for the treatment of rare diseases. Analysis of the correlation between post-translational modification of proteins and cardiovascular risks. Promotion of basic research on drug discovery and fostering in collaboration with Kyushu university hospital and pharmaceutical companies

Clinical Pharmacology and Biopharmaceutics

Teaching staff	Professor Satohiro Masuda, Ph.D. Associate Professor Nobuaki Egashira, Ph.D.
Research	The landmark of our research is to establish the rational and efficient personalized pharmacotherapy with sufficient safeness. The efficacy and safety of drug therapy is closely related to each pharmacokinetics, pharmacodynamics and toxicology. Therefore, we developed the various research techniques and intelligences as follows: 1. Clinical application of biomarkers reflecting pharmacological and toxicological responses in pharmacotherapy. 2. Establishment of countermeasures against drug-induced neurotoxicity and nephrotoxicity based on clarification of their molecular mechanisms. 3. Pharmacogenomics in personalized immunosuppressive therapy in organ transplant patients. 4. Clarification of pathophysiological role of renal drug transporters in patients with acute kidney injury and/or chronic kidney disease. 5. Establishment of personalized anticancer chemotherapy by pharmacokinetic, pharmacodynamics and pharmacogenomic analyses. 6. Pharmaceutical informatics to improve pharmaceutical practice by epidemiological approach

Translational Pharmaceutical Sciences I

Teaching staff	Professor Motohiro Nishida, Ph.D. (Concurrent Post) Professor Yoji Sato, Ph.D.
Research	See **Translational Pharmaceutical Sciences II** Development of quality evaluation methods for cellular and gene therapy products Development of quality evaluation methods for somatic and iPS/ES cells as cell substrates for production of cellular and gene therapy products Studies on biodistribution and viral safety of cellular and gene therapy products

Pharmaceutical Oncology

Teaching staff	Research Professor Myumi Ono, Ph.D. Associate Professor Kosuke Watari, Ph.D.
Research	Our main interests are development of personalized anticancer therapeutics and also drug-resistance-overcoming therapeutic strategies. [1] First, we already presented candidate molecules that are responsible for acquirement of drug resistant to anticancer agents including EGFR-TKIs. [2] Secondly, to overcome drug-resistant tumors, we are now developing two anticancer therapeutics approaches. One is development of tumor stroma-targeted drugs to suppress tumor angiogenesis and lymphangiogenesis that are expected to be effective against drug-resistant tumors, tumor growth and metastasis. Targeting tumor-associated macrophages is one approach. Another is development of novel combination therapeutics of cytotoxic anticancer agents and molecular targeting drugs.

Molecular Recognition of Chemotherapy

Teaching staff	Professor Hajime Nakashima, M. D., Ph.D.
Research	In clinical development of a new product, protocols of clinical trial in each clinical phase are very important. Approval conditions of the new product by the government would be based on those protocols. We discuss about many issues on reviewing protocols. And we also discuss about interpretation of safety data of new products.

Molecular Recognition of Chemotherapy

Teaching staff	Professor Soichi Takiguchi, Ph.D.
Research	We are studying the physiological function of a cancer metastasis-associated protein and the mechanism of bone metastasis, and more using latest established technique.

Kampo-Medicinal Chemistry

Teaching staff	
Research	

Drug Delivery System

Teaching staff	Professor Hiromu Kondou, Ph.D. Professor Hiroshi Kikuchi, Ph.D. Associate Professor Yasunari Michinaka, Ph.D.
Research	The role of drug delivery system (DDS) is to provide optimized drug therapy for patients, enhancing the efficacy and safety by controlling drug release rate and the amount to be absorbed in body. Together with this, recent research effort is targeted at making drugs easier to administer to patients. Further role of employing DDS for companies is product value maximization, including life cycle management.

For further information, please visit the following website.
http://www.phar.kyushu-u.ac.jp/eng/index.php