Kyoto University

Graduate School of Pharmaceutical Sciences

Faculty of Pharmaceutical Sciences

2015

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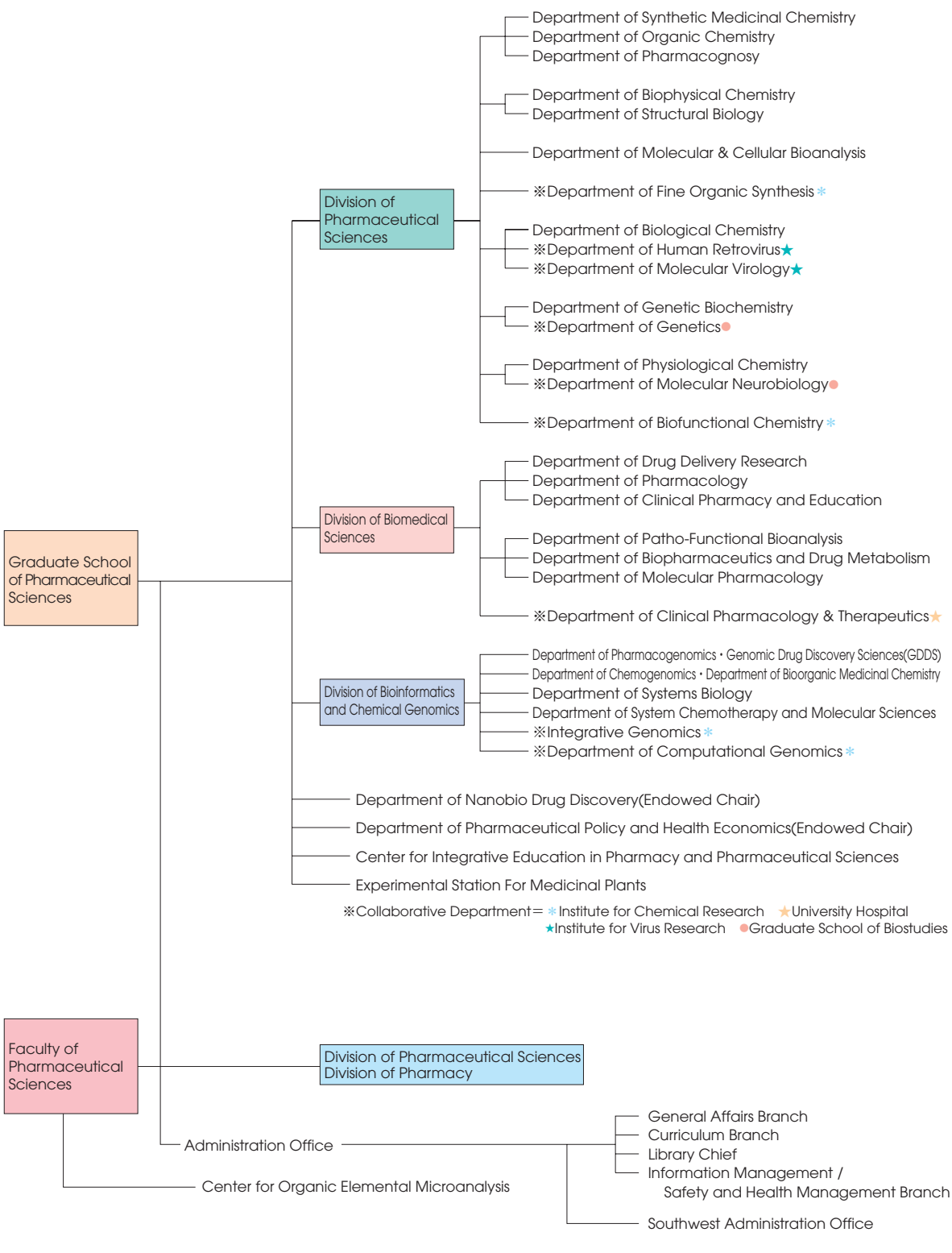
1. History

1939 March: School of Pharmacy established in the Faculty of Medicine, Kyoto University Department of Analytical Chemistry and Department of Synthetic Medical Chemistry established in the School of Pharmacy.
1940 June: Department of Organic Chemistry established.
1940 December: Department of Inorganic Chemistry established.
1941 April: Department of Pharmacognosy established.
1941 December: Doctor of Pharmaceutical Sciences newly added to academic degrees. First graduation ceremony for the School of Pharmacy in the Faculty of Medicine.
1949 May: Kyoto University reorganized under the new educational system introduced by the National School Establishment Law.
1951 April: Department of Pharmaceutics established.
1952 April: Department of Biological Chemistry established.
1953 April: Division of Pharmacy, Kyoto University Graduate School of Pharmaceutical Sciences established.
1954 April: Center for Organic Elemental Microanalysis established in the Faculty of Medicine.
1960 April: Faculty of Pharmaceutical Sciences (Division of Pharmacy) established and the following departments instituted: Analytical Chemistry, Synthetic Medical Chemistry, Organic Chemistry, Inorganic Chemistry, Pharmacognosy, Pharmaceutics, Biological Chemistry. (In accordance with establishing Faculty of Pharmaceutical Sciences, the same seven departments in the School of Pharmacy in the Faculty of Medicine were disestablished.) Center for Organic Elemental Microanalysis attached to the Faculty of Pharmaceutical Sciences.
1961 April: Division of Pharmaceutical Chemistry established. Department of Medicinal Plant Chemistry established.
1962 April: Department of Chemical Pharmacology and Department of Pharmaceutical Engineering established.
1963 April: Department of Physical Chemistry and Department of Hygienic Chemistry established.
1964 April: Department of Radiopharmaceutical Chemistry established.
1965 April: Division of Pharmaceutical Chemistry in the Graduate School of Pharmaceutical Sciences established.
1966 April: Department of Chemical Pharmacology was renamed the Department of Pharmacology, Department of Biological Chemistry renamed Department of Biochemistry.
1973 April: Experimental Station For Medicinal Plants affiliated with the Faculty of Pharmaceutical Sciences established.
1987 May: Department of Pharmaceutical Engineering renamed Department of Microbiology.
1993 April: Master's program in Pharmaceutical Control Systems (independent division) established in the Graduate School of Pharmaceutical Sciences; Pharmaceutical Informatics (transferred from the Department of Inorganic Chemistry in the Division of Pharmacy), Molecular Pharmacology (new) and Genetic Biochemistry (new) established as core departments; and Patho-Functional Bioanalysis, Drug Delivery System, Bioorganic Chemistry (Institute for Chemical Research), Biofunctional Chemistry (Institute for Chemical Research), Clinical Pharmacy (Kyoto University Hospital) established as affiliate departments.
1995 April: Doctoral program in Pharmaceutical Control Systems (independent division) established in the Graduate School of Pharmaceutical Sciences.
1997 April: Focused on the Graduate School, Divisions of Pharmaceutical Sciences, Pharmaceutical Chemistry and Pharmaceutical Control Systems reorganized into 8 major departments within 3 divisions: Drug Discovery Sciences, Pharmaceutical Life Sciences, Pharmacy and Biomedicinal Sciences.Divison of Pharmacy and Division of Pharmaceutical Chemistry in the Faculty of Pharmaceutical Sciences reorganized into one Division of Integrative Pharmaceutical Sciences.
1998 April: Experimental Station For Medicinal Plants affiliated with the Faculty of Pharmaceutical Sciences transferred to the Graduate School of Pharmaceutical Sciences.
1999 April: In accordance with establishment of the Graduate School of Biostudies, Department of Cell Biology and Department of Molecular Neurobiology established.
2002 April: Department of Pharmaceutical Informatics renamed Department of Genomic Drug Discovery Science. Department of Structural Biology established.
2002 October: Construction of new research building for the Graduate School of Pharmaceutical Sciences completed.
2003 April: Endowed chair "Neuroscience for Drug Discovery Research" established. Core Department of Drug Discovery-Medicine Collaborative Pharmaceutical Sciences affiliated with the Graduate School of Pharmaceutical Sciences established.
2003 August: Endowed chair "Theoretical Drug Design" established.
2003 September: In accordance with adoption of the 21st Century COE Program, the Department of Life Knowledge Systems established (Period: duration of implementation period for the 21st Century COE Program).
2004 April: Kyoto University becomes a national university corporation under the National University Corporation Act.
2006 April: Division of Integrative Pharmaceutical Sciences in the Faculty of Pharmaceutical Sciences reorganized into Division of Pharmaceutical Sciences and Division of Pharmacy.Center for Integrative Education of Pharmacy Frontier, affiliated with the Graduate School of Pharmaceutical Sciences, established. (Core Department of Drug Discovery-Medicine Collaborative Pharmaceutical Sciences abolished.) Department of Clinical Pharmacy and Education established.
2007 March: Renovation work on the main building for the Graduate School of Pharmaceutical Sciences completed.
2007 April: Division of Bioinformatics and Chemical Genomics established in the Graduate School of Pharmaceutical Sciences.
2007 May: Endowed chair "Nanobio Drug Discovery" established.
2008 October: Endowed chair "Systems Bioscience for Drug Discovery" established.
2009 April: Institute for Innovative NanoBio Drug Discovery and Development established.
2010 April: World-leading Drug Discovery Research Center established. Center for Development of Integrative Education in Pharmacy and Pharmaceutical Sciences established.
2012 April: Endowed chair "Pharmceutical Policy and Health Economics" established.
2014 May: Moving Experimental Staion For Medicinal Plants.

2. Chronological Lists of Deans and Directors

Toshihisa, YAMAMOTO	(1960. 4, Acting Director)
Masao, TOMITA	(1960. 5～1964. 4)
Shojiro, UEO	(1964. 5～1968. 4)
Kiichiro, KAKEMI	(1968. 5～1970. 4)
Shojiro, UEO	(1970. 5～1972. 4)
Toyozo, UNO	(1972. 5～1974. 4)
Yasuo, INUBUSHI	(1974. 5～1976. 4)
Hirouki, INOUE	(1976. 5～1978. 4)
Masayuki, NAKAGAKI	(1978. 5～1980. 4)
Hirohi, TAKAGI	(1980. 5～1982. 4)
Haruaki, YAZIMA	(1982. 5～1984. 4)
Hisashi, TANAKA	(1984. 5～1986. 4)
Hitoshi, SEZAKI	(1986. 5～1988. 4)
Fumiro, YONEDA	(1988. 5～1990. 4)
Akira, YOKOYAMA	(1990. 5～1994. 4)
Atsushi, ICHIKAWA	(1994. 5～1996. 4)
Masamichi, SATO	(1996. 5～1998. 4)
Toshisuke, KAWASAKI	(1998. 5～2000. 4)
Terumichi, NAKAGAWA	(2000. 5～2002. 4)
Mitsuru, HASHIDA	(2002. 5～2006. 3)
Kiyoshi, TOMIOKA	(2006. 4～2007. 12)
Nobutaka, FUJII	(2008. 1～2008. 9)
Nobuyuki, ITOH	(2008. 10～2010. 3)
Hideo, SAJI	(2010. 4～2014. 3)
Yoshinobu, TAKAKURA	(2014. 4～)

3. Organization



4. Staff (As of May 1, 2015)

① Administration Officers

· Dean	Yoshinobu TAKAKURA	· Member of University Council	Shuji KANEKO
· Vice-Dean	Shuji KANEKO	· Member of University Council	Kazuhisa NAKAYAMA
· Vice-Dean	Hiroaki KATO	· Head of Administration Office	Koji HIROSE

② Present Number of Staffs

Academic staff					non-academic staff			Grand Total
Professor	Associate Professor	Lecuturer	Assistant Professor	Subtotal	Administrative staffs	Technical staffs	Subtotal	
14	16	6	13	49	7	3	10	59

③ Academic Staffs and Departments

Division	Department	Professor	Associate Professor	Lecturer	Assistant Professor
Pharmaceutical Sciences	Synthetic Medicinal Chemistry	Kiyosei TAKASU	Ken-ichi YAMADA		Yousuke YAMAOKA
	Organic Chemistry	Yoshiji TAKEMOTO		Chihiro TSUKANO	Yusuke KOBAYASHI
	Pharmacognosy		Michiho ITO		
	Biophysical Chemistry	Katsumi MATSUZAKI	Masaru HOSHINO		Yoshiaki YANO
	Structural Biology	Hiroaki KATO	Toru NAKATSU		Tomohiro YAMAGUCHI
	Molecular & Cellular Bioanalysis	Yasushi ISHIHAMA	(Naoyuki SUGIYAMA)		Masaki WAKABAYASHI
	Fine Organic Synthesis ❄	Takeo KAWABATA	Takumi FURUTA		Tomoyuki YOSHIMURA Yoshihiro UEDA
	Biological Chemistry	Hiroshi TAKESHIMA	Sho KAKIZAWA		
	Human Retrovirus ★	Masao MATSUOKA		Jun-ichiro YASUNAGA	Kazuya SHIMURA
	Molecular Virology ★	Yoshio KOYANAGI			Hirotaka EBINA Kei SATO
	Genetic Biochemistry			Ayumi MIYAKE	
	Genetics ●	Tatsushi IGAKI		Shizue Ohsawa	Masato ENOMOTO
	Physiological Chemistry	Kazuhisa NAKAYAMA	Hye-won SHIN		Youhei KATO
	Molecular Neurobiology ●	Manabu NEGISHI	Hironori KATOH		Izumi OINUMA
	Biofunctional Chemistry ❄	Shiroh FUTAKI			Miki IMANISHI Toshihide TAKEUCHI
Biomedical Sciences	Drug Delivery Research	Mitsuru HASHIDA	Fumiyoshi YAMASHITA		
	Pharmacology	Akinori AKAIKE	Toshiaki KUME		Yasuhiko IZUMI
	Clinical Pharmacy and Education		Ikuko YANO		
	Patho-Functional Bioanalysis	Hideo SAJI	Masahiro ONO		Hiroyuki WATANABE
	Biopharmaceutics and Drug Metabolism	Yoshinobu TAKAKURA	Makiya NISHIKAWA		Yuki TAKAHASHI
	Molecular Pharmacology	Shuji KANEKO	Hisashi SHIRAKAWA		
	Clinical Pharmacology & Therapeutics ★	Kazuo MATSUBARA	Takayuki NAKAGAWA	Atsushi YONEZAWA	Satoshi IMAI Tomohiro OMURA Shunsaku NAKAGAWA
Bioinformatics and Chemical Genomics	Pharmacogenomics / Genomic Drug Discovery Sciences(GDDS)		Akira HIRASAWA		
	Chemogenomics / Bioorganic Medicinal Chemistry	Hiroaki OHNO Nobutaka FUJII		Shinya OISHI	
	Systems Biology	Hitoshi OKAMURA	Masao DOI	Jean-Michel Fustin	Yoshiaki YAMAGUCHI
	System Chemotherapy and Molecular Sciences	Hideaki KAKEYA	Akira HATTORI		Shinichi NISHIMURA
	Integrative Genomics ❄	Hiroyuki OGATA	Susumu GOTO		
	Computational Genomics ❄	Hiroshi MAMITSUKA			Canh Hao Nguyen
Nanobio Drug Discovery (Endowed Chair)		Kazuharu SHIMIZU Yutaka SHIMADA Tetsuo SUDO		Yoshinori TAKEI	
Pharmaceutical Policy and Health Economics(Endowed Chair)		Hiroaki KAKIHARA		Xin Xin, MA	Masaoki TAMURA Naohiko WAKUTSU
Center for Integrative Education of Pharmacy and Pharmaceutical Sciences		Yoshinobu TAKAKURA		Masahiro TSUDA	Kaori KADOYAMA
Experimental Station For Medicinal Plants		Yoshinobu TAKAKURA			
Advanced Drug Development Project			Naoyuki SUGIYAMA		

5. Students (As of May 1, 2015)

Undergraduate

Division \ Year	Capacity	1st			2nd			3rd			4th			5th			6th			Total		
		Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Pharmaceutical Sciences	50	45	(1) 9	(1) 54	(1) 40	12	(1) 52	46	(1) 9	(1) 55	53	15	68							(1) 184	(2) 45	(3) 229
Pharmacy	30	16	14	30	14	17	31	20	11	31	17	14	31	11	19	30	15	19	34	93	94	187
Total (Foreign Students)		61	(1) 23	(1) 84	(1) 54	29	(1) 83	66	(1) 20	(1) 86	70	29	99	11	19	30	15	19	34	(1) 277	(2) 139	(3) 416

	Male	Female	Total
Research Students	1	0	1

	Male	Female	Total
Non-Degree Students	2	0	2

Graduate School

Master's Course

Division \ Year	Capacity	1st			2nd			Total		
		Male	Female	Total	Male	Female	Total	Male	Female	Total
Pharmaceutical Sciences	50	29	(3) 19	(3) 48	(1) 32	(6) 13	(7) 45	(1) 61	(9) 32	(10) 93
Bioinformatics and Chemical Genomics	14	(1) 11	1	(1) 12	6	4	10	(1) 17	5	(1) 22
Total (Foreign Students)		(1) 40	(3) 20	(4) 60	(1) 38	(6) 17	(7) 55	(2) 78	(9) 37	(11) 115

Doctoral Course

Division \ Year	Capacity	1st			2nd			3rd			Total		
		Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Pharmaceutical Sciences	22	(1) 9	(1) 1	(2) 10	(2) 11	(1) 4	(3) 15	(1) 14	5	(1) 19	(4) 34	(2) 10	(6) 44
Bioinformatics and Chemical Genomics	7	1		1	(1) 2	(1) 3	(2) 5	(2) 4	4	(2) 8	(3) 7	(1) 7	(4) 14
Total (Foreign Students)		(1) 10	(1) 1	(2) 11	(3) 13	(2) 7	(5) 20	(3) 18	9	(3) 27	(7) 41	(3) 17	(10) 58

	Male	Female	Total
Research Students	0	0	0

	Male	Female	Total
Non-Degree Students	0	0	0

Doctoral Course (4 years)

Division \ Year	Capacity	1st			2nd			3rd			4th			Total		
		Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Pharmacy	15	7	2	9	5		5	5		5	7	2	9	24	4	28
Total (Foreign Students)		7	2	9	5		5	5		5	7	2	9	24	4	28

6. Number of Graduates

①Faculty of Pharmaceutical Sciences

Classification		Number
Old System	1941.12～1953. 3	402
New System		
Faculty of Medicine, Division of Pharmacy	1953. 3～1960. 3	300
Faculty of Pharmaceutical Sciences	1961. 3～2015. 3	4,160
Total		4,862

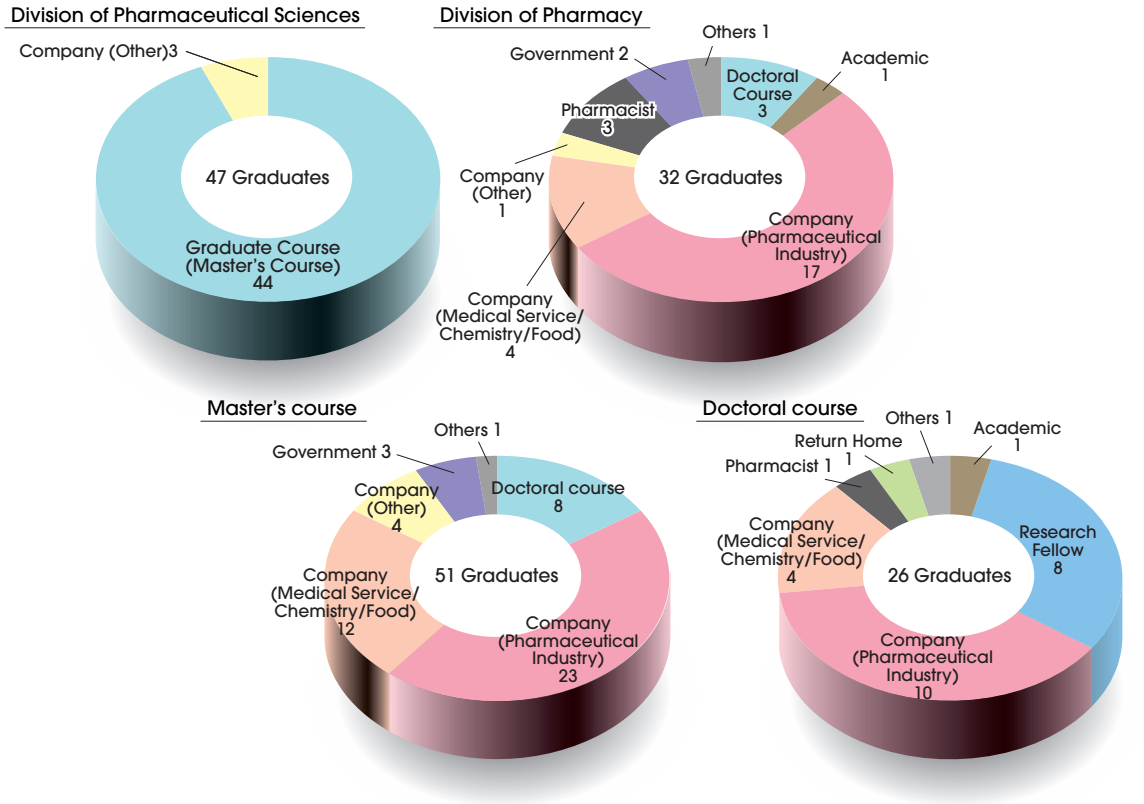
②Master's Degrees Conferred

	Number
1955. 3～2015. 3	2,578

7. Doctorates Conferred

Classification		Number
Old System (including Doctor of Medical Sciences)	1943.10～1962. 2	308
New System		
Through Graduation from Doctoral Course	1958. 9～2015. 3	858
Through Submission of Research Papers	1961. 9～2015. 3	769
Total		1,935

8. Status Post-Graduation (Graduates of 2014 academic year)



9. Books and Journals in the Library (As of May 1, 2015)

Classification	Japanese	Foreign	Total
Books	11,813	22,336	34,149
Periodicals	170	182	352
Electronic journals	about 85,000 (Available In all University staff and students)		

10. Finances*

	Accounts Closing (Fiscal 2014)	Budget (Fiscal 2015) (As of May 1, 2015)
Operating Cost Subsidies		
Personnel Expenses	507,048	
Cost of Supplies	232,194	227,257
Contract Research and Research Cooperation with Industry	368,793	223,884
Donation for Research	172,402	87,650
Grants-in-Aid for Scientific Research	216,257	241,743
Health and Labour Sciences Research Grants	27,800	
Other Grants	70,806	23,874
Total	1,595,300	804,408 (*: Unit: thousand yen)

11. Campus and Buildings (As of May 1, 2015)

	land area	building
Pharmaceutical Sciences Campus	19,106㎡	
Main Pharmaceutical Building		9,329㎡
Lecture Building		1,056㎡
Annex		884㎡
New Research Building		5,615㎡
Conservatory House		215㎡
Experimented Water Drainage Facility		144㎡
Flammable Storage Warehouse		40㎡
Warehouse		27㎡
Total	19,106㎡	17,310㎡

