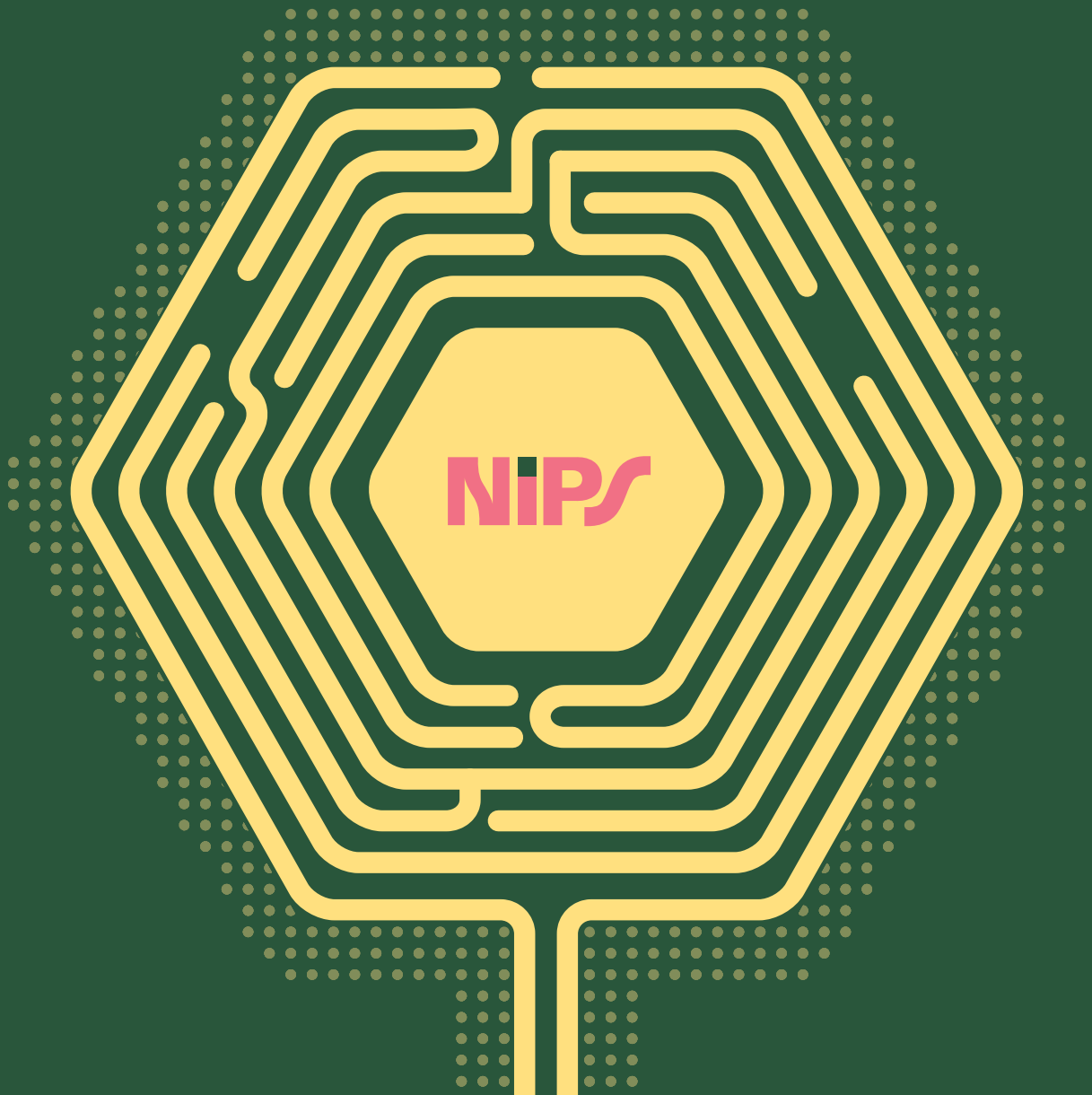
National Institute of Natural Sciences

# National Institute for Physiological Sciences 2016



# C O N T E N T S

# INTRODUCTION

National Institute for Physiological Sciences (NIPS) is an inter-university research institute for research and education on human physiology, which investigates the functions and mechanisms of human body, carries out joint studies with scientists of domestic and foreign universities, and provides education and training for graduate students and young scientists. Research of human physiology can provide us with explanations of wonderful functions of our body, scientific guidelines for healthy living, and scientific knowledge that forms the basis for elucidating the mechanisms of disease pathogenesis. The main subject of the current NIPS research is the brain and nervous system, because the brain is remarkably developed in human, and is the key organ that distinguishes human being from other species. The brain regulates and controls other organs and tissues in the body through interactions with them. Research of brain will answer questions how we sense and perceive objects, how we remember things, how we think using language, and other questions; these questions have mystified our ancestors and us from ancient times. Research of brain is expected to provide us clues how to ease and circumvent problems in the coming unprecedented aging society.

The NIPS advocates the following three missions. The first mission of NIPS is to conduct cutting-edge research in the physiological sciences at many levels, ranging from the molecule to the system or whole organism, and to elucidate the mechanisms of living body function by integrating the research results from the different levels. Recently, life science is rapidly advancing, and its research field is becoming broader and more diversified. In such an evolving situation, the NIPS has always conducted a leading role in the physiological sciences and brain science both in Japan and abroad, owing to the warm and mighty support from the researchers' community.