Research Fields

Division of Pharmaceutical Sciences

Departments Leaders	Research Fields
Synthetic Medicinal Chemistry Professor Kiyosei TAKASU	1. Synthetic methodology 2. Asymmetric reaction 3. Synthesis of biologically active molecules 4. Development of new bio- and chemo-materials 5. Molecular architecture
Organic Chemistry Professor Yoshiji TAKEMOTO	1. Development of new enantio- and stereoselective synthetic methods involving transition-metal catalysts 2. Development of environmentally friendly synthetic methods for process chemistry 3. Total synthesis of biologically important synthetic and natural products 4. Synthetic studies on multi-functional heterocyclic compounds and their use as drug-templates
Pharmacognosy Associate Professor Michiho ITO	1. Molecular cloning of enzymes responsible for biosynthesis of secondary metabolites, especially for those of monoterpene synthases 2. Phytochemical analyses of bio-active substances found in medicinal plants 3. Field surveys on medicinal plants for their diversity and sustainable use 4. Field surveys on traditional and folk medicines
Biophysical Chemistry Professor Katsumi MATSUZAKI	1. Elucidation of the action mechanisms of antimicrobial peptides 2. Initiation mechanism of Alzheimer's disease 3. Elucidation of membrane protein folding 4. Regulation of function of G-protein coupled receptors 5. Protein structure determination by NMR
Structural Biology Professor Hiroaki KATO	1. Structural-basis for pharmacologic behaviour of ATP binding Cassette transporters 2. Structural biology of translocation machinery of peroxisomal membrane proteins 3. Structural origin of catalytic power of enzymes based on ultra high-resolution structures 4. Development of a new technique of X-ray crystallography by X-ray free electron laser
Molecular & Cellular Bioanalysis Professor Yasushi ISHIHAMA	1. Development of novel analytical technologies for proteomics 2. Human proteome analysis based on single-shot LC-MS systems 3. Elucidation of intracellular phosphorylation network analysis 4. Quantitative clinical proteome analysis of tissue samples 5. Studies on the molecular targeting drug discovery based on phosphoproteomics
Fine Organic Synthesis Professor Takeo KAWABATA	1. Asymmetric synthesis based on the concept of memory of chirality 2. Organocatalytic regioselective functionalization of carbohydrates 3. Asymmetric synthesis by organocatalysis 4. Development of intelligent catalysts with programmed substrate-specificity 5. Creation of novel axially chiral molecules 6. Synthesis of nitrogen heterocycles with a tetrasubstituted carbon center 7. Structural and functional investigation of heterochiral oligomers 8. Investigation of dynamic chirality of molecules
Biological Chemistry Professor Hiroshi TAKESHIMA	1. Ca^{2+} signaling from intracellular stores 2. Novel signaling in central nervous system 3. Structure and function of muscle membrane systems
Human Retrovirus Professor Masao MATSUOKA	1. Molecular pathogenesis of human retroviruses (human T-cell leukemia virus type 1 and human immunodeficiency virus) 2. Replication of human retroviruses 3. Development of anti-HIV, and anti-HTLV-1 drugs 4. Development of animal model for human retroviral infections
Molecular Virology Professor Yoshio KOYANAGI	1. Analysis of mechanism of virus infection 2. Analysis of host factors in retroviral replication 3. Analysis of HIV-induced immunodeficiency 4. Development of novel anti-viral therapy
Genetic Biochemistry Lecturer Ayumi MIYAKE	1. Identification of genes for novel intercellular signaling molecules (growth factors, differentiation factors and hormones) 2. Structure and function of signaling molecules, and regulation of their gene expression 3. Roles of signaling molecules in metabolic regulation 4. Roles of signaling molecules in vertebrate development

Departments Leaders	Research Fields
Genetics Professor Tatsushi IGAKI	1. Mechanism of cell competition 2. Genetic basis of tissue growth regulation 3. Molecular basis of tumor progression and metastasis
Physiological Chemistry Professor Kazuhisa NAKAYAMA	1. Regulation of membrane traffic by small GTPases 2. Diverse regulatory mechanisms of endocytic pathways 3. Regulation of cell division through membrane traffic 4. Coupling mechanisms of membrane traffic and protein degradation 5. Regulation of membrane lipid asymmetry and cellular function
Molecular Neurobiology Professor Manabu NEGISHI	1. Cellular functions and signal transductions of Rho family GTPases 2. Cellular functions and signal transductions of Ras family GTPases 3. Neuronal functions and signal transductions of axon guidance factors
Biofunctional Chemistry Professor Shiroh FUTAKI	1. Creation of bioactive proteins that control cell function and genes 2. Development of peptide-based intracellular delivery systems for biomacromolecules 3. Design of peptides and proteins that induce membrane curvature 4. Design of artificial transcription factors that regulate gene expression 5. Assembly control of membrane proteins and the regulation of biological signals

Division of Biomedical Sciences

Departments Leaders	Research Fields
Drug Delivery Research Professor Mitsuru HASHIDA	1. Cell-specific delivery of nucleic acid drugs 2. In vivo disposition control of protein medicines 3. Nanotechnology-based drug delivery systems 4. Informatics-driven pharmacokinetic analysis
Pharmacology Associate Professor Toshiaki KUME Visiting Professor Akinori AKAIKE	1. Elucidation of pathogenesis and exploratory study of preventive and therapeutic agents of neurodegenerative diseases 2. Development of animal models of brain diseases using zebrafish 3. Study on function of nicotinic acetylcholine system in CNS 4. Study on neuroprotective compounds derived from food 5. Study on survival and regeneration of dopaminergic neurons
Clinical Pharmacy and Education Associate Professor Ikuko YANO	1. Optimal medication usage and its evaluation 2. Individualized pharmacotherapy based on pharmacokinetics and pharmacodynamics
Patho-Functional Bioanalysis Professor Hideo SAJI	1. Development of molecular probes for the in vivo analysis of biological function, etiological mechanisms, and action mechanisms of drugs 2. Development of radiopharmaceuticals for functional diagnosis and radionuclide therapy 3. Clarification of the biological actions of trace metals and development of physiologically active metals complexes
Biopharmaceutics and Drug Metabolism Professor Yoshinobu TAKAKURA	1. Development of nucleic acid drugs for optimized gene therapy and DNA vaccination 2. Development of nucleic acid-based nano-device/hydrogels 3. Development of exosome-based drug delivery system 4. Development of multifunctional cell therapeutics for in vivo cell therapy
Molecular Pharmacology Professor Shuji KANEKO	1. Physiology, pathology, molecular mechanisms, pharmacology, ligand screening and genome science with respect to the membrane transport proteins, especially toward TRP channels 2. The roles of neuron-glia-immune cell interaction in CNS pathology and drug action 3. Substantial background of pain and action mechanism of analgesics 4. Molecular and cellular mechanisms of drug actions and aversive effects
Clinical Pharmacology & Therapeutics (University Hospital) Professor Kazuo MATSUBARA	1. Molecular and neural mechanisms underlying pathological pain and dysesthesia 2. Reverse translational research for adverse effects of anti-cancer drugs: elucidation of the mechanisms and development of novel preventive and treatment strategies 3. Clinical and basic studies on Pharmacokinetics and Pharmacodynamics 4. Study of the pathogenic mechanism of Parkinson's disease in order to identify a potential novel cure 5. Application of biomarkers to individualized pharmacotherapy

Division of Bioinformatics and Chemical Genomics

Departments Leaders	Research Fields
Pharmacogenomics ・Genomic Drug Discovery Sciences (GDDS) Associate Professor Akira HIRASAWA	1. Discovery of novel drug target and its validation by integrative genome science 2. In Silico drug discover and design by bioinformatics 3. Ligand fishing of "orphan G-protein-coupled receptors" and structure-function analysis 4. Functional genomic study using transgenic/knockout animals
Chemogenomics ・Bioorganic Medicinal Chemistry Professor Hiroaki OHNO	1. Synthesis of structurally complex bioactive compounds 2. Novel methods for the synthesis of complex structures 3. Design and synthesis of peptides and peptidomimetics 4. Development of G protein-coupled receptor (GPCR) ligands 5. Chemical libraries
Systems Biology Professor Hitoshi OKAMURA	1. Molecular mechanisms of circadian time systems in mammals 2. Clarification of circadian time systems for development and life 3. Clarification of circadian time-associated lifestyle diseases 4. Clarification of rhythm related sleep diseases 5. Development of new drugs for tuning circadian time systems
System Chemotherapy and Molecular Sciences Professor Hideaki KAKEYA	1. Advanced chemical biology research for establishing system chemotherapy in order to cure multi-factorial diseases; e.g. cancer, infectious diseases, heart failure, immunodeficiency, diabetes, and neuronal diseases 2. HCS (high-contents screening) and HTS (high throughput screening) for identifying useful small molecules (bioprobes) 3. Natural product chemistry and medicinal chemistry for mining novel bioactive small molecules 4. Biosynthetic studies of natural products and their application to combinatorial biosynthesis
Integrative Genomics Professor Hiroyuki OGATA	1. Genomics of viruses 2. Interactions between microbial communities and their environments 3. Integration of chemical, genomics, and biomedical knowledge for drug discovery and environmental preservation
Computational Genomics Professor Hiroshi MAMITSUKA	1. Bioinformatics by integrative data mining on structured/semi-structured data in life science 2. Developing cutting-edge computer science technology, particularly machine learning and data mining, for drug discovery and molecular-level biological information analysis 3. Machine learning-based systems biology for understanding life phenomena

Center for Integrative Education in Pharmacy and Pharmaceutical Sciences

Departments Leaders	Research Fields
	1. Development of education system for drug developmental sciences 2. Development of education system for drug discovery sciences 3. Development of education system of clinical pharmacy 4. Optimization of pharmacotherapy

Endowed Chair

Departments Leaders	Research Fields
Department of Nanobio Drug Discovery Professor Kazuharu SHIMIZU	1. Drug Discovery by using miRNA microarray. 2. Research esophageal squamous cell carcinoma, (ESCC) for the molecular target. 3. Development of antibody drugs using tissues and cell lines of ESCC
Department of Pharmaceutical Policy and Health Economics Professor Hiroaki KAKIHARA	1. Optimal use and economic role of generic and brand-name drugs 2. Long-term economic impact of development of new drugs 3. Japanese policy on innovation of drugs

Department of Synthetic Medicinal Chemistry

Professor: Kiyosei Takasu, Associate Professor: Ken-ichi Yamada,
Assistant Professor: Yousuke Yamaoka

Research Projects:

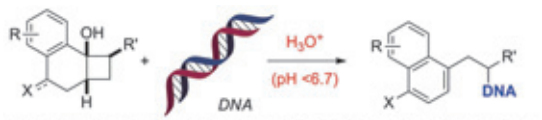
Generation of new organic molecules is essential to develop new medicines and medical substances. Organic chemists can create novel organic molecules (drug candidates and nanomachines) with chemical reactions. We must think over "What molecules do we design?", "How do we synthesize them?" and "How do we analyze their actions?" Our groups aim to contribute for the life sciences through discovery of new reactions and molecular structures.

Development of rational strategy towards total synthesis
Development of new useful reactions and new reagents
Proposal of new concepts in organic chemistry
Analysis of the dynamic conformation and interaction of molecules

1) Development of new synthetic methodology towards rapid molecular construction: A variety of natural and non-natural substances that contain polycyclic rings and an assortment of stereogenic centers have been found to exhibit attractive and specific biological activities. Owing to this, synthetic organic chemists are constantly confronted with the task of developing new reactions that can be used to prepare these complex targets in concise fashions starting from simple and readily available materials. An innovative strategy developed for this purpose relies on the use of highly convergent domino reactions. Major advantages of these, in which multiple covalent bonds are formed in single steps, include operational simplicity, time- and cost-saving, atom economy, environmental benignancy, and applicability to diversity-oriented synthesis and combinatorial chemistry.

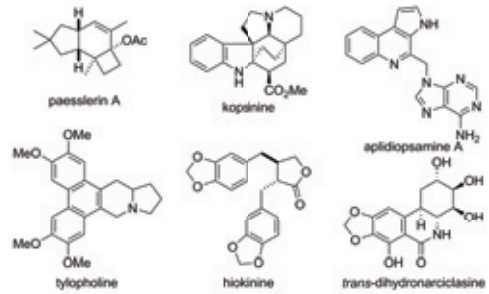
We have explored several classes of domino reactions using anionic, cationic, radical and pericylic chemistry. We recently focus on "tandem catalysis" in domino reactions, in which catalyst(s) promote more than two fundamentally different reactions in a single reactor. We have achieved rapid syntheses of structurally complex molecules including antitumor active natural products and anti-trypanosomal compounds.

2) Design and Synthesis of Biofunctional Molecules and Materials: When we wish to design artificial biologically active molecules, it is necessary to grasp their dynamic behavior and to imagine their specific interaction with biomolecules. We are now challenging to develop original biofunctional molecules based on fine organic chemistry. Recently, we developed low-pH sensitive DNA cleaving agents based on originally developed organic reactions.

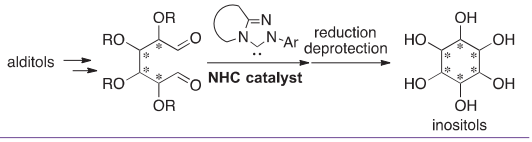


Plasmid DNAs are nicked by the molecule under weak acidic condition

3) Total Synthesis of Biologically Active Compounds: Synthesis of natural products needs comprehensive power of organic chemistry, including knowledge of a variety of organic reactions, reaction mechanism as well as structural organic chemistry. We continuously concentrate on the synthesis of natural products possessing novel chemical structure as well as potent and/or unique biological activities.



4) Synthetic Studies using Radical and Carbene Species: Radical reaction under mild conditions is one of promising tools in synthetic chemistry. Dimethylzinc or triethylborane can initiate the radical reactions by the reaction with air oxygen to produce reactive primary methyl or ethyl radicals, respectively. This method is effective to generate the radicals from ethers by abstraction of the hydrogen atom at the α-position of oxygen, or, from iodoalkanes by iodine atom abstraction without use of toxic tin reagents. We also utilized chiral N-heterocyclic carbenes (NHC) as a ligand or an organocatalyst to realize enantioselective transformations. Development of general and selective entry to bioactive rare inositols from abundant alditols is under investigation using NHC catalyst.



Recent publications

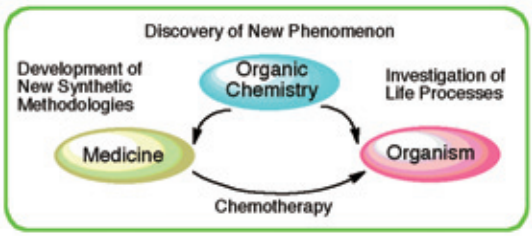
- Kuroda, Y.; Harada, S.; Oonishi, A..; Yamaoka, Y.; Yamada, K.; Takasu, K. Organocatalytic Activation of the Leaving Group in the Intramolecular Asymmetric S_N2' Reaction *Angew. Chem. Int. Ed.* **2015**, *in press.*
- Kuwano, S.; Harada, S.; Kang, B.; Raphael, O.; Yamaoka, Y.; Takasu, K.; Yamada, K. Enhanced Rate and Selectivity by Carboxylate Salt as a Basic Co-catalyst in Chiral *N*-Heterocyclic Carbene-Catalyzed Asymmetric Acylation of Secondary Alcohols. *J. Am. Chem. Soc.* **2013**, 135, 11485-11488.
- Nagamoto, Y.; Yamaoka, Y.; Fujimura, S.; Takemoto, Y.; Takasu, K. Synthesis of Functionalized Polycyclic Aromatic Compounds via a Formal (2+2)-cycloaddition. *Org. Lett.* **2014**, 16, 1008-1011.
- Nagamoto, Y.; Hattori, A.; Kakeya, H.; Takemoto, Y.; Takasu, K. pH-Sensitive DNA Cleaving Agents: In Situ Activation by Ring Contraction of Benzo-fused Cyclobutanols. *Chem. Commun.* **2013**, 49, 2622-2624.

Department of Organic Chemistry

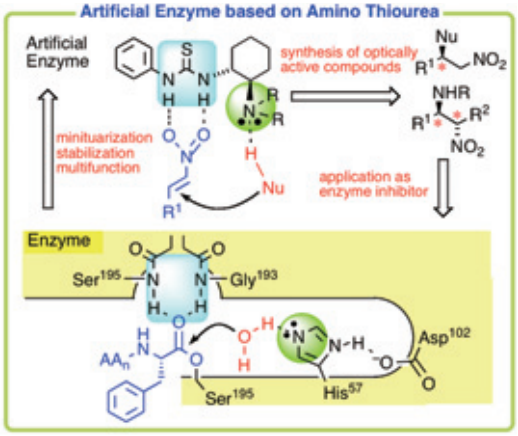
Professor: Yoshiji Takemoto, Lecturer: Chihiro Tsukano,
Assistant Professor: Yusuke Kobayashi

Research Projects:

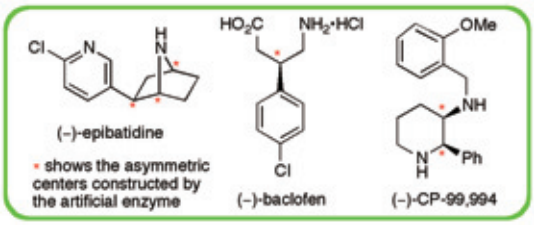
The aims of organic chemistry are structure analysis, reactivity investigation, and synthesis of organic molecules. The significance of organic chemistry in pharmaceutical sciences is clearly represented by the following facts: medicines are organic molecules which adjust life processes to cure disease, and the targeted life processes are composed of organic reactions. Taking into account these characteristics, our research programs are directed toward developing new methodologies for efficient construction of bioactive molecules and investigation of life processes by utilizing these organic molecules.



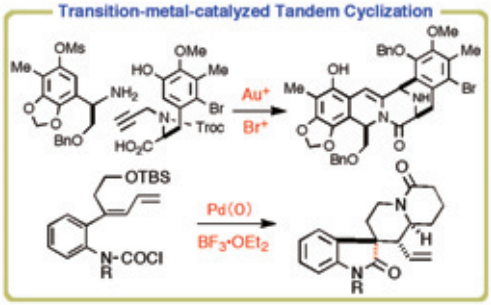
1) Development of Artificial Enzymes and Their Applications: Is it possible to create organic molecules, which can catalyze reactions in place of enzymes? This was the starting point of our journey toward development of artificial enzymes, so-called organocatalysts . A close examination of enzymes, such as serine protease, gave us an idea to design a small molecule, which possess a hydrogen bonding site together with a basic amino functionality.

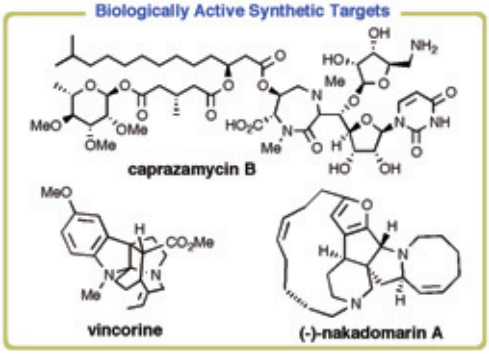


As a result of broad screening, a series of bifunctional thioureas have been found to catalyze a wide range of stereoselective transformations. Furthermore, by using these technologies, asymmetric total syntheses of (–)-epibatidine, (–)-CP-99,994 and (–)-baclofen have been achieved.



2) Development of Metal-Catalyzed Reactions for Efficient Synthesis of Biologically Active Compounds: To realize a quick approach to a broad range of complex molecules, a variety of metal-catalyzed reactions have been discovered. Examples include (1) tandem diethylzinc-promoted radical addition-Pd-catalyzed allylic substitution, (2) spirooxindol formation through Pd-catalyzed carbosilylation-Sakurai-type cyclization, and (3) gold-catalyzed tandem addition-cyclization reaction. The applications of these powerful methods toward total syntheses of bioactive natural products and multi-functionalized bioprobes, are in progress.





Recent publications

- Dearomatizing Conjugate Addition to Quinolinyl Amidines for the Synthesis of Dehaloperophoramidine via Tandem Arylation and Allylation, Ishida, T.; Ikota, H.; Kurahashi, K.; Tsukano, C.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 10204-10207.
- A Powerful Hydrogen-Bond-Donating Organocatalyst for the Enantioselective Intramolecular Oxa-Michael Reaction of α, β-Unsaturated Amides and Esters, Kobayashi, Y.; Taniguchi, Y.; Hayama, Y.; Inokuma, T.; Takemoto, Y. *Angew. Chem. Int. Ed.*, **2013**, *52*, 11114-11118.
- Synthesis of 3-Acyl-2-arylindole via Palladium-catalyzed Isocyanide Insertion and Oxypalladation of Alkyne, Nanjo, T.; Yamamoto, S.; Tsukano, C.; Takemoto, Y. *Org. Lett.* **2013**, *15*, 3754-3757.

Department of Pharmacognosy

Associate Professor: Michiho Ito

Research Projects:

We human beings have a long history of using various natural resources as plants and animals for curing disease and wounds. Natural medicines selected among those trials have been handed down to this century and still being used in our daily life. Also numerous pharmaceutics have been developed from compounds of natural products which were isolated from plants and microbes. However, natural medicines still include mysteries to be uncovered and potentials for creation of another pharmaceutics. Our studies on these mysteries and potentials are performed based on fieldworks and the following combination of lab-works.

1) Therapeutic use of incense and balm: "Kho-Doh", an incense ceremony, is one of the most elegant and traditional culture of Japanese; a small piece of agarwood of the highest quality is heated on a thin mica plate above charcoal, and a subtle fragrant arise from the piece is breathed in for tasting. Recent pharmacological studies indicate that the fragrant of agarwood might be a potent sedative, and which was experimentally exhibited using our new assay system. Further analyses on the active compounds and their mode of actions are under performance in the lab. Fragrant natural medicines other than agarwood, such as patchouli and spikenard that are often found in ingredients of Japanese sachet, are also analyzed for their potentials for therapeutic use.

2) Biosynthetic enzymes of secondary metabolism in medicinal plants: A large number of medicinal natural products are categorized as secondary metabolites, which differ from primary metabolites and are unique to plants. Among these we are focusing on fragrant volatiles which are mainly found in essential oil and resin of plants. Biosynthetic pathways and enzymes committed to them are studied through a combination of molecular biological techniques and conventional genetics. Agarwood, which was already mentioned in 1), and perilla, a common Labiatae kitchen herb, are materials of recent topics.

3) Fieldwork: In order to understand mechanisms and functions of secondary metabolism in plants, it is essential for researchers to know and experience the target with their own five senses, we suppose. Therefore, we perform field surveys (= fieldworks) and cultivate plant materials (= works) in our experimental station (= field); collecting experimental materials is certainly an object of the fieldworks, however, new ideas might be generated as results of watching and touching the target in the fieldworks. An interview to old healer in village is a common means for collecting information of folk medicines, which sometimes seems unlikely to the pharmaceutical sciences; how one could make mutual understanding with interviewee would be a key for these interviews. Our recent field is Indochina (Viet Nam, Lao PDR, Thailand, etc.) for pursuing agarwood, perilla, and unknown folk medicines.

4) Regulatory sciences on natural medicines (crude drugs): Medicinal plants and other natural materials are used as Kampo medicines and ingredients of different natural medicines. Many of these are used not only as pharmaceuticals but also as spices and materials for health foods; they have both natures of medicines and foods. A natural medicine that has different names in different countries may make troubles when it is traded internationally; it may be used in a wrong way to evoke unexpected side effects. In order not to happen the negative events in use of natural medicines, and to secure the safe use of natural medicines and their products, proper identification methods and other techniques and knowledge that will be useful for regulation on natural medicines are required. These knowledge and techniques are another tagets for our studies.

Recent publications

- Naoko Sato-masumoto, Michiho Ito, Domain swapping approach to regiospecific hydroxylation by geraniol and linalool synthases from perilla. Phytochemistry, **102**, 46-54 (2014).
- Hiroaki Takemoto, Michiho Ito, Yoshinori Kobayashi, Inhalation administration of valerena-4,7(11)-diene from Nardostachys chinensis roots ameliorates restraint stress-induced changes in murine behavior and stress-related factors. Biol. Pharm. Bull., **37** (4), (2014).
- Yukie Kumeta, Michiho Ito, Characterization of δ-guaiene synthases from cultured cells of Aquilaria, responsible for the formation of the sesquiterpenes in agarwood. Plant Physiology, **154** (4) 1998-2007 (2010).

Department of Biophysical Chemistry

Professor: Katsumi Matsuzaki, Associate Professor: Masaru Hoshino,
Assistant Professor: Yoshiaki Yano

Research Projects:

Biomembranes, which play important roles in cell functions, can be considered as supramolecular complexes composed of proteins (such as receptors and ion channels), diverse lipids, and oligosaccharides attached to proteins and lipids. Therefore, to elucidate the structures and functions of biomembranes, understanding of protein-lipid interactions is essential. Our current research projects are listed below.

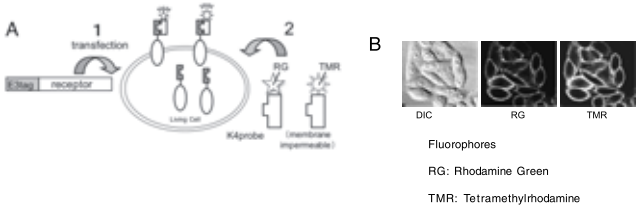
1) Elucidation of the action mechanisms of antimicrobal peptides: Antimicrobial peptides, which play an important role in innate immunity, have been isolated from many living species including human for 20 years. Shortly after the discovery of magainin 2, the first antimicrobial peptide from vertebrates, our laboratory started studying the action mechanism of antimicrobial peptides, such as magainin 2 and tachyplesin 1. We revealed for the first time that these peptides bound to bacterial membranes selectively, followed by forming dynamic peptide · lipid supramolecular-complex pores that allow mutually coupled transmembrane transport of ions, lipids, and peptides themselves. We are currently designing hybrid peptides and macromolecule-attached peptides to develop novel therapeutic agents.

2) Alzheimer's disease: The conversion of soluble, nontoxic amyloid beta peptide (Aβ) to aggregated, toxic Aβ is considered to be the key step in the pathogenesis of Alzheimer's disease. However, the mechanism of the aggregation remains unknown. It has been shown that, in Alzheimer's disease brain, Aβ is bound to the glycosphingolipid GM1-ganglioside (GM1). We have focused on microdomains in plasma membranes, called 'lipid rafts', which are mainly composed of cholesterol and sphingolipids including GM1, and revealed that Aβ specifically recognizes a ganglioside cluster, the formation of which is facilitated by cholesterol in raft-like liposomes, then undergoes a conformational transition to a β-sheet-rich structure, and the conformationally altered form of Aβ serves as a seed for the aggregation of the protein. Based on these findings, we have proposed "GM1-mediated Aβ accumulation model". In recent studies, we fluorescently visualized time- and concentration-dependent accumulation of Aβ on living cell membranes for the first time.

3) Elucidation of membrane protein folding: The folding principles of membrane proteins should be quite different from those of water-soluble proteins. However, experimental examination of the folding of membrane proteins is rather challenging due to their poor solubility and the difficulty in their isolation and purification. Our strategy is to elucidate thermodynamic parameters for forces that generally drive the folding of membrane proteins (e.g., van der Waals, H-bond, and ionic interactions) by using model transmembrane helices (folding units of membrane proteins) in the context of helix-lipid and helix-helix interactions.

4) Regulation of function of G-protein coupled receptors: We are developing new methods to control functions of GPCRs, which are important drug targets. We recently developed a labeling method named 'coiled-coil tag-probe labeling system' to quickly label cell-surface receptors in living cells with synthetic fluorescent probes, enabling easy and sensitive detection of receptor internalization after agonist stimulation. We are currently using this technology to elucidate and control complex behaviors of GPCRs in living cell membranes.

5) Protein structure determination by NMR: High-resolution NMR spectroscopy is established as a fundamental tool for the determination of detailed three dimensional structures of biomolecules such as proteins and nucleic acids in solution. This technique provides us detailed information about not only static but also dynamic nature of proteins, including protein folding, conformational change upon ligand binding at amino acid residue resolution. We are investigating the folding process of proteins and model peptides by using high-resolution NMR. We are also developing a novel method to analyze highly aggregative proteins to which current NMR is not applicable.



Coiled-coil labeling method.
(A) Labeling principle. (B) Confocal images for RG-K4 and TMR-K4 aquired 5 min after incubation with CHO cells expressing E3-β2 adrenoceptors.

Recent publications

- Yano et al. Cholesterol-induced lipophobic interaction between transmembrane helices using ensemble and single-molecule FRET. *Biochemistry* **54**, 1371, 2015.
- Ueno et al. Comparison between the aggregation of human and rodent amyloid β-proteins in GM1 ganglioside clusters. *Biochemistry* **53**, 7523, 2014.
- Kawano et al. A dimer is the minimal proton-conducting unit of the influenza A virus M2 channel. *J. Mol. Biol.* **426**, 2679, 2014.

Department of Structural Biology

Professor: Hiroaki Kato, Associate Professor: Toru Nakatsu,
Assistant Professor: Tomohiro Yamaguchi

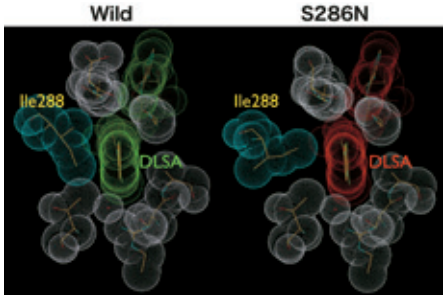
Research Projects:

Three-dimensional structure determination of biological macromoleculaes is the most powerful and important way to understand biological phenomenon. However, static views of those structures are not enough, because those molecules undergo distinct structural changes during they express functions or as a control of these functions. General objectives of this department are to understand mechanisms of protein molecules based on dynamic motion involved in their functions. We aim to capture the structural changes of molecular machineries at atomic resolution X-ray crystallography and try to determine their four-dimensional structures using kinetic X-ray crystallography. Our current research subjects are listed below.

1) Structural-basis for pharmacologic behaviour of ATP binding Cassette transporters: ATP Binding Cassette (ABC) transporters comprise a family of structurally related membrane proteins sharing well-conserved nucleotide binding domains. They commonly use ATP hydrolysis as an energy source for transport of the substrate across the lipid bilayer membrane. One of the most famous and important ABC transporters is P-glycoprotein, also called ABCB1 or MDR1. It is a multi-drug transporter which not only plays essential roles in normal physiology by protecting tissues from various toxic xenobiotics and endogenous metabolites but also contributes to multidrug resistance (MDR) in tumors, a major obstacle to effective chemotherapeutic treatment. Understanding the mechanism of the multidrug transport is crucial for designing drugs of good bioavailability and efficient cancer chemotherapy. Because of low thermal stability and low crystallizability of human P-glycoprotein (hP-gp), we searched for ABC transporters closely resembling hP-gp in the genome of *Cyanidioschyzon merolae*, a thermophilic unicellular eukaryote and found CmABCB1 whose amino acid sequence, multidrug specificity, and kinetics of ATP hydrolysis are most similar to those of hP-gp. We determined the high-resolution crystal structure of CmABCB1 and elucidated its gating mechanism in the substrate transport. Moreover, we discovered a novel inhibitor, which disables the diverging outward motions of the trans-membrane helices by clamping them from the outside of the transporter, and the mode of action of the inhibitor supports our proposed gating mechanism. Based on the inward-open state structure we determined, we try to elucidate the outward-open state structure and some dynamic structures between them. Those structures will allow us to unveil pharmacologic behavior of ABC transporters, especially to solve the ambivalent issue in controlling multi-drug transporters.

2) Structural and functional studies on translocation machinery of membrane proteins to an organelle: Peroxisome is a single layered-membrane organelle, and translocation of peroxisomal membrane proteins (PMPs) is involved with a peroxin (peroxisomal biogenesis protein) which functions as a specific chaperone. First of all, we want to understand the targeting mechanism of PMPs to peroxisome. Perhaps, in the cytosol all the newly synthesized PMPs would be bound to a peroxin, Pex19p. Pex19p transports PMPs from cytosol to the peroxisomal membranes where PMPs are inserted by the assistance of Pex3p and Pex16p, the other types of peroxins. Among them, we consider that the recognition of PMPs by Pex19p is one of the key events in the whole process, because Pex19p is required for the exact translocation of PMPs into peroxisome. However, still obscure is the nature of the structural motives that are shared by PMPs and are recognized by Pex19p. If such binding motives are revealed, the artificial motives are fused into the target membrane proteins to be overexpressed using a cell-free translation.

3) Structural origin of catalytic power of enzymes: Enzymes are protein molecules which can accelerate the speed of the chemical reaction. We study firefly luciferase in order to elucidate the structural basis of the catalytic machinery of enzymes using X-ray crystallography. Firefly luciferase catalyzes the emission of yellow-green light. We could catch the structural movement in the emission reaction using kinetic X-ray crystallography with luciferase - DLSA complex structure. DLSA is our synthetic compound which mimics to luciferyl-AMP intermediate molecule of the reaction. Ile288 of Wild-type luciferase is close to oxyluciferin moiety of DLSA and red-emitting Ser286Asn mutant does not cause the structural difference of Ile288. Therefore we conclude that luciferase controls the emission color using Ile288. Now we try to elucidate why is its quantum yield about 90%. On the other hand, a plant hormone, gibberellin receptor is expected to be evolved from a lipid hydrolytic enzyme, lipase. We determined the receptor structure by X-ray crystallography, and have been elucidating molecular evolution of the receptor through the structural-basis of signal transduction mechanism of gibberellin.



Bioluminescent control in Japanese firefly luciferase

A Japanese firefly emits yellow-green light and its S286N mutant in which a single amino acid residue, Ser286 is replaced by Asn emits red light. We determined the crystal structures of the wild-type and S286N mutant luciferases in complex with DLSA. We found that the hydrophobic side chain of Ile288 was close to DLSA in the wild-type but not in S286N mutant. Therefore the degree of molecular rigidity of oxyluciferin in the excited state, that is controlled by the movement of Ile288, is important for the color control mechanism of bioluminescence during the emission reaction.

Recent publications

- Shimada *et al.* Structural basis for gibberellin recognition by its receptor GID1. *Nature*, **456**, 520, 2008.
- Nakatsu *et al.* Structural basis for the spectral difference in luciferase bioluminescence. *Nature*. **440**, 372, 2006.
- Kodan *et al.* Structural basis for gating mechanisms of a eukaryotic P-glycoprotein homolog. Proc Natl. Acad. Sci. USA, **111**, 4049, 2014.

Department of Molecular & Cellular Bioanalysis

Professor: Yasushi Ishihama,
Associate Professor: Naoyuki Sugiyama (Advanced Drug Discovery Research Project),
Assistant Professor: Masaki Wakabayashi

Research Projects:

We have advocated elucidating the cellular functions through the measurement of biomolecules based on analytical chemistry. In particular, we have focused on proteome science consisting of mass spectrometry, nano-separation science, computational science and cell biology to develop the methodologies for the functional analysis of cells. More specifically, we are conducting research on the following five topics;

1) Development of novel analytical technologies for proteomics
2) Human proteome analysis based on single-shot LC-MS systems
3) Elucidation of intracellular phosphorylation network analysis
4) Quantitative clinical proteome analysis of tissue samples
5) Studies on the molecular targeting drug discovery based on phosphoproteomics

Unlike genomic and transcriptomic researches, proteomics is still immature in terms of the measurement technologies and the complete analysis of proteome has not been established yet. The final goals of proteomics are to uncover the cellular protein events such as (1) protein expression/degradation, (2) protein localization, (3) protein interaction, (4) protein post-translational modifications (PTM) and (5) protein processing/splicing in proteome-wide.

We are aiming to develop novel approaches to tackle the technical barriers and to explore proteomic researches for clarifying the biological problems.

In order to analyze the entire proteome expressed in cells, we are focusing on developing efficient separation systems based on nanoLC-MS using meter-long monolithic silica capillary columns with the world's highest performance beyond theoretical plate number 1,000,000. So far, our systems allowed to expand the measurable dynamic range of highly complex proteomics samples, achieving the analysis of *Escherichia* coli expressed proteome on a microarray scale (see Figure1). This system is currently applied to more complex proteome such as human. We are also developing new technologies for quantitative proteomics as well as high sensitivity proteomics.

In cellular signal transduction network, reversible phosphorylation is one of the key events to transduce the signal into nucleus to control the gene expression. Approximately 30% of human proteins were estimated to be phosphorylated. We have developed a highly selective enrichment method for phosphopeptides and applied to proteome-wide acquisition of cellular phosphorylation status. Consequently, we found that at least 70% of human proteins are phosphorylated, which are 2-fold more than that registered in the public protein database such as UniProt. The next step is to intertwine the kinases with their substrates for revealing the whole picture of signaling network by using experimental and computational approaches.

Our phosphoproteomics system has been also employed to carry out *in vivo* phosphoproteome profiling of the molecular-targeting drugs, which would facilitate drug discovery for cancer therapy. Furthermore, we are exploring the functional analysis of newly discovered phosphorylation molecules. In addition to phosphorylation, we recently started other PTMome analysis to evaluate the cellular and molecular functions.

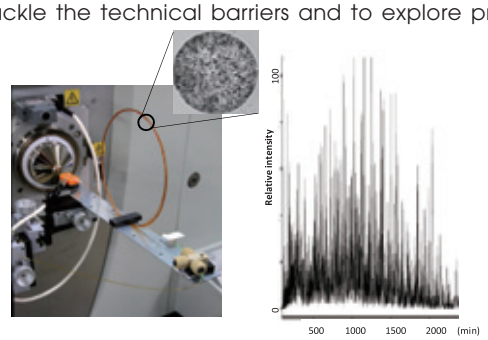


Figure 1 Complete proteome analysis by nanLC-MS.
(Left) nanoLC-MS system with 3.5 meter monolithic silica column. (Right) Total ion current chromatogram of E. coli proteome. Analysis on a microarray scale was achieved

Recent publications

- Tsai et al., Large-scale determination of absolute phosphorylation stoichiometries in human cells by motif-targeting quantitative proteomics. *Nat. Commun.*, **6**, 6622, 2015.
- Yamana et al., Rapid and deep profiling of human induced pluripotent stem cell proteome by one-shot nanoLC-MS/MS analysis with meter-scale monolithic silica columns. *J. Proteome Res.* **12**, 214-21, 2013.
- Imami et al., Temporal profiling of lapatinib-suppressed phosphorylation signals in EGFR/HER2 pathways. *Mol. Cell. Proteomics* **11**, 1741-57, 2012.
- Sugiyama et al., Phosphopeptide enrichment by aliphatic hydroxy acid-modified metal oxide chromatography for nano-LC-MS/MS in proteomics applications. *Mol. Cell. Proteomics* **6**, 1103-9, 2007.

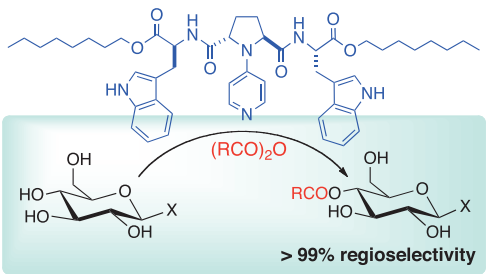
Department of Fine Organic Synthesis

Professor: Takeo Kawabata, Associate Professor: Takumi Furuta,
Assistant Professor: Tomoyuki Yoshimura, Yoshihiro Ueda

Research Projects:

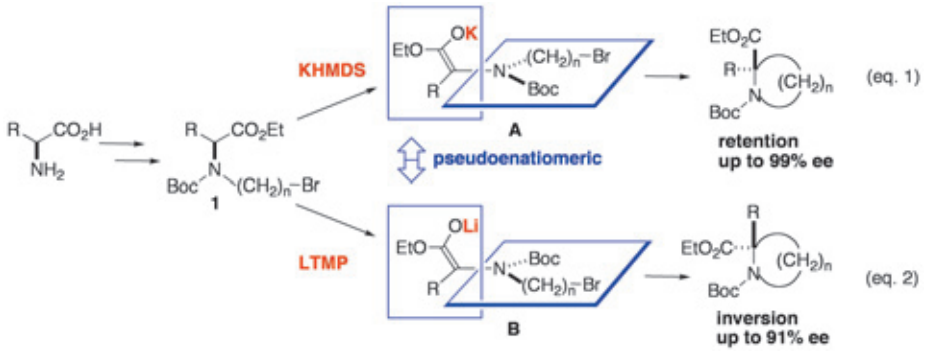
The research interests of the laboratory include the development of advanced molecular transformation, total synthesis of biologically active products, and molecular recognition. Programs are active in the areas of asymmetric alkylation of carbonyl compounds based on "memory of chirality", nucleophilic catalysis for fine organic syntheses, synthesis of unusual amino acids and nitrogen heterocycles, creation of axially chiral compounds with an inner hydrogen bond, synthesis and properties of homochiral oligonaphthalenes, and the structural and functional investigation of heterochiral oligomers. Current research topics are shown below.

1) Regioselective Acylation of Carbohydrates by Nucleophilic Catalysis: Direct regioselective functionalization of multi-functionalized substrates is one of the goals of current research toward the development of advanced molecular transformation for the next generation. We have developed a highly regioselective acylation of carbohydrates with chiral nucleophilic catalysts. Treatment of a glucose derivative with 1 mol% of a catalyst and 1.1 mol eq. of isobutyric anhydride in chloroform at -20 °C gave the 4-acylated glucose derivative and the 3-acylated surrogate in a 99:1 ratio in 98% yield. The corresponding 6-isomer, 2-isomer, and the di-acylated isomers were not detected at all. The corresponding reaction with 10 mol% of 4-dimethylaminopyridine proceeded in a random way, giving 6-, 4-, 3-, and 2-isomers in a ratio of 38:23:38:1 in a combined yield of 69% together with 19% of the di-acylated isomers and 10% recovery. Thus, discrimination of four hydroxyl groups of the glucose derivative has been achieved by the catalyst via dynamic molecular recognition.



2) Stereochemical Diversity in Asymmetric Cyclization via Memory of Chirality

N-(ω-bromoalkyl)-α-amino acid derivatives **1**, readily prepared from L-α-amino acids, gave cyclic amino acids with a tetrasubstituted carbon center by the treatment with KHMDS in DMF. Chirality of the parent amino acids was almost completely preserved during an enolate-formation and cyclization process, giving aza-cyclic amino acids in up to 99% ee with retention of configuration (eq. 1). Mechanistic investigation indicated that the asymmetric cyclization proceeds via an axially chiral enolate intermediate **A**. On the other hand, generation of the pseudoenantiomeric enolate **B** was accomplished simply by changing the conditions for enolate-formation. As the consequence, treatment of **1** with lithium 2,2,6,6-tetramethylpiperidide (LTMP) in THF gave cyclic amino acids with inversion of configuration in up to 91% ee. Thus, both enantiomers of cyclic amino acids with a tetrasubstituted carbon center were prepared in high enantiomeric purity from readily available L-α-amino acids.



Recent publications

- Kawabata, T. *et. al.*, Total Synthesis of Ellagitannins via Regioselective Sequential Functionalization of Unprotected Glucose. *Angew. Chem. Int. Ed.* **2015**, *54*, 6177-6180.
- Kawabata, T. *et. al.*, Asymmetric Induction via Short-Lived Chiral Enolates with a Chiral C-O Axis. *J. Am. Chem. Soc.* **2013**, *135*, 7102-7105.
- Kawabata, T. *et. al.*, Chemoselective Oxidation by Electronically Tuned Nitroxyl Radical Catalysts. *Angew. Chem. Int. Ed.* **2013**, *52*, 8093-8097.
- Kawabata, T. *et. al.*, Asymmetric α-Arylation of Amino Acid Derivatives by Clayden Rearrangement of Ester Enolates via Memory of Chirality. *J. Am. Chem. Soc.* **2013**, *135*, 13294-13297.

Department of Biological Chemistry

Professor: Hiroshi Takeshima, Associate Professor: Sho Kakizawa

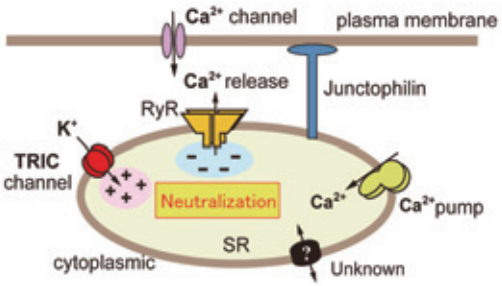
Research Projects:

In living organism, biomacromolecules physically and functionally interact with each other and induce chemical reactions to establish flexible life processes. We are dealing with biochemical and gene-handling studies on membrane proteins toward unlocking the molecular basis of life. Our efforts contribute to not only the global progress of basic biology, but also the healthcare field, for example, identifying reliable target proteins for pharmaceutical development and locating mutations in human genetic diseases. Our current research projects are listed below.

1) Ca^{2+} signaling from intracellular stores: Intracellular Ca^{2+} signaling is triggered by Ca^{2+} influx and Ca^{2+} release for the physiological regulation of a wide variety of cellular functions. In excitable cells, machinery for Ca^{2+} release from the endo/sarcoplasmic reticulum (ER/SR) is well organized and is essential for regulating muscle contraction and neural excitability. We are focusing on the Ca^{2+} release mechanism and molecular architecture of the ER/SR as intracellular stores. Our current aims are to clarify physiological roles of Ca^{2+} release mediated by ryanodine receptors, sets of ryanodine-sensitive intracellular Ca^{2+} release channels, to define functions of junctophilin contributing to junctional membrane complexes between the plasma membrane and the ER/SR, and to identify novel protein ER/SR components essential for Ca^{2+} store functions. The figure below shows major components in the juctional membrane complex for cardiac excitation-contraction coupling. Our previous studies demonstrated that cardiac Ca^{2+} signaling absolutely requires Ca^{2+} channel, TRIC channel, RyR and JP. Knockout mice lacking the components exhibit heart failure at early embryonic stages. Genetic mutations in Ca^{2+} channel and RyR cause familial cardiac myopathy and arrhythmia, respectively. Moreover, our biochemical analysis identified several membrane proteins with unknown functions in the ER/SR.

2) Novel signaling in central nervous system: Information processing and cellular organization in the central nervous system (CNS) is in mystery. Uncharacterized protein components from the brain indicates the existence of unknown intercellular and intracellular signaling in CNS. Our group identified several receptor-like membrane proteins specifically expressing in the brain, including DNER (delta-notch-type EGF repeat containing protein) and BSRPs (brain-specific receptor-like proteins), and started to survey their roles in brain development and function. Interestingly, both knockout mice lacking DNER and BSPRs show motorcoordination defects and probably share cerebellar dysfunction.

3) Structure and function of muscle membrane systems: There are many strange membrane structures in striated muscle cells, for example the transverse tubule, Z-tubule, triad and diad, junctional SR and longitudinal SR (see textbook for histology). Because molecular mechanisms for such membrane structures are almost unknown, we would like to identify proteins contributing to these membrane structures. Our previous screening identified a series of muscle membrane proteins with unknown functions, namely the "mitsugumin" family. Recent studies found that mitsugumin 29 partially restricts the ultrastructure of the transverse tubule and is involved in physiological and histological defects during muscle aging. Moreover, mitsugumin 53 is involved in repair of membrane damage in striated muscle. Therefore, it is thought that mitsugumin 53 is a responsible gene of muscular dystrophy.



Components for Ca^{2+}-induced Ca^{2+} release (CICR) in cardiac muscle cells.
Ca^{2+} influx mediated by Ca^{2+} channels induces channel opening of ryanodine receptors (RyR) and triggers Ca^{2+} release from the sarcoplasmic reticulum (SR). This CICR requires the colocalization of Ca^{2+} channel and junctophilin within junctional membrane complex supported by junctophilin because the loss of the close association between Ca^{2+} channels and RyR disconnects Ca^{2+} effects. TRIC channels are likely to act as counter-ion channels that function in synchronization with Ca^{2+} release from intracellular stores and maintain an efficient Ca^{2+} release. Moreover, unidentified SR protein components might have important roles as channels and Ca^{2+} binding proteins. Our findings are expected as not only development of biochemistry but also the clinical application.

Recent publications

- Tao S. et al. Facilitated hyperpolarization signaling in vascular smooth muscle overexpressing TRIC-A channels. ***J. Biol. Chem***. 288, 15581-15589, 2013.
- Kakizawa S. et al. Nitric oxide-induced calcium release via ryanodine receptors regulates neuronal function. ***EMBO J***. 31, 417-428, 2012.
- Yamazaki D. et al. TRIC-A channels in vascular smooth muscle contribute to blood pressure maintenance. ***Cell Metab***. 14, 231-241, 2011.

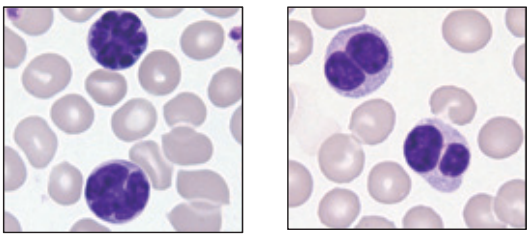
Department of Human Retrovirus

Professor: Masao Matsuoka, Lecturer: Jun-ichirou Yasunaga,
Assistant Professor: Kazuya Shimura

Research Projects:

Both human T-cell leukemia virus type 1 (HTLV-1) and human immunodeficiency virus (HIV) are pathogenic human retroviruses. HTLV-1 promotes proliferation of $CD4^+$ T cells, which leads to leukemia while HIV destroys $CD4^+$ T cells resulting in onset of acquired immunodeficiency syndrome (AIDS).

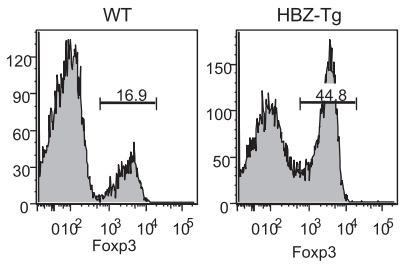
HTLV-1 causes a neoplastic disease, adult T-cell leukemia (ATL), and the inflammatory diseases, such as HTLV-1 associated myelopathy in a small part of the HTLV-1-infected individuals. We found that HTLV-1 bZIP factor (HBZ) gene is expressed in all ATL cells and supports growth of T-cells. In addition, we have established HBZ transgenic mice (HBZ-Tg), and observed that HBZ-Tg developed T-cell lymphomas and systemic inflammatory diseases, suggesting that HBZ is critical in pathogenesis of HTLV-1. Immunological analyses revealed that T-lymphoma tissues in HBZ-Tg frequently expressed Foxp3, a master molecule of regulatory T cell (Treg). Interestingly, the suppressive function of Tregs from HBZ-Tg was impaired compared with non-Tg littermates, suggesting that HBZ expression increases dysfunctional Tregs resulting in malignant transformation and inflammatory disorders *in vivo*. Those phenotypes of HBZ-Tg are very similar to those of HTLV-1 carriers. HBZ is considered to play the important roles in oncogenesis, although the precise mechanism has not been clarified. HBZ modulates various signaling pathways, such as NF-κB, TGF-β, and NFAT signaling pathways. We are analyzing their significances in leukemogenesis of HTLV-1-infected cells.



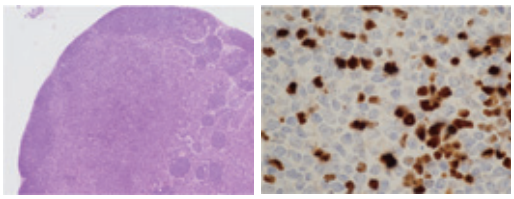
ATL cells have a hyper-segmented nuclei.

AIDS is caused by HIV infection, through the depletion of $CD4^+$ T lymphocytes. In early times, AIDS was feared as one of the most fatal diseases, with a very poor prognosis. However, due to the development of potent anti-HIV drugs, efficient anti-HIV/AIDS therapies were established, and HIV infection has become a relatively controllable chronic viral disease. Nevertheless, complete eradication of the virus from infected patients has not been achieved yet. In order to suppress viral replication and prevent the development of AIDS, lifelong medication with anti-HIV drugs is required. Drug-resistance mutations are often identified even in treatment-naïve HIV-infected patients. To overcome these obstacles, we are developing novel anti-HIV drugs, and studying anti-HIV drug resistance mechanism.

We previously developed fusion inhibitors that block the fusion step between the virus and the host cell, and an integrase inhibitor that interferes with the integration of the viral DNA into the host chromosome. Recently, we focused on quite novel anti-HIV compounds targeting viral replication step(s) other than those targeted by preexisting drugs. Interestingly, these inhibitors show anti-viral activity not only against HIV but also, against other viruses such as hepatitis C virus and human herpes simplex virus. We are now evaluating anti-viral activity *in vivo*.



Regulatory T-cells are increased in HBZ transgenic mouse (HBZ-Tg).



HBZ-Tg develop T-cell lymphomas, which express Foxp3.

Recent publications

●Yamamoto-Taguchi N, Satou Y, Miyazato P, Ohshima K, Nakagawa M, Katagiri K, Kinashi T, and Matsuoka M. HTLV-1 bZIP factor induces inflammation through labile Foxp3 expression. PLoS Pathogens, 9: e1003630, 2013.

●Satou Y, Yasunaga J, Zhao T, Yoshida M, Miyazato P, Takai K, Shimizu K, Ohshima K, Green PL, Ohkura N, Yamaguchi T, Ono M, Sakaguchi S, Matsuoka M. , while ociated myelopathy (HAM)uding HTLV-1 associated myelopathy (HAM/TSP)HTLV-1 bZIP factor induces T-cell lymphoma and systemic inflammation *in vivo*. PLoS Pathogens 7: e1001274, 2011.

●Fujii M and Matsuoka M. Human T-cell leukemia virus type 1 and 2. Fields Virology, 6th edition, Lippincott Williams & Wilkins, p1474-1501, 2013.

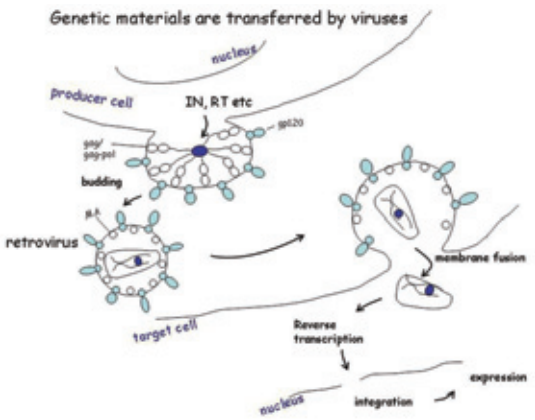
Department of Molecular Virology

Professor: Yoshio Koyanagi, Assistant Professor: Hirotaka Ebina, Kei Sato

Research Projects:

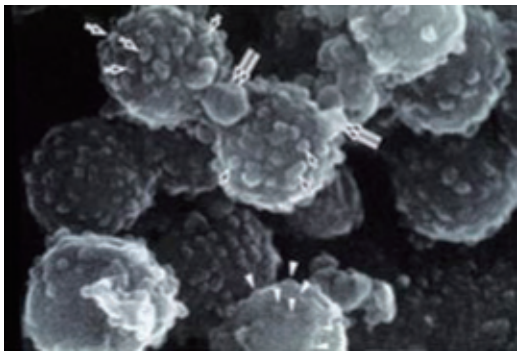
It is clear that virus researches have provided strong advances to Cell Biology. Therefore, we believe that our efforts will contribute to Medical and Pharmaceutical Sciences. Our research themes have been arranged below.

1) How virus infects cell and replicates? Viral genome moves from virion-produced cell to adjacent naive cells (See figure below). This is a most significant characteristic of virus. Elucidation of the mechanism of this infection event is a primary theme.



2) How cellular factors influence viral replication? Virus cannot replicate without cells. Since it has been found that many cellular factors promote or suppress human immunodeficiency virus (HIV) replication, we wish to learn the mechanisms from aspect of Immunology and Virology (See right figure).

3) Why HIV causes immunodeficiency in human? The mechanism of the immunodeficiency remains unclear. We have been analyzing how the immunodeficiency occurs using *in vitro*-cell culture models and *in vivo*-animal models. We developed a mouse system that human immune system is transplanted in SCID mouse and in this human-chimera mouse, abundant CD4 cell killing can be reproduced with HIV infection.



4) Why do we need novel anti-viral therapy? Although development of anti-HIV therapies has been accelerating, treatment for HIV cure has not yet been established. Therefore, we have tried to develop novel strategy for HIV proviral DNA from genome editing technology.

Recent publications

- Sato K, Takeuchi SJ, Misawa N, Izumi T, Kobayashi T, Kimura Y, Iwami S, Takaori-Kondo A, Hu WS, Aihara K, Ito M, An DS, Pathak VK, and Koyanagi Y. APOBECD and APOBECF potently promote HIV-1 diversification and evolution in humanized mice. PLoS Pathog, 10:e1004453, 2014.
- Ebina H, Misawa, Kanemura Y, and Koyanagi Y. Harnessing the CRISPR/Cas9 system to disrupt latent HIV-1 provirus. Sci. Rep. 3 : 2510, 2013.
- Sato, K, Misawa N, Iwami S, Satou Y, Matsuoka M, Ishizaka Y, Ito M, Aihara K, An DS, and Koyanagi Y. HIV-1 Vpr accelerates viral replication during acute infection by exploitation of proliferating $CD4^+$ T cells *in vivo*. PLoS Pathog, 9:e1003812. 2013.

Lab URL : http://www.virus.kyoto-u.ac.jp/Lab/KoyanagiHP/saito/TOP.html

Department of Genetic Biochemistry

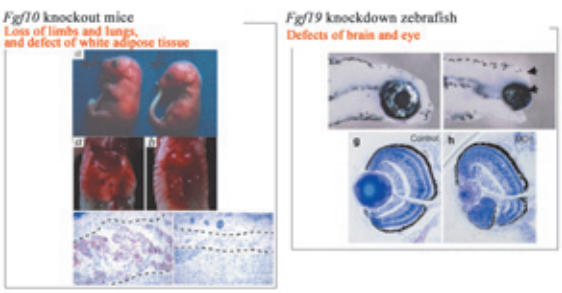
Lecturer: Ayumi Miyake

Research Projects:

In vertebrates, multiple cells interact each other to form various tissues. Secreted proteins are implicated in the intercellular interaction. Therefore, secreted proteins have come to be recognized as key mediators of many fundamental processes in embryonic development. We have focused on elucidating the roles of secreted proteins in the embryonic development and investigated the mechanisms controlling the form of a developing tissue by using the reverse genetics approach. In reverse genetics, a novel gene of unknown function is first identified, and the function of the novel gene is examined by using the loss-of- and gain-of-function approaches. Our efforts contribute to not only the global progress of life science, but also the development of the regenerative medicine. More detailed explanation about each project is described below.

1) Identification of novel Fgfs and their roles in the embryonic development: The prototypic fibroblast growth factors (Fgfs) were originally isolated from bovine brain as mitogen for fibroblasts. Afterwards, several proteins, which were identified by the process of various experiments, were named as Fgf by structural homology. The Fgf family consisted of nine members (Fgf1~9). Most Fgfs are secreted from cells and have multiple biological activities including roles in mitogenesis and cellular differentiation. Fgfs have been shown to play important roles in development of multiple tissues in addition to angiogenesis and repair of tissue injury. These important roles of Fgfs in the development prompted us to identify a novel Fgf based on structural homology. We identified nine *FGFs* including *Fgf10, 16, 17, 18, 19, 20, 21, 22,* and *23*. We examined their roles in the development of tissues. We generated *Fgf10* and *Fgf18* knockout mice. Fgf10 plays crucial roles in multi-organ development including the limbs, lungs, and adipose tissue. Fgf18 plays crucial roles in normal development of the bones and lungs. We examined the activity of Fgf20 using culture cells. We have shown that Fgf20 enhances the survival of dopaminergic neurons and promotes their differentiation from ES cells. Degeneration of dopaminergic neurons causes Parkinson's disease. Therefore, Fgf20 is expected to be useful in prevention and treatment of Parkinson's disease. Furthermore, we have shown that Fgf19 is required for normal development of forebrain and eye, and that Fgf21 is required for the formation of erythrocytes by an analysis of *Fgf19*- and *Fgf21*-knockdown zebrafish embryos, respectively. In hematopoiesis, the molecular mechanism behind the activity of Fgf21 is different from that of erythropoietin, which is used as a therapeutic agent for anemia. Therefore, Fgf21 is expected to be applied to the development of medicine. We are now investigating the roles of Fgfs and the molecular mechanisms behind the action of Fgfs in the development by using the loss-of-function approaches in mice and zebrafish,

2) Identification of novel secreted proteins other than Fgf and their roles in the embryonic development: Recently, a lot of genes of unknown function are shown by DNA database. It is expected that a lot of genes encoding the secreted proteins are included in that. We identified many cDNAs encoding the novel putative secreted proteins by searching DNA databases. Furthermore, we investigated the spatiotemporal expression patterns of the genes and selected several novel secreted proteins that might contribute to the organ's. Among them, *ectodin*, a secreted bone morphogenetic protein (BMP) inhibitor, is expressed as a "negative" image of mouse enamel knots. We propose that *ectodin* is critical for robust spatial delineation of enamel knots and cusps by an analysis of *ectodin*-deficient mice. We have shown that *fibin* expressed in the lateral plate mesoderm is a secreted signal essential for pectoral fin bud initiation in that it potentially acts downstream of retinoic acid and wnt signaling by an analysis of *fibin*-knockdown zebrafish embryos. In addition, we have identified several novel secreted proteins that might contribute to the brain's formation and investigated the roles in brain development.



***Fgf10* knockout mice and**
***Fgf19* knockdown zebrafish embryos**

In *Fgf10* knockout mice (right panels), loss of limbs and lungs (upper and middle panels, respectively) and defects of white adipose tissue (lower panels) were observed. In *Fgf19* knockdown zebrafish embryos (right panels), defects of brain and small eyes were observed (upper panels) cmpared with wild-type embryos (left panels). In eyes of *Fgf19* knockdown zebrafish embryos (left panels), lens defects and abnormal patterning of retina were observed (lower panels).

Recent publications

- Miyake *et al.*, Fgf16 is required for specification of GABAergic neurons and oligodendrocytes in the zebrafish forebrain. *PLoS One* **9**, e110836, 2014.
- Miyake *et al.*, Fgf22 regulated by Fgf3/Fgf8 signaling is required for zebrafish midbrain development. *Biol. Open* **2**, 515, 2013.
- Miyake *et al.*, Neucrin, a novel secreted antagonist of canonical Wnt signaling, plays roles in developing neural tissues in zebrafish. *Mech. Dev.*, **128**, 577, 2012.

Department of Genetics

Professor: Tatsushi Igaki, Lecturer: Shizue Ohsawa,
Assistant Professor: Masato Enomoto

Research Projects:

Cell-cell interactions in multicellular organisms play crucial roles in coordination of cell proliferation, differentiation, and cell death during development and homeostasis. However, little is known how cells communicate each other within animals to establish a multicelular system. We are exploring the molecular basis of cell-cell communication utilizing a powerful genetics of *Drosophila*. Especially, our research focuses on the mechanisms of cellular 'competition' and 'cooperation' within epithelium.

1) Mechanism of cell competition

'Cell competition' is a form of cell-cell interaction in which cells with higher fitness ('winners') survive and proliferate at the expense of neighboring cells with lower fitness ('losers'). Loser cells, but otherwise viable cells, are eliminated by cell death when confronted with winner cells. It has been suggested that cell competition is involved in a variety of biological processes such as organ size control, tissue homeostasis, cancer progression, and the maintenance of stem cell population. In developing *Drosophilai* maginal epithelia, clones of cells mutant for apico-basal polarity genes such as *scribble* (*scrib*) or discs large(*dlg*) lose their epithelial integrity and are eliminated by cell competition when confronted with wild-type cells. We have discovered that the *Drosophila* tumor necrosis factor (TNF) Eiger and its downstream JNK signaling play a central role in this process. Interestingly, Eiger-JNK signaling is required for both losers and winners to drive cell competition. Elevated Eiger signaling in mutant 'loser' cells promotes JNK-dependent cell death of these cells (Igaki *et al., Dev Cell,* 2009), while elevated Eiger signaling in surrounding wild-type 'winner' cells facilitates elimination of mutant neighbors through JNK-dependent engulfment machinery (Ohsawa *et al., Dev Cell,* 2011) (Fig. 1). Our study reveals that cell competition could be an evolutionarily conserved fail-safe mechanism by which animals protect against neoplastic development. To dissect the upstream mechanisms of cell competition, we have established and performed a genetic screen for genes that regulate this cell elimination. We have also established new models of cell competition using different types of mutations to understand the molecular mechanism and the physiological roles of cell competition.

2) Mechanism of tissue growth and tumor progression through cell-cell communication

Cell-cell interactions between oncogenic cells and surrounding normal cells in the tumor microenvironment play crucial roles in cancer progression. However, the mechanisms by which each oncogenic alteration cooperates with others to drive tissue growth and tumor progression through cell-cell communication remain elusive. We have been studying the mechanism of tumor growth and metastasis using the *Drosophila* model of tumor progression (Igaki *et al., Curr Biol,* 2006). Furthermore, we have performed a genetic screen in *Drosophila* imaginal epithelium to identify mutations that cause 'non-autonomous' tumor progression through cell-cell communication. The results from our screen revealed that defects in mitochondrial respiratory function in conjunction with Ras activation potently induce tumor progression of surrounding tissue. Mechanistically, Ras activation and mitochondrial dysfunction cooperatively stimulate production of ROS, which causes activation of JNK signaling. JNK cooperates with oncogenic Ras to inactivate the Hippo pathway, leading to upregulation of the inflammatory cytokine Unpaired (Upd, an IL-6 homolog). The secreted Upd further cooperates with Ras signaling in neighboring cells with normal mitochondrial function, causing benign tumors to exhibit metastatic behavior (Ohsawa *et al., Nature,* 2012) (Fig. 2). These findings provide a novel mechanistic basis for interclonal tumor progression driven by 'oncogenic inflammation' through Ras activation and mitochondrial dysfunction, the frequent alterations in human malignancies. We have also discovered that oncogenic cells with elevated Src activity promote growth of surrounding tissue via JNK-dependent regulation of the Hippo pathway (Enomoto and Igaki, *EMBO Rep,* 2012). are also establishing new models of cellular 'cooperation' that regulate tissue growth and/or tumor progression through cell-cell communications.

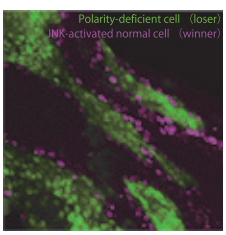


Fig. 1 Cell competition in *Drosophila* epithelium

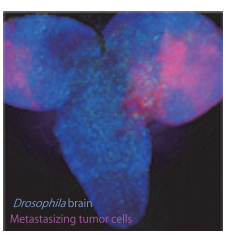


Fig. 2 Tumor metastasis in the *Drosophila* brain

Recent publications

- Nakamura *et al.*,
  Mitochondrial defects trigger proliferation of neighbouring cells via a senescence-associated secretory phenotype in *Drosophila*.
  Nat Commun, 5, 5264 (2014)
- Enomoto and Igaki,
  Src controls tumorigenesis via JNK-dependent regulation of the Hippo pathway in *Drosophila*.
  EMBO Rep, 14, 65-72 (2013)
- Ohsawa *et al.*,
  Mitochondrial defect drives non-autonomous tumour progression through Hippo signalling in *Drosophila*.
  Nature, 490, 547-551 (2012)
- Ohsawa *et al.*,
  Elimination of oncogenic neighbors by JNK-mediated engulfment in *Drosophila*.
  Dev Cell 20, 315-328 (2011)

Department of Physiological Chemistry

Professor: Kazuhisa Nakayama, Associate Professor: Hye-won Shin,
Assistant Professor: Youhei Kato

Research Projects:

1) Regulation of intracellular membrane traffic by small GTPases:

Normal functions of a human body, which consists of ~6.0 X 10^{13} cells, rely strictly on the normal function of every cell. There are a variety of intracellular organelles, in which specific proteins are present. Furthermore, it is essential for each cell to function properly that each protein is transported from an organelle where it is synthesized to another organelle or the plasma membrane where it fulfills its function.

Transport of proteins between secretory organelles, including the endoplasmic reticulum, the Golgi apparatus, endosomes and lysosomes, and the plasma membrane are mediated by membrane-enclosed structures, primarily carrier vesicles (Fig. 1). These transport processes are known generically as "membrane traffic". Carrier vesicles are formed at a donor organelle by accumulation of cargo proteins and assembly of coat proteins (Fig. 2, green) under the control of the Arf family of small GTPases (Fig. 2, red). These vesicles subsequently fuse with an appropriate acceptor organelle to deliver the

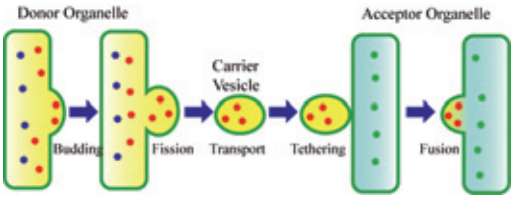


Fig. 1 Vesicular transport

cargo molecules under the control of another family of small GTPases, Rabs (Fig. 2, blue).

Transport processes between the *trans*-Golgi network (TGN), endosomes and the plasma membrane are extremely complicated (Fig. 2). Because there are ~20 Arf members and ~60 Rab members in mammals, these transport processes undergo complex regulation of these small GTPases and coat proteins. By focusing upon the functions of Arfs, Rabs and coat proteins, our research group aims at elucidation of the regulation of membrane traffic, especially at the TGN and endosome levels.

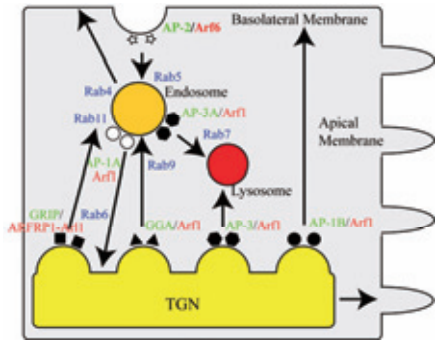


Fig. 2 Sorting of proteins at the TGN and endosomes

2) Regulation of mitosis and cytokinesis by membrane traffic:

During cell division, intracellular organelles undergo disassembly, reassembly and dynamic relocalization, and are distributed equally into two daughter cells (Fig. 3). Because these mitotic processes require supply and removal of specific proteins and biological membranes, morphological changes in the organellar structures during mitosis are under the regulation of membrane traffic.

Several of small GTPases in the Arf and Rab families and their effector proteins are localized on the Golgi apparatus, recycling endosomes, the central spindle and the midbody during mitosis and cytokinesis. Localization of these proteins changes temporally and spatially. Our research group aims at elucidation of the roles of membrane traffic in the spacial and temporal regulation of cellular functions including mitosis.

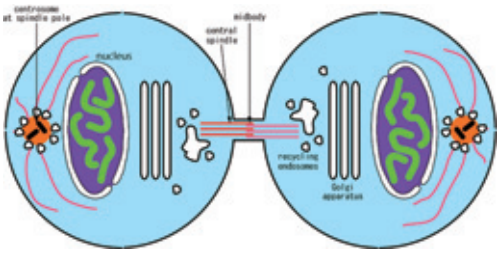


Fig. 3 Localization of intracellular organelles during cell division

Recent publications

- Takatsu, H.et al., Mitosis-coupled, microtubule-dependent clustering of endosomal vesicles around centrosomes. *Cell Struct. Funct.*, **38**, 31-41, 2013.
- Takahashi, S. et al., Rab11 regulates exocytosis of recycling vesicles at the plasma membrane. *J. Cell Sci.*, **125**, 4049-4057, 2012.
- Makyio, H. et al., Structural basis for Arf6–MKLP1 complex formation on the Flemming body responsible for cytokinesis. *EMBO J.*, **31**, 2590-2603, 2012.
- Takatsu, H. et al., ATP9B, a P4-ATPase (a putative aminophospholipid translocase), localizes to the trans-Golgi network in a CDC50-independent manner. *J. Biol. Chem.*, **286**, 38159-38167, 2011.
- Man, Z. et al., Arfaptins are localized to the *trans*-Golgi by interaction with Arll, but not Arfs. *J. Biol. Chem.*, **286**, 11569-11578, 2011.

Department of Molecular Neurobiology

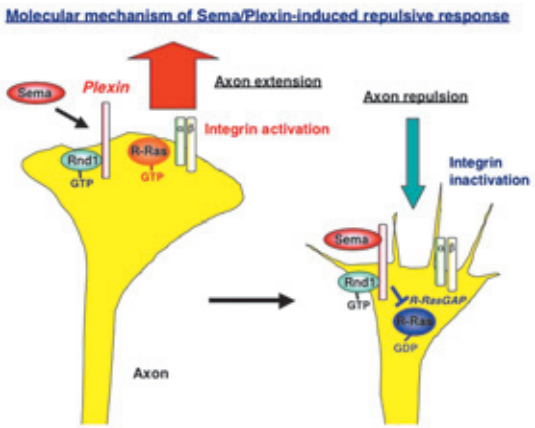
Professor: Manabu Negishi, Associate Professor: Hironori Katoh,
Assistant Professor: Izumi Oinuma

Research Projects:

The mission of the lab is to understand the way in which neurons elaborate and guide their neurites and neural circuits are formed. In the developing nervous system, neurite outgrowth is an essential process underlying the formation of the highly specific pattern of connections between neurons.

One of our major focuses has been on the intracellular signal transduction systems involving the Rho family of small GTPases that allow extracellular guidance signals to instruct the neurite formation, elongation and guidance of the neurites. Rho family GTPases and their signaling partners play important roles in the reorganization of the actin cytoskeleton for neuronal morphological changes. Among them, Rho has been known to induce neurite retraction, while Rac and Cdc42 have been shown to be involved in neurite outgrowth. We have examined a signal transduction pathway for Rho-induced neurite retraction, and we revealed that G12 family of heterotrimeric G proteins activates Rho and activation of Rho triggers neurite retraction through Rho-associated kinase. On the other hand, concerning the Rac and Cdc42-mediated neurite outgrowth, we revealed that RhoG, another Rho family GTPase, is a key regulator in NGF-induced neurite outgrowth in PC12 cells, acting downstream of Ras and upstream of Rac1 and Cdc42. We have identified Elmo as a downstream effector of RhoG. Active RhoG specifically binds to Elmo, and RhoG-Elmo-Dock180 (Rac-especific GEF) activates Rac and promotes neurite outgrowth.

Axon guidance represents a key stage in the formation of neuronal network. Axons are guided by a variety of guidance factors, such as semaphorins, ephrins and netrin. Plexins function as receptors for the repulsive axonal guidance molecules semaphorins. We found that the semaphorin 4D (Sema4D) receptor Plexin-B1 directly stimulates the intrinsic GTPase activity of R-Ras, which has been shown to promote neurite outgtowth by activating integrins, in response to Sema4D. This activity requires the interaction of Plexin-B1 with the Rho family small GTPase Rnd1. The down regulation of R-Ras activity by the Plexin-B1-Rnd1 complex is essential for the Sema4D-induced growth cone collapse in hippocampal neurons. Furthermore, the downregulation of R-Ras activity is also required for the Sema3A-induced growth cone collapse. We then conclude that Plexins mediate semaphorin-induced repulsive signaling by acting as a GAP for R-Ras. We here characterized the downstream signaling of Plexin-B1-mediated R-Ras GAP activity. Sema4D suppressed R-Ras activity in hippocampal neurons and dephosphorylated Akt and GSK-3β and phosphorylated CRMP-2, a microtubule polymerization stimulator, through its inhibition of R-Ras activity. Therefore, Plexin-B1 inactivates PI-3K and Akt, and activates GSK-3β through R-Ras GAP activity, inducing growth cone collapse.



Recent publications

- Tanaka *et al.* Pragmin, a novel effector of Rnd2 GTPase, stimulates RhoA activity. *J. Biol. Chem.* **281**, 10355, 2006.
- Oinuma *et al.* Semaphorin 4D/Plexin-B1-mediated R-Ras GAP activity inhibits cell migration by regulating β_1 integrin activity. *J. Cell Biol.*, **173**, 601, 2006.
- Ito *et al.* Sema4D/plexin-B1 activaes GSK-3β through R-Ras GAP activity, inducing growth cone collapse. *EMBO reports*, **7**, 704, 2006.
- Oinuma *et al.* R-Ras controls axon specification upstream of GSK-3β through integrin-linked kinase. *J. Biol. Chem.* **282**, 303, 2007.
- Saito *et al.*, Plexin-B1 is a GTPase activeting protein for M-Ras, remodeling dendrite morphology. *EMBO reports.* **10**, 614(2009)
- Hiramoto-Yamaki *et al.* Ephexin 4 and EphA2 mediate cell migration through a RhoG-dependent mechanism. *J. Cell Biol.* **190**, 461(2010)

Department of Biofunctional Chemistry

Professor: Shiroh Futaki,

Assistant Professors: Miki Imanishi, Toshihide Takeuchi

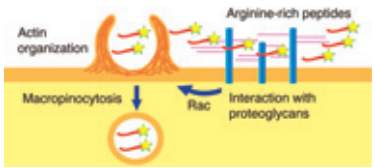
Research Projects:

The ultimate goal of our research is the regulation of cellular functions by designed peptides and proteins, aiming at elucidation of biological functions as well as development of novel functional biodevices having therapeutic potentials.

1) Development of membrane-permeable peptide vectors: Arginine-rich peptides, including octaarginine (R8), HIV-1 Tat, and branched-chain arginine-rich peptides, belong to one of the major classes of cell-permeable peptides which deliver various proteins and macromolecules to cells. The importance of the endocytic pathways has recently been demonstrated in the cellular uptake of these peptides. We have previously shown that macropinocytosis is one of the major pathways for cellular uptake and that organization of the F-actin accompanies this process. In this study, using proteoglycan-deficient CHO cells, we have demonstrated that the membrane-associated proteoglycans are indispensable for the induction of the actin organization and the macropinocytic uptake of the arginine-rich peptides. We have also demonstrated that the cellular uptake of the Tat peptide is highly dependent on heparan sulfate proteoglycan (HSPG), whereas the R8 peptide uptake is less dependent on HSPG. This suggests that the structure of the peptides may determine the specificity for HSPG, and that HSPG is not the sole receptor for macropinocytosis. Comparison of the HSPG specificity of the branched-chain arginine-rich peptides in cellular uptake has suggested that the charge density of the peptides may determine the specificity. The activation of the Rac protein and the actin organization was observed within a few minutes after the peptide treatment. These results strongly suggest the possibility that the interaction of the arginine-rich peptides with the membrane-associated proteoglycans quickly activates the intracellular signals and induces actin organization and macropinocytotis.

2) Creation of artificial transcription factors manipulating circadian rhythm: Regulation of a target gene at will is one of the most prospective themes in the post-genomic era. An artificial transcription factor with desired DNA binding specificity could work as a powerful tool to control target genes. The C_2H_2-type zinc finger motif is one of the most typical DNA binding motifs. We have developed artificial zinc finger transcription factors with novel DNA binding specificity and succeeded in inducing resetting of circadian clock or regulating gene expression patterns to be circadian rhythmic. In addition, we are developing TALE proteins that have new DNA binding specificities. Our approach using artificial DNA binding proteins would be useful for elucidating the mechanisms of biological phenomena such as circadian rhythm.

3) Design of artificial receptor channel proteins: Ion channels and receptors are among the most biologically important classes of membrane proteins that transmit outside stimuli into cells. The creation of artificial proteins with these functions is a challenge in peptide/protein engineering in view of the creation of novel functional nano-devices as well as understanding the biological machinery. We have developed a novel Fe(III)-gated ion channel system that is comprised of assemblies of a channel forming peptide alamethicin bearing an extramembrane segment. The extramembrane segment contains a pair of diiminoacetic acid derivatives of lysine (Ida) residues. Addition of Fe(III) lead to the conformational switch in the extramembrane and the eventual increase in the channel current. This strongly suggests the possibility of establishing novel channel and sensor systems by transmitting an extramembrane conformational switch to the channel current levels. In addition, there are many reports on the creation of artificial ion channels that have a sensing function of the external ligands. However, most of them have been designed so that the interaction with ligands leads a decreased channel current, and very few of them have a function that can detect the ligand with the increased membrane current as are usually seen in natural ligand-gated ion channels. The system established by us is rather simple and may need further sophistication. However, we believe that this concept can extensively be applicable for the creation of various ligand-gated ion channels with novel receptor functions.



Interaction of arginine-rich peptides with membrane-associated proteoglycans leads activation of Rac protein followed by actin organization and induction of macropinocytosis. Thus, arginine-rich peptides are efficiently taken up by the cells with cargo molecules.

Recent publications

- Nakase et al. Molecular interplays involved in the cellular uptake of octaarginine on cell surfaces and the importance of syndecan-4 cytoplasmic V domain for the activation of protein kinase Cα. *Biochem Biophys Res Commun* **446**, 857, 2014.
- Tsuji et al. Creating a TALE protein with unbiased 5'-T binding. *Biochem Biophys Res Commun* **441**, 262, 2013.
- Noshiro et al. Construction of a Ca^{2+}-gated artificial channel by fusing alamethicin with a calmodulin-derived extramembrane segment. *Bioconjug Chem* **24**, 188, 2013.

Department of Drug Delivery Research

Professor: Mitsuru Hashida, Associate Professor: Fumiyoshi Yamashita

Research Projects:

The use of drug delivery systems is novel concept involving administration technology for optimizing chemotherapy to control the distribution of drugs and it is one of the most important fields and/or basic technologies supporting drug discovery and development in the pharmaceutical sciences associated with biomedicine and gene medicine. We have already developed a targeting system for macromolecules using physicochemical properties and a gene delivery system. Recently, we have also carried out an analysis of pharmacokinetic properties using novel informatics approaches. Our current research projects are listed below.

1) Cell-specific targeting system for gene medicine

Gene therapy using plasmid DNA and oligonucleotides is expected to lead to epoch-making treatment methods for refractory diseases such as cancer and acquired immunodeficiency syndrome and/or congenital diseases. To realize novel treatment methods at the gene level, it is essential to be able to effectively deliver the gene medicine to the nucleus or cytoplasm of the target cells. However, gene medicine is unstable because of nucleases and is hardly taken up by the cells because of the nature of the negatively charged macromolecules. Therefore, it is difficult to achieve sufficient therapeutic effects by the injection of naked gene medicines. We have developed ligand modified cationic liposomes and polymers that are specifically taken up by the target cells through receptor mediated endocytosis. Now, we are applying this cell-specific targeting system to the gene therapy of cancer and inflammatory diseases.

2) Controlled distribution of protein medicines

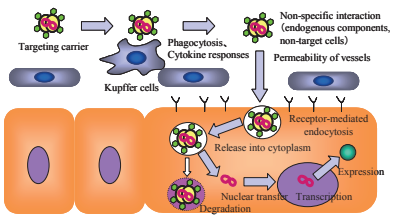
Although physiological active proteins are drug candidates, they are inactivated by proteases and/or secreted antibodies. In addition, physiologically active proteins are eliminated by urinary secretion and uptake by Kupffer cells in the liver. Therefore, the time spent by physiologically active proteins in the blood stream is very limited. As far as distribution is concerned, it is very rare for the target sites to be reached. Such properties are an obstacle to their clinical application. Therefore, chemical modification of physiological active proteins is expected to solve many problems including, but not only, the control of their distribution. We have succeeded in closely controlling the distribution of catalase or super oxide dismutase resulting in, for example, sustained blood circulation, hepatocyte-surface adsorption, hepatocyte-selective accumulation, and nonparenchymal cell-selectivity. Now, we are applying and evaluating the use of these derivatives to prevent cancer metastasis, which involves hydrogen peroxide.

3) Novel drug delivery carriers based on nanotechnology

In general, the discontinuous structure and high permeability of new vessels induced by tumor angiogenesis enable macromolecules to pass through their walls easily. To date, hydrophilic polymers, polymeric micelles, and liposomes have been developed as tumor-selective targeting carriers. However, these carriers have a heterogeneous size and structure. Recently, dendrimers, which have regulatory-branched and nano-sized molecules, have been developed. We have developed novel safe dendrimers, which consist of amino acids and/or polyethylene glycol for tumor-selective targeting. Now, we are studying the application of these novel dendrimers to the diagnosis and treatment of tumors.

4) Analysis of pharmacokinetic properties by using novel informatics approaches

Drug discovery studies have been dramatically improved by high-throughput chemical synthesis and pharmacological screening techniques. However, almost all of the "hit" compounds have unsuitable pharmacokinetic properties, resulting in their withdrawal during the later stages of drug discovery and development. Effective and efficient drug discovery can be carried out by computer screening of virtual compounds prior to real chemical synthesis. We are developing techniques for data acquisition from the literature as well as large-scale data visualization, and analysis of the relationship between pharmacokinetic properties and chemical structures. We expect that these techniques and the information derived from their use will be of great help in accelerating drug R&D.



Development of a cell-specific targeting system for gene medicine

In order to achieve efficient gene expression in target cells, it is essential to control non-specific interactions, vessel permeability, recognition of target cells, endosomal escape, nuclear transfer, and transcription. In addition, uptake of gene medicines induces proinflammatory cytokines which may induce side-effects. However, a multifunctional carrier can solve these problems allowing the use of gene therapy to treat a variety of refractory diseases.

Recent publications

- Suppression of experimental arthritis with self-assembling glycol-split heparin nanoparticles via inhibition of TLR4-NF-κB signaling. Babazada H, Yamashita F, Hashida M. Journal of Controlled Release. 194: 295-300, 2014
- Targeted gene integration using the combination of a sequence-specific DNA-binding protein and phiC31 integrase. Nakanishi H, Higuchi Y, Yamashita F, Hashida M. Journal of Biotechnology. 186: 139-147, 2014
- Development of anionic bubble lipopolyplexes for efficient and safe gene transfection with ultrasound exposure in mice. Kurosaki T, Kawakami S, Higuchi Y, Suzuki R, Maruyama K, Sasaki H, Yamashita F, Hashida M. Journal of Controlled Release. 176: 24-34, 2014

Department of Pharmacology

Professor: Akinori Akaike, Associate Professor: Toshiaki Kume,
Assistant Professor: Yasuhiko Izumi

Research Projects:

The trouble with a higher brain dysfunction due to neurodegenerative disease such as the Alzheimer's diseases and Parkinson s diseases and cerebral ischemia has features in the neuronal death of the neuron group of a specific area of brain by the process of apoptosis and necrosis. We investigate the mechanisms of the neuronal death and the exploratory research of low-molecular compounds that control the neuronal death accompanied by the neurodegenerative disease and cerebral ischemia and using the techniques of in vivo experiment system that used the brain disease model animal and in vitro system including the primary neuronal cultures. Our current research projects are listed below.

1) Elucidation of pathogenesis and exploratory study of preventive and therapeutic agents of neurodegenerative diseases

"Amyloid hypothesis," which amyloid β protein (Aβ) that plays an important role in the development of Alzheimer's disease, has been recognized, but the toxic mechanisms of Aβ have still unsolved. We previously identified the toxic conformer of Aβ42 with a turn at positions 22 and 23 ("toxic turn"). Our recent study suggested that oxidative stress is a key factor of the oligomerization and cognitive impairment induced by Aβ overproduction in vivo. However, the involvement of the toxic conformer in Aβ42-induced oxidative damage remains unclear. To investigate this mechanism, we examined the levels of intracellular reactive oxygen species (ROS) and neurotoxicity in rat primary neurons using E22P-Aβ42, a mutant that induces a turn at positions 22 and 23. E22P-Aβ42 induced greater ROS production than Wt-Aβ42 in addition to potent neurotoxicity. Trolox (a radical scavenger) and Congo red (an aggregation inhibitor) significantly prevented the neurotoxicity and intracellular ROS induced by E22P- Aβ42 and Wt- Aβ42, respectively. These results suggest that A≤42-mediated toxicity is caused by the turn that favors toxic oligomers, which increase generation of ROS. We currently investigate the in vivo effect of toxic conformer of Aβ42.

2) Study on function of nicotinic acetylcholine system in CNS

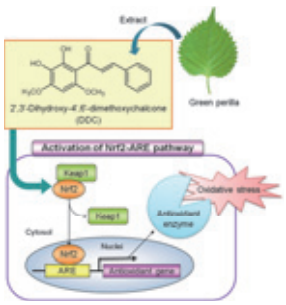
We previously reported that long-term exposure to nicotine of cerebral cortical neurons prevented neuronal death induced by glutamate and amyloid β protein. Furthermore, we also reported that central-type acetylcholinesterase inhibitors including donepezil protected cortical neurons against glutamate neurotoxicity via the stimulation of nicotinic acetylcholine receptors. Then, we are currently examining detailed mechanisms of the neuroprotective effect of acetylcholinesterase by the nicotinic receptor stimulation.

3) Study on neuroprotective compounds derived from food

For overcoming these neurodegenerative diseases, it is necessary to manage them from the point of view of preventive medicine because neuronal death has already occurred at the onset. In addition, it is important to slow the progress not only by the drug treatment but also by the auxiliary use of food with the neuroprotective effect because the symptoms gradually progress for a long period of several years or more. Our aim is to explore and analyze the neuroprotective or neuroregenerative compounds derived from food for the management of aging risk, such as dementia. We previously identified DDC from green perilla as a novel functional component and clarified that DDC induced upregulation of intracellular antioxidant enzymes. We are currently investigating the neuroprotective actions of several components derived from foods including green perilla

4) Study on survival and regeneration of dopaminergic neurons

With respect to Parkinson disease characterized by selective loss of dopaminergic neurons in the substantia nigra, we reported that dopaminergic neurons were particularly vulnerable to cellular stress because they are rich in dopamine, which can easily undergo autoxidation, as a neurotransmitter. Therefore, we are exploring the compounds which regulate the abnormal autoxidation of dopamine as candidates for dopaminergic neuroprotective drugs. In addition, dysfunction of protein quality control is implicated in Parkinson disease. We are examining the novel neuroprotective mechanisms by clarifying the role of proteasome and autophagy in dopaminergic neuronal death. Furthermore, the study aimed at regeneration of the nigrostriatal dopaminergic projection is in progress. By the use of original methods, the mechanism by which dopaminergic axons innervate striatal neurons is investigated. Findings which will be obtained from this study might be applicable to stem cell-derived cell transplantation therapy.



Schematic representation of cytoprotective mechanism of DDC.
DDC was extracted and isolated from the leaves of green perilla. DDC activated Nrf2-ARE pathway, a cellular defense system against oxidative stress. Nrf2, a transcriptional factor, is translocated to the nucleus and bound to antioxidant response element (ARE), resulting in the transcriptional activation of a number of antioxidant enzymes. Cells treated with DDC acquired resistance to oxidative damage.

Recent publications

- Izumi *et al.* Endogenous dopamine is involved in the herbicide praquat-induced dopaminergic cell death. *Toxicol Sci.* **139**, 466, 2014
- Wakita *et al.* Staurosporine induces dopaminergic neurite outgrowth through AMP-activated protein kinase/mammalian target of rapamycin signaling pathway. *Neuropharmacology*. **77**, 39, 2014
- Izuo *et al.* Toxicity in rat primary neurons through the cellular oxidative stress induced by the turn formation at positions 22 and 23 of Aβ42. *ACS Chem Neurosci.* **3**, 674, 2012
- Izumi *et al.* Isolation, identification, and biological evaluation of Nrf2-ARE activator from the leaves of green perilla (Perilla frutescens var. crispa f. viridis). *Free Radic Biol Med.* **53**, 669, 2012

Department of Clinical Pharmacy and Education

Associate Professor: Ikuko Yano

Research Projects:

A new educational system for the 6-year pharmacy program started in April, 2006 to train knowledgeable and skilled pharmacists to correspond with social needs. According with this educational change, Department of Clinical Pharmacy and Education was established in 2006. Since students in Faculty of Pharmaceutical Sciences, Kyoto University undergo clinical clerkship in Kyoto University Hospital, Associate Professor in this department engages in pharmacist activities in Kyoto University Hospital, appointed as a Vice Director, and also pursues teaching and research activities in a close relation with Department of Clinical Pharmacy (Department of Pharmacy, Kyoto University Hospital).

Students in the 6-year pharmacy program take new educational programs in accordance with the Model Core Curriculum for Pharmaceutical Education in Japan such as early exposure to clinical settings (Kyoto University Hospital and community pharmacies) and new classes including SGD (small group discussion) and PBL (problem-based learning). After the pharmaceutical common achievement test (computer-based test (CBT) and objective structured clinical examination (OSCE)), the 5th-grade students take the long-term clinical clerkship in community and hospital pharmacies (11 weeks each), and deeply understand the clinical pharmacology and the roles of pharmacist and pharmaceutical sciences in the medicine.

Department of Clinical Pharmacy and Education promotes the research in order to develop the scientific basis for pharmacist activities.

1) Optimal medication usage and its evaluation

Optimal medication usage means the safe, effective and economical pharmacotherapy. We investigate the relationship between patient characteristics including genetic information and pharmacological and/or side effects for the optimal and individualized pharmacotherapy.

2) Therapeutic drug monitoring and individualized pharmacotherapy

Therapeutic drug monitoring is needed for the drug with a large inter- and intra-individual variability in pharmacokinetics, and with a narrow therapeutic range. Since a very limited number of blood concentrations per a patient are available routinely, the statistical method based on the population pharmacokinetics is useful to investigate the characteristics of clinical data.

3) Pharmacokinetics and pharmacodynamics in disease states

Clinical pharmacokinetics in the drug development process is usually obtained from a small number of healthy volunteers under limited conditions. Therefore, it is valuable to understand pharmacokinetics in several disease states or with concomitantly used drugs. We investigated mechanisms underlying phenomena experienced in clinical cases.

Department of Clinical Pharmacy and Education contributes to these clinical educational and research projects in the standpoint of medical professional. Graduates from Kyoto University are expected to be active in various fields, not only as pharmacy practitioners, but also pharmaceutical researchers with clinical spirits, faculty members in School of Pharmacy, and staff in regulatory sciences and public health.

Recent publications

- Hashi *et al.* Effect of *CYP2C19* polymorphisms on the clinical outcome of low-dose clobazam therapy in Japanese patients with epilepsy. *Eur. J. Clin. Pharmacol.* **71**, 51, 2015
- Nakanishi *et al.* Impact of P-glycoprotein and breast cancer resistance protein on the brain distribution of antiepileptic drugs in knockout mouse models. *Eur. J. Pharmacol.* **710**, 20, 2013
- Yano *et al.* Significance of trough monitoring for tacrolimus blood concentration and calcineurin activity in adult patients undergoing primary living-donor liver transplantation. *Eur. J. Clin. Pharmacol.* **68**, 259, 2012

Department of Patho-Functional Bioanalysis

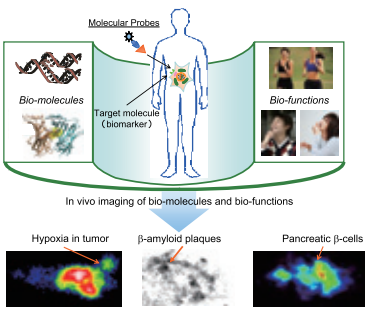
Professor: Hideo Saji, Associate Professor: Masahiro Ono,
Assistant Professor: Hiroyuki Watanabe

Research Projects:

A wide range of biological functions are established via the interactions of many biomolecules; therefore, the clarification of such molecular interactions is necessary for the elucidation of biological functions. Our department is developing analytical methods that visualize the interactions among molecules occurring in living and functioning bodies (*in vivo*) as real-time spatial and temporal images using photon technology (molecular imaging), studying biological functions and etiology using this method, and developing clinical diagnostic methods and therapeutic agents based on the characterization of pathological conditions (Figure). Our current research projects are outlined below.

1) Development of molecular probes for the *in vivo* analysis of biological function, etiological mechanisms, and action mechanisms of drugs

We are currently conducting research on development of radiolabeled and optical molecular probes, which are reagents for molecular imaging, on the basis of analysis of the relationships among the structure, activity, and distribution. For example, we have succeeded in development of radiolabeled molecular imaging probes, imaging and the quantitative evaluation of the neurotransmission process such as nicotinic acetylcholine and dopamine systems in the human brain. Furthermore, using these radiolabeled imaging probes, we have succeeded in evaluating the *in vivo* interactions of various neurotransmission functions, their changes due to drugs, and therapeutic effects. We have also developed several radiolabeled imaging probes for imaging of β-amyloid plaques and neurofibrillary tangles in the brain and evaluated their clinical effectiveness. We also develop radiolabeled molecular probes effective for molecular imaging of receptors of endocrine peptides and transporters of pharmaceuticals. Moreover, we have developed a self-quenching activatable fluorescence probe for in vivo near-infrared optical imaging, which is activated by the interaction with specific molecule or under cellular microenvironment in vivo and emits fluorescence.



In addition, with the molecular design concept of bifunctional compounds having both a moiety related to physiologic activities and a moiety that emits detection signals of radiation and fluorescence, within the same molecule, we are conducting research for the development of molecular probes derived from physiologically active peptides or proteins.

2) Development of radiopharmaceuticals for functional diagnosis and internal radionuclide therapy

The nuclear medicine techniques, in which a radioactive compound (radiopharmaceutical) is administered to patients, and radioactivity from the radioactive compound is detected and processed into images, are used as a clinical imaging method excellent for functional diagnosis. We are conducting research into the development and clinical use of radiopharmaceuticals based on the characterization of physiological conditions and diseases. These studies are applications of molecular imaging studies to clinical diagnosis. For example, for the diagnosis of vulnerable atherosclerotic plaques, which are a primary cause of cerebral and myocardial infarction, we demonstrated the effectiveness of the glucose derivative (^{18}F)FDG as a radiopharmaceutical. We have also successfully developed radiolabeled imaging probes for tumor hypoxia region that plays a crucial role in tumorigenesis. We are simultaneously conducting research for the development of ^{99m}Tc-labeled radiopharmaceuticals for nuclear medicine diagnosis; that is, we are systematically investigating the formation of complexes of Tc, a transition metal, and developing functional radiopharmaceuticals labeled with ^{99m}Tc. We are also developing radiopharmaceuticals for internal radionuclide therapy, which are effective for the treatment of tumors and for the palliation of bone pain.

3) Clarification of the biological actions of trace metals and development of physiologically active metal complexes

Trace metals present in our body are not only essential for homeostasis and various physiologic functions, but are also involved in many pathologic conditions. For example, zinc, copper, and iron have been suggested to be involved in cerebral ischemia, Parkinson's disease, Alzheimer's disease, and diabetes mellitus, but the mechanism of their involvement remains mostly unknown. Therefore, we are studying the relationships of zinc with physiologic functions and their mechanisms, to relate the physiologic actions of metals to the development of therapeutic agents. This research is expected to open a new field in drug development.

Recent publications

- Cui M, et al., Smart near-infrared fluorescence probes with donor-acceptor structure for in vivo detection of β-amyloid deposits. *J. Am. Chem. Soc.*, **136** (9), 3388-3394 (2014).
- Shimizu Y, et al., Micelle-based activatable probe for in vivo near-infrared optical imaging of cancer biomolecules. *Nanomedicine*, **10** (1), 187-195 (2014).
- Yoshimura M, et al., Feasibility of amylin imaging in pancreatic islets with β-amyloid imaging probes. *Sci. Rep.*, **4**, 6155 (2014).

Department of Biopharmaceutics and Drug Metabolism

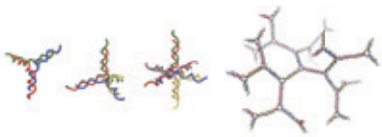
Professor: Yoshinobu Takakura, Associate Professor: Makiya Nishikawa,
Assistant Professor: Yuki Takahashi

Research Projects:

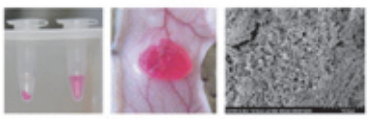
To realize ideal drug therapy by optimizing drug design and delivery, we are focusing on the studies on the drug-body interaction based on the scientific background of biopharmaceutics, pharmacokinetics and drug delivery system. Our current research projects are listed below.

1) Development of nucleic acid drugs for optimized gene therapy and DNA vaccination therapy: Efficient transgene expression in target cells is required for realizing gene therapy and DNA vaccination, in which a therapeutic protein or antigen is administered to patients in genetic form. We have succeeded in developing plasmid vectors that express interferon for a long period of time and proved their efficacy on the treatment for cancer and atopic dermatitis. We are trying to design fusion proteins to control their tissue distribution after in vivo gene transfer.

2) Development of nucleic acid-based nanodevice and hydrogels: DNA containing CpG motifs (CpG DNA) induce cytokine production through Toll-like receptor-9 (TLR-9), so such DNA are expected to be used in the treatment for cancer, autoimmune diseases and allergic diseases. We have successfully developed DNA assemblies by using the property to form double stranded helical structure with a strand having a complementary sequence. These unique products, named as polypodna, are DNA assembly with branches; multiple pods extend from the center of the assembly. We have demonstrated that CpG DNA-induced immune activation is significantly increased by building it up into such branched structures as tri-, tetra- or hexapodna. Dendritic DNA and DNA hydrogels were also prepared by connecting the assemblies using ligases. Hydrogels can release drugs in a sustained manner, so that DNA-based therapeutic systems for chemo-immunotherapy have been under development.

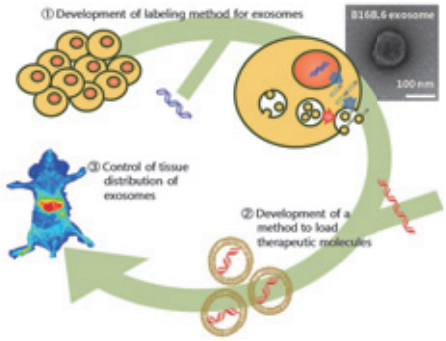


Putative 3D strcuture of polypodna and DNA dendrimer.

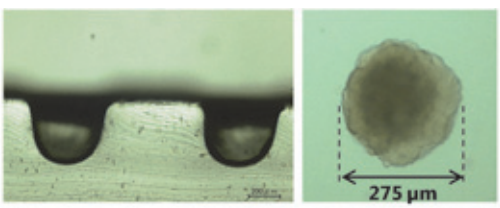


Spontaneous formation of self-gelatinizable nudeic acid (left), an image after intradermal injection (center) and SEM image of inner structure of DNA hydrogel (right).

3) Development of exosome-based drug delivery system: Exosomes are membrane vesicles of which diameter is approximately 100 nm and are secreted from cells. Exosomes work as endogenous delivery carriers for protein, RNA and DNA, so that they are expected to be developed as delivery system for these molecules. To develop exosome-based delivery systems, we have been trying to develop a method to control the tissue distribution of exogenously administered exosomes. Thus far, we have succeeded in visualizing the in vivo disposition of exosomes through the development of a highly sensitive method to label exosomes. We have also found that macrophages are an important factor that determines the tissue distribution of exosomes.



4) Development of multifunctional cell therapeutics for in vivo cell therapy: Recent progress in the technology for culture and differentiation of a variety of cells, including induced pluripotent stem cells, has increased the possibility of cell-based therapy. The effectiveness of such therapies depends not only on the properties of cells, but also on their in vivo fate. We have been trying to develop multi-functional cell therapeutics that can be applicable for the next generation therapy. In a study to increase the survival of transplanted cells, we have found that synthetic adhesion molecules can increase the survival of cells and improve the efficacy of cell-mediated treatment for skin wound. In addition, we have established a technology to construct multicellular spheroids, and demonstrated that the spheroid formation is useful to increase the survival of cells transplanted and effective for the treatment of diabetic model mice.



Cross-sectional image of PDMS microwells (left) and microscopic image of a multicellular spheroid of insulin-secreting cells (right).

Recent publications

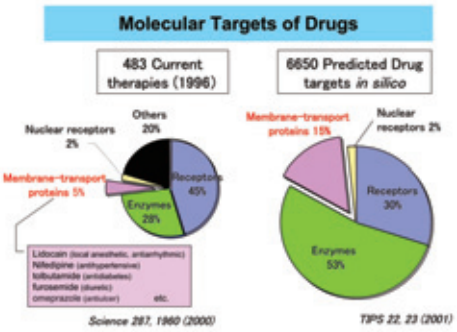
- Kusamori *et al.* Transplantation of insulin-secreting multicellular spheroids for the treatment of type 1 diabetes in mice. *J Control Release* **173**, 119-124, 2014.
- Takahashi *et al.* Visualization and *in vivo* tracking of the exosomes of murine melanoma B16-BL6 cells in mice after intravenous injection. *J Biotechnol* **165**, 77-84, 2013.
- Mohri *et al.* Design and development of nanosized DNA assemblies in polypod-like structures as efficient vehicles for immunostimulatory CpG motifs to immune cells. *ACS Nano* **6**, 5931-5940, 2012.

Department of Molecular Pharmacology

Professor: Shuji Kaneko, Associate Professor: Hisashi Shirakawa

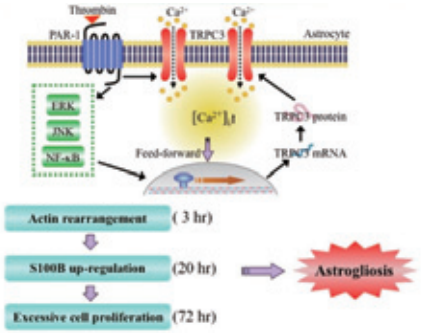
Research Projects:

A comprehensive analysis of molecular targets of drug therapy revealed that the largest subgroup is cell membrane receptors (45%), and the next is enzymes (28%), while membrane-transport proteins account for only 5% of all current drug targets; however, the drugs targeting membrane-transport proteins are strong, effective and frequently used in the therapeutic treatment. On the other hand, 6650 predicted proteins of potential drug targets are composed of 30% cell membrane receptors, 53% enzymes, and 15% membrane-transport proteins (see left panel). Consequently, it is considered that membrane-transport proteins will be the promising molecular targets of drug development. In our Department of Molecular Pharmacology, membrane-transport proteins, especially ion channels and transporters in the central nervous system, are focused on, and a variety of studies are in progress as follows:



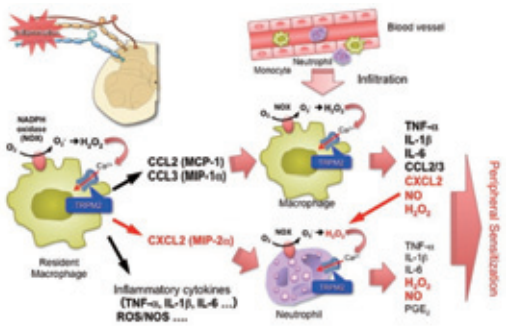
1) Study on the role of TRP channels involved in the pathophysiology of cerebrovascular diseases

Cerebrovascular diseases including cerebral infarction and intracerebral hemorrhage are severe neurological deficits in which generation of reactive radical moieties and inflammatory responses cause neuronal death and abnormal activation of glial cells after excessive overflow of neurotransmitters. On the other hand, TRP (transient receptor potential) channel is a family of nonselective cation channels, which may have important roles in nonexcitable cells, such as glial cells and immune cells. Therefore we focused on the mechanisms of abnormal glial activation that are involved in the chronic pathogenesis of cerebral stroke. So far, we have identified the pivotal role of TRPC3 in the thrombin-induced activation of astrocytes (see right panel). We now address the physiological and pathophysiological roles of other TRP channels in glial cells including astrocytes, microglia and oligodendrocyte precursor cells using genetically modified animals.



2) Study on the roles of TRP channels and transporters involved in the chronic pain

Injury of sensory neurons and surrounding inflammatory lesions cause chronic pain that is not always responsive to conventional analgesics. Since the mechanism underlying chronic pain is now well understood, we focused on the roles of glial cells and immune cells in the interaction with sensory neurons that aggravate pain sensation. We have clarified the role of astroglial glutamate transporter GLT-1 in the generation of neuropathic pain, and are investigating the algesic roles of TRPM2 expressed in monocytes/macrophages and microglia (see right panel). In addition, we are analyzing the involvement of TRP channels in the grave peripheral neuropathy induced by several kinds of antineoplastic agents such as oxaliplatin.



3) Study on the action mechanisms of antidepressants and addictive drugs

We have established an in-vitro chronic experimental system in which midbrain and limbic slices are cocultured for the study of addictive mechanisms of psychostimulants, narcotic analgesics, other addictive drugs such as MDMA on dopaminergic neuronal networks. We also developed an in-vitro raphe slice culture for the study of chronic effects of antidepressants such as SSRI, SNRI and tricyclic antidepressants on serotonergic neuronal networks.

Recent publications

- Munakata et al., Transient receptor potential canonical 3 inhibitor Pyr3 improves outcomes and attenuates astrogliosis after intracerebral hemorrhage in mice. **Stroke** 44, 1981-1987 (2013)
- Nagayasu et al., Chronic effects of antidepressants on serotonin release in rat raphe slice cultures: high potency of milnacipran in the augmentation of serotonin release. **Int J Neuropsychopharmacol**. 16, 2295-306 (2013)
- Zhao et al., Acute cold hypersensitivity characteristically induced by oxaliplatin is caused by the enhanced responsiveness of TRPA1 in mice. **Mol Pain**. 8, 55 (2012)
- Haraguchi et al., TRPM2 contributes to inflammatory and neuropathic pain through the aggravation of pronociceptive inflammatory responses in mice. **J Neurosci**. 32, 3931-3941 (2012)

Department of Clinical Pharmacology & Therapeutics

Professor: Kazuo Matsubara, Associate Professor: Takayuki Nakagawa,
Senior Lecturer: Atsushi Yonezawa,
Assistant Professor: Satoshi Imai, Tomohiro Omura, Shunsaku Nakagawa

Research Projects:

The aim of our laboratory is to establish the scientific bases of appropriate drug usage and pharmaceutical practice. The efficacy and safety of drugs are closely related to their pharmacokinetics and pharmacodynamics. We have systematically developed the research from drug transport analyses based on the molecular levels to the clinical pharmacokinetics. We are also trying to elucidate the mechanisms underlying adverse effects of anti-cancer reagents, and are studying the mechanisms underlying neurodegenerative disease. To settle the problem found in the pharmacotherapy, we attempt to feedback the achievements of basic research to clinical practice. Topics currently undergoing are outlined below:

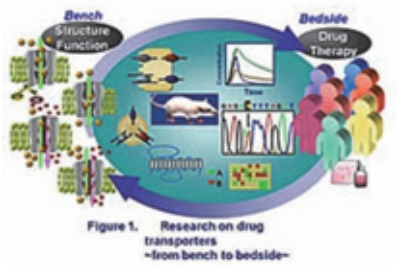
1) Molecular and neural mechanisms underlying pathological pain and dysesthesia: The physiological (acute) pain is transient and necessary for the alarm system that warns us and helps to protect from tissue damage, while pathological (chronic) pain is usually persistent and unnecessary for survival and protective role. Pathological pain is mediated through plastically altered pain pathways induced by a variety of causes, while it is often resistant to current therapeutic approaches. To elucidate the molecular mechanisms underlying pathological pain/dysesthesia, we are investigating (1) the roles of nociceptors (mainly TRP channels) expressed in sensory neurons in the generation of pathological pain/dysesthesia, and (2) the possible involvement of neuroimmune response mediated by the reciprocal interaction between peripheral/central nervous and immune systems.

2) Reverse translational research for adverse effects of anti-cancer drugs: elucidation of the mechanisms and development of novel preventive and treatment strategies: Anti-cancer drugs used in chemotherapy frequently exhibit a variety of adverse effects. Some of them are dose-limiting adverse effects in anti-cancer chemotherapy, but effective clinical preventive and treatment strategies have not been established. We are trying to elucidate the molecular mechanism underlying the uncontrolled adverse effects, in which the findings are originally obtained from the bedside, by in vitro and in vivo experiments (reverse-translational research), and to propose effective preventive and treatment strategies. We are now investigating the mechanism of nephrotoxicity induced by cisplatin, interstitial lung disease induced by EGFR inhibitors (gefitinib and erlotinib), peripheral neuropathy induced various types of anti cancer drugs in cell cultures and animal models.

3) Clinical and basic studies on Pharmacokinetics and Pharmacodynamics: Pharmacokinetics consists of four processes, which are regulated by several pharmacokinetic factors, such as drug transporters and drug-metabolizing enzymes. We carry out clinical and basic studies on Pharmacokinetics and Pharmacodynamics (PK/PD). For example, it has been clarified that the efficacy and adverse effects of platinum anticancer drug cisplatin and anti-diabetic drug metformin depended on the characteristics of organic cation transporters. Also, novel riboflavin transporter RFVT has been identified. It has been indicated that RFVT mutation caused a rare disease. Then, we now try to clarify the mechanism and discover new therapeutic drugs of this rare disease.

4) Study of the pathogenic mechanism of Parkinson's disease in order to identify a potential novel cure: Parkinson's disease (PD) is the most common movement disorder caused by dopaminergic neuronal degeneration. It is characterized by the symptoms of resting tremor, rigidity, and akinesia. Many medical treatments have been developed; however, there is no fundamental cure. The goal of our research is to reveal the pathogenic mechanism of PD and to identify a novel cure. We recently reported that zonisamide (antiepileptic drug) and oxicam (non-steroidal anti-inflammatory) prevent cell death in a PD model, and we seek to advance our research to improve the clinical outcome for PD patients.

5) Application of biomarkers to individualized pharmacotherapy: Design of a dosing plan for immunosuppressiveagents, tacrolimus and cyclosporine, is difficult because of large intra- and interindividual variability in the pharmacokinetics. To overcome these clinical problems, the development of individual immunosuppressive therapies based on the genomic, biochemical and population pharmacokinetic analyses have been attempted. We also focus on biomarkers that predict drug-mediated kidney injury.



Figures 1. Research on drug transporters –from bench to bedside–

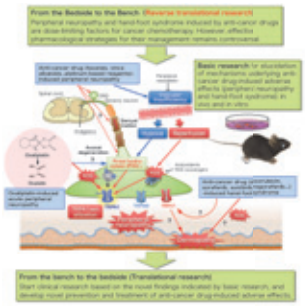


Figure 2. Reverse translational research for adverse effects of anti-cancer drugs

Recent publications

- Yoshimatsu H, Yonezawa A, Yao Y, Sugano K, Nakagawa S, Omura T, Matsubara K: Functional involvement of RFVT3/SLC52A3 in intestinal riboflavin absorption. *Am J Physiol Gastrointest Liver Physiol*, **306**: G102-110 (2014)
- Nakagawa S, Omura T, Yonezawa A, Yano I, Nakagawa T, Matsubara K: Extracellular nucleotides from dying cells act as molecular signals to promote wound repair in renal tubular injury. *Am J Physiol Renal Physiol*, **307**: F1404-1411 (2014)
- Imai S, Ikegami D, Yamashita A, Shimizu T, Narita M, Niikura K, Furuya M, Kobayashi Y, Miyashita K, Okutsu D, Kato A, Nakamura A, Araki A, Omi K, Nakamura M, James Okano H, Okano H, Ando T, Takeshima H, Ushijima T, Kuzumaki N, Suzuki T, Narita M: Epigenetic transcriptional activation of monocyte chemotactic protein 3 contributes to long-lasting neuropathic pain. *Brain*, **136**: 828-843 (2013)
- Omura T, Asari M, Yamamoto J, Kamiyama N, Oka K, Hoshina C, Maseda C, Awaya T, Tasaki Y, Shiono H, Shimizu K, Matsubara K: HRD1 levels increased by zonisamide prevented cell death and caspase-3 activation caused by endoplasmic reticulum stress in SH-SY5Y cells. *J Mol Neurosci*, **46**: 527-535 (2012)

Department of Pharmacogenomics · Genomic Drug Discovery Sciences (GDDS)

Associate Professor: Akira Hirasawa

Research Projects:

What's GDDS

The genomic drug discovery science is the science field of discovery of the new drug, the medicine of the effect to be higher and the medicine with few side effects, using the genome information. Our research projects are performed on major 3 themes; 1. Function of G protein-coupled receptors (GPCR), which are in cell membrane and play important roles on bio-reactions. 2. Development of microarray techniques, which are took notice as the techniques of comprehensive gene analysis. 3. Bioinformatics sciences, which is necessary to analyze a lot of information including genomic information.

GPCR

The Human Genome Project is now completed, and that enables access to every human G-protein coupled receptor (GPCR), which represents the single most important drug targets for medical therapy. Many of novel GPCR discoveries were based solely upon their shared sequence identities and characteristic seven transmembrane-spanning structure encoded therein. This sequence conservation allowed for powerful cloning techniques through DNA technology (in particular PCR technology) and in silico screening of GPCRs using genome or cDNA sequence data. Information from genome sequencing estimated the existence of 700-800 GPCRs in the human genome: about 250 of GPCRs are identified as receptors for known ligands, and the rest are still orphan receptors (oGPCRs). Recognized for the potential of oGPCRs as targets of novel drug discovery, oGPCRs have attracted a tremendous level of attention in terms of continued identification of their endogenous ligands and elucidation of their physiological functions.

Microarray

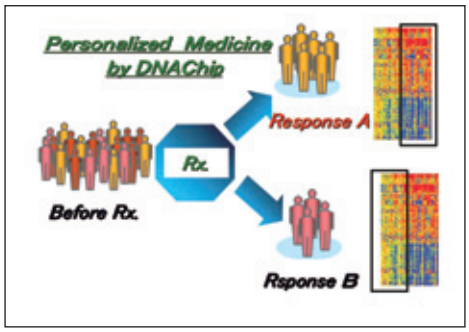
A microarray is one of the most important basic technology for drug discovery from the aspect of genomics. The focus of genome research will be shifted to functional analysis of genes including the determination of precise transcript unit as transcriptome.

The target validation is one of the critical point of drug discovery. The gene expression pattern (i.e. profile) of disease specific status could be obtained by DNA chip technology that makes it accelerate to find candidate molecules of drug target. Microarrays enable the comprehensive analysis of gene expression of various disease status including model animals and cellular activity. The process of target validation would be aided by the databases which conjugate the data of gene expression and that of pharmacology, physiology, biochemistry, molecular biology and so on. We are interested in the construction of databases of gene expression data, gene expression analysis of disease model animals and human disease status, and finally discovering the candidate molecule of the effective novel drug target and revealing the mechanisms of human disorders.

Pharmacogenomics

Pharmacogenomics is the study of how an individual's genetic inheritance affects the body's response to drugs. The term comes from the words pharmacology and genomics and is thus the intersection of pharmaceuticals and genetics. Pharmacogenomics holds the promise that drugs might one day be tailor-made for individuals and adapted to each person's own genetic makeup. Environment, diet, age, lifestyle, and state of health all can influence a person's response to medicines, but understanding an individual's genetic makeup is thought to be the key to creating personalized drugs with greater efficacy and safety. Pharmacogenomics combines traditional pharmaceutical sciences such as biochemistry with annotated knowledge of genes, proteins, and transcriptome scanning in particular.

Expression monitoring by DNA microarray is the most biologically informative application of this technology at present. Microarray technology has important applications in pharmacogenomics: drug discovery and development, drug safety and molecular diagnostics. DNA chips will facilitate the integration of diagnosis and therapeutics, as well as the introduction of personalized medicines.



Recent publications

- Takeuchi M, Hirasawa A, Hara T, Kimura I, Hirano T, Suzuki T, Miyata N, Awaji T, Ishiguro M, Tsujimoto G. FFA1-selective agonistic activity based on docking simulation using FFA1 and GPR120 homology models. Br J Pharmacol. **168**(7): 1570-1583, 2013.
- Ichimura A et al. Dysfunction of lipid sensor GPR120 leads to obesity in both mouse and human. *Nature*. **483**(7389): 350-354, 2012.
- Hirasawa A et al. Free fatty acids regulate gut incretin glucagons-like peptide–1 secretion through GPR120. *Nat. Med.* **11**: 90-94, 2005.

Department of Chemogenomics · Department of Bioorganic Medicinal Chemistry

Professor: Hiroaki Ohno, Nobutaka Fujii
Lecturer: Shinya Oishi

Research Projects:

In drug discovery it is necessary to understand physiological and pathogenetic processes, which have been identified by genomic and epigenomic studies. In our lab we are interested in using synthetic organic chemistry to probe the structure and function of biologically relevant molecules. This could lead to the development of novel therapeutics. We are actively involved in the design of useful molecules, such as drug candidates or research tools and in the development of novel synthetic methods:

1) Synthesis of structurally complex bioactive compounds: Small molecule drug discovery has become increasingly challenging. Despite advances in combinatorial synthesis and high-throughput screening, such technologies still have limitations. Another problem is a lack of therapeutic targets, as drugs have already been developed for many diseases. Our approach is to use complex molecules to target biomolecular interactions that have not yet been probed in drug discovery. We are interested in the synthesis of biologically active compounds, such as macrocyclic peptides and alkaloids with highly complex ring systems.

2) Novel methods for the synthesis of complex structures: Structure-activity relationship (SAR) studies and structural optimization are needed to improve the biological activity and bioavailability of potential drug candidates. This becomes very costly in terms of time and money when using very complex molecules. We are developing new synthetic methodologies that can be used to construct complex core structures commonly found in biologically active molecules. We are particularly interested in atom-economic transition metal catalysis using gold and palladium.

3) Design and synthesis of peptides and peptidomimetics: Recombinant DNA technology has facilitated the preparation of peptides and proteins. In contrast, chemical synthesis of peptides and proteins via the stepwise assembly of amino acids can provide an alternative approach for the preparation of antimicrobial peptides with unique structures (secondary metabolites) and peptides/proteins containing post translational modifications. We are developing novel synthetic approaches to peptides and peptidomimetics with functional moieties. These are employed in our medicinal and bioorganic chemistry programs.

4) Development of G protein-coupled receptor (GPCR) ligands: GPCRs are promising drug targets because these are involved in many physiological functions and pathological conditions. In our group, novel chemokine receptor antagonists have been developed using anti-HIV peptides. One antagonist is in clinical trials for the treatment of acute myeloid leukemia. We are also investigating novel small molecules or peptides as GPCR ligands to regulate the reproductive system. Furthermore, using SAR data we have designed molecular probes to investigate receptor localization and translocation.

5) Chemical libraries: Chemical libraries can be a valuable resource in drug discovery. We have synthesized natural products with unique bioactivity (e.g. alkaloids) and biomolecules with important physiological functions (e.g. peptide hormones). Synthetic intermediates for these functional molecules are also included in our library. These compounds cannot be obtained commercially and we have a number of ongoing collaborative screening projects.

Recent publications

- Ohno *et al.* Gold-Catalyzed Cascade Cyclization of 2-Alkynyl-*N*-Propargylanilines via the Rearrangement of a Propargyl Group. *Angew. Chem. Int. Ed.*, in press (2015).
- Fujii *et al.* Development of Novel Neurokinin 3 Receptor (NK3R) Selective Agonists with Resistance to Proteolytic Degradation. *J. Med. Chem.*, **57**, 8646 (2014).
- Oishi *et al.* Kinesin Spindle Protein Inhibitors with Diaryl Amine Scaffolds: Crystal Packing Analysis for Improved Aqueous Solubility. *ACS Med. Chem. Lett.*, **5**, 566 (2014).
- Fujii *et al.* Total Synthesis of (-)-Quinocarcin via Au(I)-Catalyzed Regioselective Hydroamination. *Angew. Chem. Int. Ed.*, **51**, 9169 (2012).

Department of Systems Biology

Professor: Hitoshi Okamura, Associate Professor: Masao Doi,
Assistant Professor: Yoshiaki Yamaguchi, Senior Lecturer: Jean-Michel Fustin

Research Projects:

How TIME is generated and tuned? We will clarify the secret of generation and tuning of TIME in mammalian circadian system by multi-layered view at intracellular, intercellular and individual levels. Through clarifying the integration network mechanism of TIME, we will develop new drugs for tuning TIME.

The subject of our study is circadian timing system in mammals. In this system, the circadian TIME generated at molecular clock in the suprachiasmatic nucleus (SCN) evokes the synchronized oscillation of molecular clocks in the whole body. Between them, TIME is transmitted in multilayer systems: 1) intracellular system of generation of cyclic TIME, 2) Intercellular system for synchronizing TIME, and 3) Symphony of TIME in individuals.

1. Clarification of clock machinery to generate TIME

1.1 Identification of all components of CLOCK

We try to isolate all parts of transcription-translation machinery. We focus SCN since most components of the SCN will be dedicated to generate TIME. From the point of the functional specialization of brain, and from the general rule that CELL expresses a limited number of genes to play specific physiological role, SCN must be rich in expressing TIME-related genes. In this project we will isolate All genes expressed in SCN by in situ hybridization, and then target these genes targeting.

1.2 PER associating proteins (PAS) and transcription-translation feedback loop of clock genes

To explain the generation of cyclic TIME, transcription & translation feedback loop of clock genes is hypothesized. This theory is supported by the number of molecular and genetic studies of clock genes. We will clarify this by the whole description of molecular clock components. Per1 & Per2 genes will have the key role for robustness of oscillation. It is known that PER1 & PER2 proteins form huge molecular complex. Thus, we will isolate the all components of PER associating proteins (PAS), and clarify the transcription and translation feedback loop of clock genes.

1.3 Clock genes and cell metabolism, birth, and death

Why virtually all cells in the body have the clock inside the cell? We will identify how clock genes work on the energy metabolism, cell cycles, and cell death.

2. Intercellular system for synchronizing TIME

2.1 Region-specific knockdown of SCN

SCN biological clock is composed of thousands of clock cells which are subdivided into several groups. We will perform region-specific knockdown of these subdivisions to address the functional subdivision of SCN.

2.3 Geography of SCN

SCN clock cells are highly organized in time and space. For example, in our real-time luciferase-imaging system at cell level, time is generated and synchronized in a very highly organized system. We will complete and theorize the time-space geography of the SCN.

3. Symphony of TIME in individuals

3.1 SCN-adrenal pathway: conversion of time signals from nerve impulse to hormones

Standard time produced in the SCN is released via central and peripheral autonomic nervous system. Sympathetic nerve impulses are conducted to the adrenal gland and converted to the endocrine signals. We will clarify this system by focusing adrenal glands.

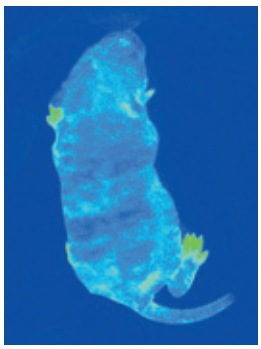
3.2 glucocorticoid is the mediators of central time

Glucocorticoid is a mediator of TIME. We will clarify the molecular mechanism how glucocorticoid regulates the peripheral clocks.

3.3 Timing system outside the SCN

In some environmental conditions such as restriction feeding, extra-SCN regions might sometimes generate rhythm independent on SCN. We will clarify the system at its molecular level.

Through above studies at 1), 2), and 3), we will draw the systems of TIME at molecular levels, which will help the drug discovery for tuning the rhythm.



Mouse luminescence in the Per1-promotor-luciferase transgenic mouse

Biological rhythm is a fundamental life system which is established under the day-night cycle derived from the rotation of the earth. This rhythm is observed in all eukaryotes including mammals. This rhythm is generated at the transcription level, which is reflected to hormonal and behavioral levels. Our laboratory is dedicated to dissect out the molecular machinery of clock genes and clock related disorders. We visualized the oscillating clock genes at cell level, and revealed the molecular link of molecular clock to cell cycles and metabolism. We will clarify the secrets of time in mammalian circadian system by multi-layered view at intracellular, intercellular and individual levels. At last, we will develop new drugs for tuning TIME.

Recent publications

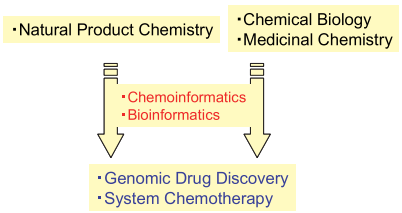
- Matsuo *et al.* Control mechanism of the circadian clock for timing of cell division. *Science* **302**, 255, 2003.
- Doi *et al.* Salt-sensitive hypertension in circadian clock-deficient *Cry*-null mice involves dysregulated adrenal Hsd3b6. *Nature Medicine*, **16**, 67, 2010.
- Doi *et al.* Circadian regulation of intracellular G-protein signaling mediates intercellular synchrony and rhythmicity in the suprachiasmatic nucleus. *Nature Commun.* **2**, 327, 2011.
- Fustin *et al.* RNA-methylation-dependent RNA processing controls the speed of the circadian clock. *Cell*, **155**, 793, 2013.
- Yamaguchi *et al.* Mice genetically deficient in vasopressin V1a and V1b receptors are resistant to jet lag. *Science*, **342**, 85, 2013.

Department of System Chemotherapy and Molecular Sciences

Professor: Hideaki Kakeya, Associate Professor: Akira Hattori,
Assistant Professor: Shinichi Nishimura

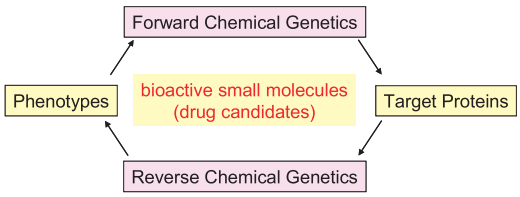
Research Projects:

Chemical biology based on forward/reverse chemical genetics is a new research paradigm that accelerates drug development and the functional analysis of genes and proteins. Diversity of small molecules is one of the most important points to facilitate the success of chemical biology. As such, we have been screening two types of chemical libraries: a natural products library and a synthetic chemical library. After identifying bioactive small molecules, their modes of actions and targets are investigated using a chemical biology-based approach.



Recent major projects are as follows:

1. **Advanced chemical biology research for establishing system chemotherapy in order to cure multi-factorial diseases; e.g. cancer, heart failure, immunodeficiency, infectious diseases, diabetes, and neuronal diseases.**
2. **HCS (high-contents screening) and HTS (high-throughputs screening) for identifying useful small molecules (bioprobes).**
3. **Natural product chemistry and medicinal chemistry for mining novel bioactive small molecules.**
4. **Biosynthetic studies of natural products and their application to combinatorial biosynthesis.**

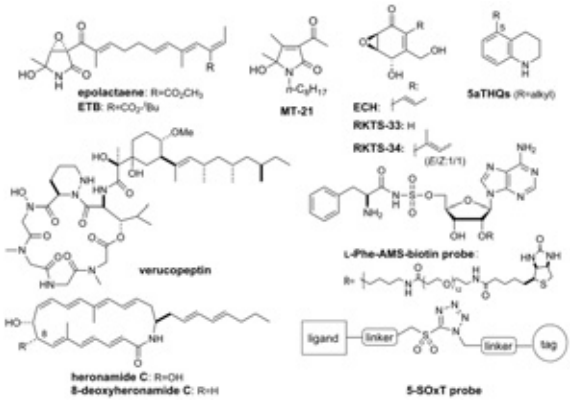


We have discovered epolactaene from *Penicillium* sp. to be a neuronal differentiation inducer, and have identified MT-21 and ETB (epolactene *tert*-butyl ester) as potent apoptosis inducers based on Structure-Activity Relationships (SAR) studies. Using a biotin-labeled probe of epolactaene/ ETB, human Hsp 60 (heat-shock protein 60) was identified as a binding protein of epolactaene/ ETB in vitro as well as in situ. Moreover, it was suggested that Cys442 of Hsp60 is responsible for the covalent binding with epolactaene/ETB as well as the inhibition of chaperone activity by epolactaene/ ETB. Epolactaene/ETB would be highly useful tools to understand the function of human Hsp60 and the mechanisms of molecular chaperones.

We have also found a small molecule, ECH, produced by a fungal strain that selectively inhibits apoptosis induced by the death-receptor system. Using chemical biology-based approaches, we revealed that ECH inhibits Fas-mediated apoptosis by blocking activation of procaspase-8 in the DISC (death-inducing signaling complex). In addition, ECH also inhibits Fas ligand-dependent apoptosis in CTL-mediated cytotoxicity. Based on the detailed SAR studies of ECH, RKTS-33&34 were developed as novel nonpeptide inhibitors targeting death receptor-mediated apoptosis.

Hypoxia-inducible factor (HIF) is deeply involved in cancer progression. During the course of our screening for HIF-signaling modulators, we re-discovered verucopeptin, produced by *Actinomodura*-like sp., as a new HIF-signaling inhibitor. We determined the absolute stereochemistry of verucopeptin by the spectroscopic analysis and synthetic approaches. Verucopeptin decreased the amount of HIF-1α protein, whereas it did not affect the level of HIF-1β protein. Further analysis of the inhibitory mechanism by verucopeptin is on going.

Irreversible modification is one of the most promising strategies to identify cellular receptors of bioactive small molecules. Recently we developed a 5-sulfonyl tetrazole probe, which enabled chemical tagging of binding proteins against a ligand. The studies on modes of action for antifungal molecules heronamides and 5aTHQs (5-alkyl-1,2,3,4-tetrahydroquinolines), as well as the development of an affinity probe to identify adenylation domain-containing modules in nonribosomal peptide synthetase (NRPS)-polyketide synthase (PKS) hybrids and NRPSs are also undertaken.



Recent publications

- Sugiyama, R. *et al.* 5-Alkyl-1,2,3,4-tetrahydroquinolines, new membrane-interacting lipophilic metabolites, produced by combined culture of *Streptomyces nigrescens* and *Tsukamurella pulmonsis*. *Org. Lett.* **17**, 1918, 2015.
- Goto, Y. *et al.* UCHL1 provides diagnostic and antimetastatic strategies due to its deubiquitinating effect on HIF-1α. *Nat Commun.* **6**, 6153, 2015.
- Ishikawa, F. *et al.* Profiling nonribosomal peptide synthetase activities using chemical proteomic probes for adenylation domains. *ACS Chem. Biol.* doi: 10. 1021/acschembio. 5b00097, 2015.
- Sugiyama, R. *et al.* Structure and biological activity of 8-deoxyheronamide C from a marine-derived *Streptomyces* sp.: heronamides target saturated hydrocarbon chains in lipid membranes. *J. Am. Chem. Soc.* **136**, 5209, 2014.
- Otsuki, S. *et al.* Chemical tagging of a drug target using 5-sulfonyl tetrazole. *Bioorg. Med. Chem. Lett.* **23**, 1608, 2013.
- Fustin, JM. *et al.* RNA-methylation-dependent RNA processing controls the speed of the circadian clock. *Cell*, **155**, 793, 2013.
- Kishimoto, S. *et al.* Tumescenamide C, an antimicrobial cyclic lipodepsipeptide from *Streptomyces* sp. *Tetrahedron*, **68**, 5572, 2012.
- Nishimura, S. *et al.* Marine antifungal theonellamides target 3β-hydroxysterol to activate Rho1 signaling. *Nat. Chem. Biol.* **6**, 519, 2010.

Integrative Genomics

Professor: Hiroyuki Ogata, Associate Professor: Susumu Goto

Research Projects:

Our laboratory aims to understand the diversity and functioning of complex living systems based on large scale life science data towards application in biomedical sciences and environmental conservation. We develop new bioinformatics methods allowing integrated analyses of molecular data such as drug structure, metabolites, and genomic information and higher level knowledge about cells, organisms, populations and environments. Current research projects involve viral and microbial genomics, prediction of drug-microbiome interactions, and investigation of the functional link between microorganisms and the environmental changes.

1. Genomics of viruses

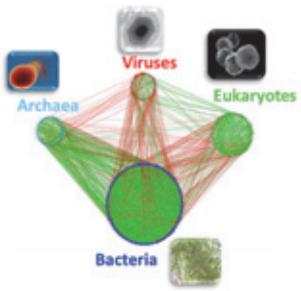
Viruses are generally considered as small biological objects with only a handful of genes sufficient for their rapid replication. However, relatively large viruses such as herpesviruses and poxviruses possess a few hundreds genes. Furthermore, recent studies have revealed the existence of much larger viruses encoding more than 300 up to 2,500 genes. Such giant viruses, comparable to cells in their dimension, show a huge genomic diversity. Including these giant viruses, viruses possess various mechanisms to evade host defense systems and to reprogram intracellular machinery of their hosts for their replication. Viruses are also considered to contribute to the evolution of their hosts through horizontal gene transfer and the host-parasite arms race. However, our knowledge on viruses is limited compared to the knowledge on cellular organisms. We are interested in revealing functions of their genomes and the roles of viruses in various ecosystems through comparative genomics. We also develop new bioinformatics methods helping such comparative genomics.

2. Interactions between microbial communities and their environments

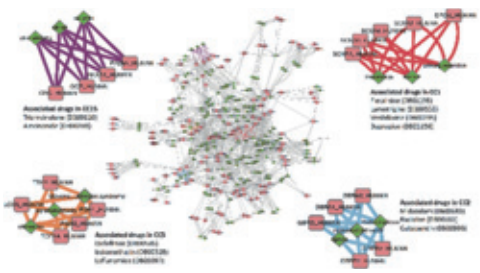
Bacteria and unicellular eukaryotes play important roles in various environments. We study microorganisms (from viruses, bacteria, unicellular eukaryotes to zooplankton) in animal gut and marine ecosystems in terms of their community structure and functioning. Our focus is on the characterization of their diversity and the interactions among them as well as the relationships between the dynamics of microbial communities under varying environmental conditions. Our research interests include the identification of enzymes and secondary metabolites with new pharmacological activity from large scale genetic data.

3. Integration of chemical, genomics, and biomedical knowledge for biomedical sciences and environmental preservation

To help the research communities in genomics and biomedical sciences, we develop a suite of bioinformatics tools and various databases through an integrated web environment named GenomeNet (http://www.genome.jp/). GenomeNet integrates major molecular biology databases such as the KEGG database (http://www.kegg.jp/) developed in Kyoto University, as well as other databases of genes, proteins, enzyme reactions, metabolic compounds, drugs, and drug side effects. Currently, we put much effort in integrating metagenomic data generated at a population level (e.g. Human microbiomes) or at a global scale (e.g. *Tara* Oceans expedition data). We also started an integrated database project for proteomics data from various species including human. Certain pathogens evade the host immune system by altering the surface proteins ("antigenic variation"), but its mechanism is still unclear. In this regard, we collect and organize the information of antigenic variations and relevant gene families to uncover the mechanism and to utilize it in clinical practice (varDB, http://www.vardb.org/). These resources are freely available through GenomeNet to the communities. We also develop various bioinformatics and statistical methods for medical and pharmacological sciences such as prediction methods for the side effects of drugs.



Prediction of species interaction networks



Prediction of drug-drug interactions

Recent publications

- Hingamp *et al.*; Exploring nucleo-cytoplasmic large DNA viruses in *Tara* Oceans microbial metagenomes. *ISME J.* **7**, 1678, 2013.
- von Dassow *et al.*; Life cycle modification in open oceans accounts for genome variability in a cosmopolitan phytoplankton. *ISME J.*, doi: 10.1038/ismej.2014.221., 2014.
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Department of Computational Genomics

Professor: Hiroshi Mamitsuka, Assistant Professor: Canh Hao Nguyen

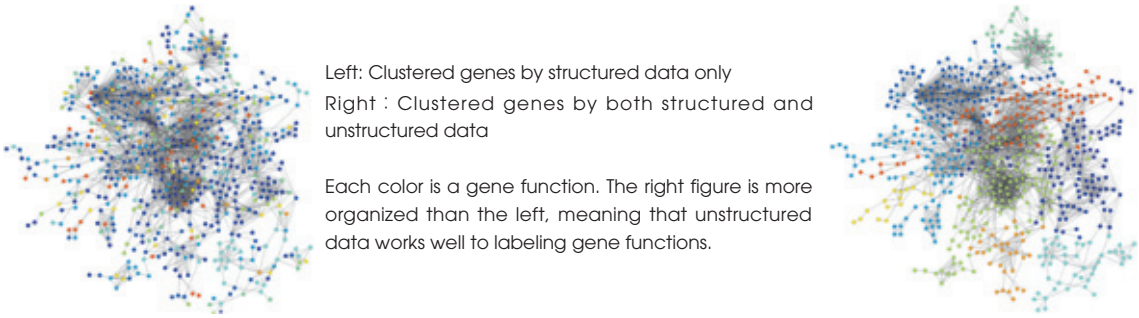
Research Projects:

Recent development in experimental biotechnology and nation-wide or international projects in life sciences have generated a variety of different types of biological data. They are currently stored in a lot of publicly available databases, which can be accessed through the internet. These databases, however, do not seem to have been used thoroughly in terms of understanding the mechanisms of life sciences. So it must be useful to systematically analyze the data by using the techniques in information sciences. This approach is generally called "bioinformatics", and in particular, so-called machine learning, data mining and statistics would be key techniques for this purpose. Machine learning (and data mining as well) is a research field in computer science to develop the methods which efficiently capture the property, such as patterns, rules and hypothesis etc., of given data. The data format which has been used for a long time in this field is a simple table (each example is a row, and each attribute of an example is a column). To deal with this type of structured data, a lot of techniques have been already proposed in machine learning and statistics. On the other hand, there exist a lot of different types of datasets in life sciences, such as genome sequences, chemical structures and signal transduction pathways, which are unstructured (Note that a table is called structured data). Each of them cannot be a table easily, and even if it can, some important information might be dropped off when we transform unstructured data into structured data. Thus it would be valuable to develop a new approach of machine learning for unstructured data. We note that this approach for unstructured data must be worth contributing not only to promoting the findings in life sciences but also to the development of computer science itself. Currently our laboratory has developed a variety of new techniques in the above direction, which will be kept in this fiscal year as well. Below we will briefly show three topics which we have conducted in our laboratory, including on-going projects.

1) Integrative mining from unstructured and structured data: Recent biological data are, in many cases, represented by graphs, such as gene regulatory networks, metabolic pathways and protein-protein interactions, etc. We are developing a technique for combining this type of unstructured information with structured data. An example is clustering genes using both gene networks (unstructured data) and cDNA microarray expressions (structured data). This approach is for predicting the function of an arbitrary gene. We currently focus on the network with high modularity, and in the future, our attention will be extended to variety types of networks, including that with the scale-freeness

2) Data mining from tree structured glycans: We have developed a probabilistic model-based approach for mining patterns from labeled ordered trees, or two-dimensional chemical structures of glycans (carbohydrate sugar chains). Our approach realizes multiple tree alignment and the findings of some patterns peculiar to each class of glycans. We, in the future, will develop a method for automatically classifying a variety of glycans based on our current approach.

3) Text mining from biomedical documents: A typical example of unstructured data which are accumulated in a rapid speed is biomedical documents. We are now developing roughly three approaches for text mining, i.e. acquiring new information from biomedical documents. The first is a method, which can be categorized into the field of information retrieval, to find the most relevant document to a given query phrase like "what is the function of a gene of Mad Cow Disease?" The second is a probabilistic model-based approach for finding a new co-occurrence of biological entities, like a pair of some small molecule and a disease, from a currently available set of co-occurrences. The third is a probabilistic model-based approach for clustering documents with multiple fields.



Left: Clustered genes by structured data only
Right : Clustered genes by both structured and unstructured data

Each color is a gene function. The right figure is more organized than the left, meaning that unstructured data works well to labeling gene functions.

Recent publications

- Takigawa *et al.* Mining Significant Substructure Pairs for Interpreting Polypharmacology in Drug-Target Network. *PLoS One*, **6**(2), e16999, 2011.
- Takigawa and Mamitsuka. Graph Mining: Procedure, Application to Drug Discovery and Recent Advance. *Drug Discovery Today*, **18**(1-2), 50-57, 2013.
- Ding *et al.* Similarity-based Machine Learning Methods for Predicting Drug-target Interactions: A Brief Review. *Briefings in Bioinformatics*, **15**(5), 737-747, 2014.

Department of Nanobio Drug Discovery

Professor: Kazuharu Shimizu, Ph.D. , Yutaka Shimada, M.D., Ph.D. , Tetsuo Sudo
Lecturer: Yoshinori Takei, Ph.D.

Research Projects:

1. Background and aims

Recent advances in the field of engineering, including nano, material, and analytical technology, contribute to produce huge amount of bio-information, which helps progress of genomic, genetic, epigenetic, and proteomic studies. Systems biology, a new approach on the basis of those accumulated bio-information, allows novel methods for both discovery of novel drugs and biomakers, and creation of innovative diagnostic tools and therapeutic methods."**Nanobio**" research, an integrated research between "nano" -material technology and "bio"-logy, will not only provide cutting-edge bio-information to the drug discovery science field, but also expand the range of research options in the medical and pharmacological field.

In our laboratory, we will use Nanobio technology not only for elucidation of changes in genome function under physiological and pathological conditions, but also for establishment of novel diagnostic and therapeutic tools of cancers.

2. Research directions

Using nanobio analytical devices, such as DNA microarray, we will collect novel genome-wide bio-information that cannot be obtained by conventional analytical devices. In combination of these new information and high quality clinical specimens, we seek to develop (1) new methods for diagnosis, (2) tailor-made therapy and (3) targeted therapy of cancers.

1: From mRNA expression profiling to "Tailor-made" therapy.

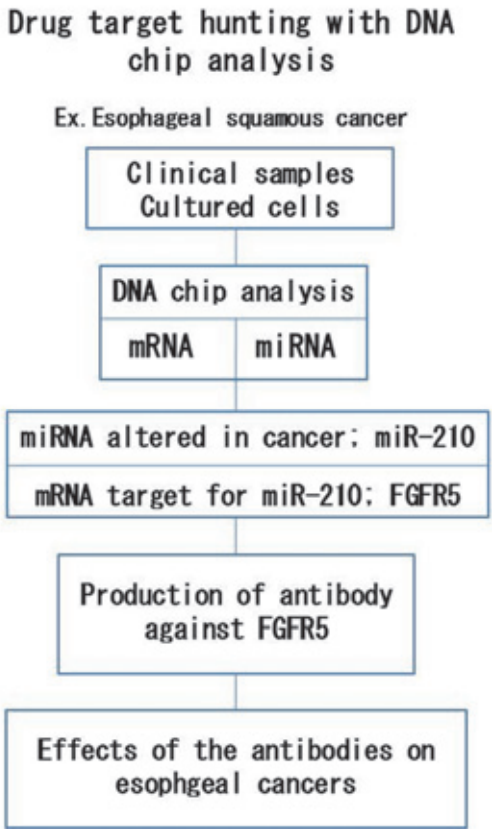
Most of current gene counseling are to diagnose diseases or to stratify patients by a single gene marker. In contrast, using a comprehensive gene expression data set, we are trying to establish mathematical models to predict a survival rate, sensitivity to chemo-radiation therapy, and distant metastasis for patients with various malignancies, especially esophageal cancer. To establish a reliable stratification strategy using these prediction models will enable us to perform "Tailor-made" therapy.

2: Functional analysis of microRNA (miRNA)

MicroRNAs are short RNA molecules that do not code proteins. With microarray technique we are investigating microRNA functions in normal cell differentiation and in malignant characteristics of tumor cells. As an outcome from this project, we indicated that low expression level of miR-210 is correlated to good prognosis of patients with esophageal cancers.

3: Development of antibody drugs

We found that FGF5 is a target for miR-210 and that high expression level of FGFR5 is correlated to good prognosis of patients with esophageal cancers. An antibody against FGFR5 inhibits cell proliferation of primary cultured cells derived from esophageal cancers. We are studying mechanism of the inhibition of cell proliferation, in order to develop new antibody drugs against esophageal cancers.



Recent publications

●S.Tsuchiya et al. MicroRNA-210 regulates cancer cell proliferation through targeting fibroblast growth factor receptor-like 1 (FGFRL1). J Biol Chem. 286,420-428,2011
●Y.Shimada et al. Expression analysis of fibroblast growth factor receptor-like 1 (FGFRL1) in esophageal squamous cell carcinoma. Esophagus 11 (1), 48-53, 2014

Department of Pharmaceutical Policy and Health Economics

Professor: Hiroaki Kakihara, Senior Lecturer: Xin Xin Ma,
Assistant Professor: Masaoki Tamura, Naohiko Wakutsu

Research Projects:

The Department of Pharmaceutical Policy and Health Economics was established in April 2012 by the endowment of the Japan Pharmaceutical Manufacturers Associations (JPMA).

Medicines provide a fundamental tool for ensuring that a population remains both healthy and productive. Considering how Japanese healthcare system manages use of medicines as well as how public policies could play a role in the development of new drugs and technology will be critical for Japanese social and economic prosperity, particularly in an aging population. Our research is focused on the relationship between pharmaceutical industry and an economy and its implication to public policy. The key areas of research include short-run and long-run efficient usage of generic drugs and research and development in the pharmaceutical industry and economic growth.

More specifically our research projects include the following topics:

1. Efficient usage of generic drugs and brand name drugs

Drugs are an essential part of medical practice and share the large part of economic expenditure. Generic drugs, which contain the same therapeutic substance as the original formulation, are expected to lead to greater market competition and therefore lower prices. Although generic drugs are shown to provide the same level of efficacy, their market share and sales accounts in Japan are still lower than those in the United States and European countries. Our research focuses on revealing the mechanism of decision making on prescribing generic and brand name drugs by physicians, pharmacists and patients based on economic discipline.

2. Pharmaceutical industry and its effects on economy

2-1. Impact of the investment on research and development (R&D) in the pharmaceutical industry on output of new drugs

The pharmaceutical industry is one of the most R&D-intensive industries in the economy, and spending on drug R&D has even grown recently. One of the key questions to understand the role of the pharmaceutical industry in the economy is how spending on R&D turns into the number of innovative new drugs approved for use.

2-2. Effects of development of new drugs on health, specifically on life expectancy and quality of life

The health benefits from new drugs include longer life and reducing limitations on daily activities. The ultimate and most important goal of pharmaceutical industry is to produce new products bringing longer and better life to all the population. Our research thus aims to study the impact of the approval and use of new drugs on the health of the Japanese population.

2-3. Effects of development of new drugs on the economy

New products are a key driver of economic growth. The pharmaceutical industry produces greater number of new products on average than many other industries. Our research tries to qualitatively evaluate the impact of development of new drugs on the economy.

2-4. Evaluation of the role of the pharmaceutical industry in the macro economy

One of our research goals is to identify the impact of pharmaceutical industry on the macroeconomy through employment and production. We conduct decomposition analyses to examine the effect of pharmaceutical industry on the labor market and GDP per capita.

3. Vaccination and public policies

3-1. Determinants of vaccination behavior

Vaccination prevents individuals from contracting a disease and it has been a helpful public-health tool to control infectious disease outbreaks. Individuals' vaccination decision making influences other members of the society due to indirect effect for non-vacinees. Our research aims to explore individuals' decision making on vaccination. The demand for vaccine could be studied in the frame of a standard economic theory unlike many other clinical services where a large part of the decisions depends on other agents such as physicians.

3-2. Effective and efficient vaccination policies

It is important to build effective public health policies on vaccination as they determine the population health. Our research aims to explore better policy options regarding vaccination policies in terms of both effectiveness and efficiency.

The group is led by Prof. Hiroaki Kakihara and the members include Senior Lecturer. Xin xin Ma, Assistant Prof. Masaoki Tamura, Naohiko Wakutsu.

Center for Integrative Education in Pharmacy and Pharmaceutical Sciences

The center is an adjunct facility of the Faculty and Graduate School of Pharmaceutical Sciences, and was established in April, 2010 as a base unit for the development of integrative education/research in pharmacy and pharmaceutical sciences. The center consists of three departments: Department of Education for Drug Developmental Sciences, Department of Education for Drug Discovery Sciences, and Department of Education of Clinical Pharmacy. The specialists in the Division of Bioinformatics and Chemical Genomics are in charge of education/research into information sciences. Through close collaboration, the center offers the human resource development program described below.

The mission of the Faculty and Graduate School of Pharmaceutical Sciences is to establish a global center for innovative drug discovery and development, and optimization of pharmacotherapy. Through its curricula at both the undergraduate and graduate levels, the school aims to train world leaders in the pharmaceutical sciences. In accordance with this mission, the education programs cover not only the basic sciences, but also specialized sciences associated with industrial drug discovery and development, the theorization of pharmacotherapy theories at medical institutions, and the sciences behind governmental pharmaceutical regulations.

The mission of the center is to create an integrated education/research system to meet the recent advances in drug discovery and development, and in pharmacotherapy. The human resource development program includes:

1. Pharmaceutical R&D exercise I

The students take on roles as members of the research section of a pharmaceutical company, and discuss the strategy to discover a novel drug candidate. Through small group discussion, the team, consisting of 5-6 students, makes a presentation to supposed representatives of the company on the concept of development, social and therapeutic contributions, revenue and post-marketing management of the drug.

2. Pharmaceutical R&D exercise II

The students take on roles as members of the developmental section of a pharmaceutical company. They make a presentation to supposed doctors and/or other medical staff about clinical research on a novel drug candidate. To do this, the students prepare presentation documents/slides using the investigator's brochure, protocol, clinical report form and informed consent. "Exercise I" is assumed to be on early stage of R&D, and "Exercise II" is a later stage.

3. Integrated pharmaceutical exercise

This exercise consists of two exposure programs. Early exposure to pharmacy and pharmaceutical sciences is scheduled immediately after admission, whereas exposure to industrial drug discovery and development is in the third year.

4. Laboratory for medical ethics

This exercise deals with medical safety issues, such as adverse events and medical errors/malpractice. Through experiences as medical staff and small group discussion with medical staff, the students learn about safety management strategies and prerequisites for provision of the best medical care.

Experimental Station for Medicinal Plants

Medicinal plants have served human beings as traditional medicines and been used for making pharmaceutical products. Recent revival of interest in Kampo medicine made it to be established in Japanese community, while a variety of compounds produced by plants were shown to be a good stock for new drug development. Many people in the world have realized that plants harbored a huge pool of a variety of compounds for drug development. As this awareness becomes common, wild plants are now generally recognized as potential resources for useful compounds, and which leads countries to make strict rules on import and export of plant materials.

The station covers an area of 3,042 square meters consisting of herbarium gardens, nurseries, experimental fields and greenhouses. Various species of important medicinal plants appeared in Japanese Pharmacopoeia and rare plants collected in fieldworks abroad are cultivated in these places and used for training of undergraduate students as well as for research works of pharmaceutical sciences.

1) Herbarium Gardens: This area shows medicinal plants of Japanese Pharmacopoeia, Japanese and European folk medicines, Labiatae and other herbs and some medicinal trees of temperate zone. These plants are used for student training and also for exercises of the training course for "Pharmacist accredited with knowledge of Kampo and natural medicines".

2) Greenhouses: Medicinal plants of the tropical zone, such as cinnamon, frankincense, turmeric, long pepper, and more, are grown in the greenhouses.

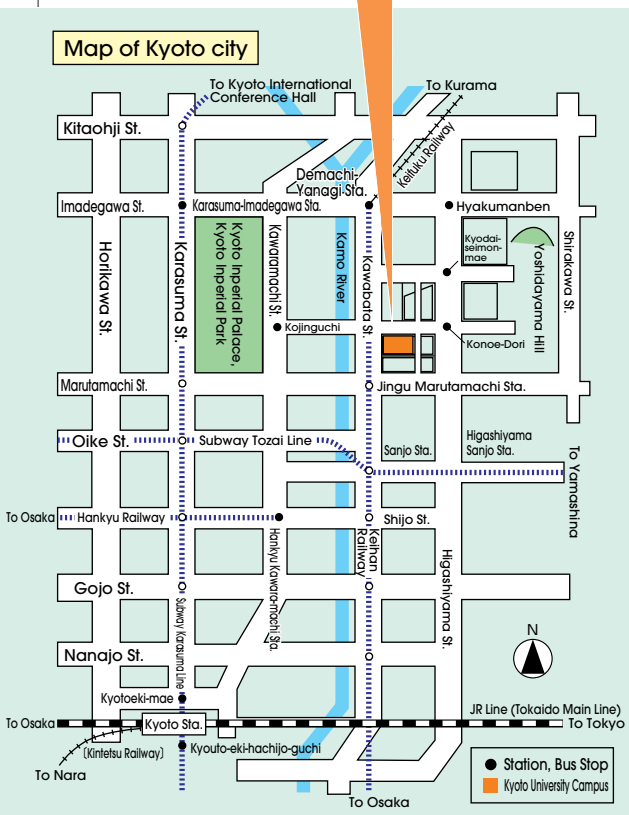
3) Nurseries and Experimental Fields: Since 1980's, genetic and phylogenic studies and breeding of perilla have been performed in the fields. Pure strains of perilla kept here counted more than 5700 now.

4) Herbarium and Natural Medicine Specimens: Specimens collected in fieldworks in countries of the Middle and Near East, Central and South-East Asia are kept in the herbarium and utilized for teaching and research works.

Center for Organic Elemental Microanalysis

Since the establishment in 1954, the Center for Organic Elemental Microanalysis has performed elemental analysis and offered great support in providing the necessary data of newly synthesized compound or chemical structure analysis for our Graduate School of Pharmaceutical Sciences, other universities research centers, other public or state research centers, or private research institutions.

Graduate School of Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences



by Walk

10 min walk to North-East from Keihan Jingu Marutamachi Station

by Bus

Railway Station: JR Kyoto Station
Get a bus at: Kyoto-Eki-Mae bus stop D2
Bus number: 206
Destination: Kita-ohji Bus Terminal via Higashi-yama-dori
Bus stop: Konoe-dori 40 min

Railway Station: Hankyu Kawara-machi Station
Get a bus at: Shijo-kawara-machi bus stop on Shijo St. (East bound)
Bus number: 201
Destination: Gion/Hyaku-man-ben
Bus stop: Konoe-dori 20 min
Bus number: 31
Destination: Takano/Iwakura
Bus stop: Konoe-dori
Get a bus at: Shijo-kawara-machi bus stop on Kawaramachi St. (North bound)
Bus number: 17
Destination: Kin-rin-shako
Bus stop: Kohjin-guchi 15 min

Railway Station: Subway (Karasuma line) Imadegawa
Get a bus at: Karasuma-Imadegawa bus stop (East bound)
Bus number: 201
Destination: for Hyaku-man-ben/Gion
Bus stop: Konoe-dori 15 min

Railway Station : Subway (Tozai line) Higasi-yama
Get a bus at: Higashi-yama-sanjo bus stop
Bus number : 206
Destination : for Kita-ohji Bus Terminal via Higashi-yama-dori
Bus stop : Konoe-dori 15min
Bus number : 201
Destination : for Hyaku-man-ben/Senbon-imade-gawa
Bus stop : Konoe-dori 15min
Bus number : 31
Destination : for Takano/Iwakura
Bus stop : Konoe-dori 15min

by Taxi

from JR Kyoto Station, 15-30 minutes

Kyoto University
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Faculty of Pharmaceutical Sciences

June, 2015

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