The second mission of NIPS is to promote the research in Japan, playing a role of research hub. The NIPS conduct joint studies with researchers from domestic or foreign universities and research institutes. The NIPS provides specialized equipments, such as newly developed electron microscopes and human brain imaging apparatus, to the researchers. The NIPS also holds workshops and international symposia to promote domestic and international research collaboration.

This year, the NIPS starts a new research support program "Advanced BioImaging Support Platform", in collaboration with the National Institute for Basic Biology (NIBB).

The third mission of NIPS is to educate and nurture young scientists. The NIPS is responsible for directing the Ph.D. course of study in physiological sciences in SOKENDAI (the Graduate University of Advanced Studies). About 50 graduate students are enrolled in the 5-year Ph.D. course. In addition, the NIPS contributes to the training or education of graduate students and young scientists from many universities and research institutes (including private sector institutes) by providing various training and teaching courses.

In addition to these three missions, the NIPS extends its effort to disseminate scientific information and to publicize its work. Please visit our website (http://www.nips.ac.jp/) for more information.

Organization of the NIPS was renovated in 2016, to make our Institute more friendly for potential research collaborators. "To elucidate comprehensively human body functions by integrating the research results from the different levels" is the ultimate goal stated as the article #1 of the NIPS constitution-like dictum which was announced at the time of NIPS foundation. We all are trying our best step by step to go forward for achieving this goal. Your understanding, and continued support of our activities is cordially appreciated.

M.D., Ph.D., Director General

**IMOTO, Keiji**

1976 M.D., Kyoto University. 1980 Staff Doctor, Utano National Hospital, 1985 Assistant Professor of Medical Chemistry, Faculty of Medicine, Kyoto University. 1995 Professor of Department of Information Physiology, NIPS and of Department of Physiological Sciences, School of Life Science, Sokendai. 2013 Director General, NIPS, and Vice President, NINS.
Specialty: Neuroscience, Neurophysiology

# Outlines of Institute

National Institute for Physiological Sciences (NIPS) is an Inter-university Research Institute for research and education on human physiology. NIPS researchers are investigating human body and brain functions as well as their mechanisms through joint studies with domestic and foreign scientists, and providing specialized techniques and large-scale equipment for shared use as well as education and training for graduate students and young scientists.

## Organization

NAOJ, NIFS, NIBB, NIPS and IMS were reorganized into NINS by reason of enforcement of the National University Corporation Law.

The NIPS currently comprises 6 departments, 19 divisions, 4 centers, 18 sections, Research Enhancement Strategy Office and Technical Division.

## Joint Studies

As an inter-university research institute, NIPS entertains proposals for joint studies from domestic and foreign physiological scientists. Applications from domestic and foreign scientists are reviewed and controlled by the inter-university ad hoc committee.

## Graduate Programs

The NIPS carries out two graduate programs.

### 1.Graduate University for Advanced Studies

The NIPS constitutes the Department of Physiological Sciences in the School of Life Science of the Graduate University for Advanced Studies. The University provides a five-year Ph. D. course, namely including both Master and Doctor courses, or a four-year Medical Science course. However, those who have completed a master's course in other universities or are qualified at an equivalent or higher level are eligible to apply for the three-year Ph. D. course which is consistent with Master course. The degree conferred on graduation is Doctor of Philosophy.

### 2.Graduate Student Training Program

Graduate students enrolled in other universities and institutes are trained to conduct researches for fixed periods of time under the supervision of NIPS professors and associate professors.

## Exchange Programs

To activate international collaborations among physiological scientists in the Institute and foreign organizations, scientist exchange programs are conducted.

## System management

Management Council, Educational and Research Council and Board of Directors are established at NINS to inspect significant matters of management, education, research and administration.

Advisory Committee for Research and Management in NIPS advises the Director-General on important matters in management of the Institute.

## Administration

Administration of the institutes is managed at Okazaki Administration Office of NINS.

# A Short History of the Institute

In 1960, many physiologists affiliated with the Physiological Society of Japan initiated a discussion on how to establish a central research institute for physiological sciences in this country.

In recent years, remarkable progress has been made in the life sciences throughout the world, particularly in the fields of molecular biology, cellular biology and physiology, and in areas concerning information processing and regulatory systems of higher animals. In view of these developments, there was a consensus among physiologists in Japan that a new type of research organization must be created, in parallel with the laboratories in universities, to pursue new approaches in the life sciences.

Through discussions among the physiologists, the following characteristies of such a new institute were considered to be of utmost importance.

1. Investigators from different fields should be able to collaborate on research projects in the life sciences with minimal restrictions.
2. Research communication among scientists from many fields should be closely coordinated.
3. Specialized, large-scale equipment required for multidisciplinary research, not routinely available in smaller laboratories of educational institutions, should be accessible, and proper training and maintenance should be provided. A Committee for the Foundation of a Physiological Institute was organized by Drs. MOTOKAWA K., KATSUKI Y., NATORI R., TOKIZANE T., INOUE A., UCHIZONO K., and many other leading physiologists in 1965. Thereafter, in order to establish such an institute, considerable effort was made by scientists and related government officials.

   The following time table describes the history leading to the foundation of the Institute:

**Nov., 1967**

The Science Council of Japan officially advised the then Prime Minister, SATO Eisaku, that the establishment of an institute for Physiological Sciences was important, and urgently necessary for the promotion of life sciences in Japan.

The Science Council of the Monbusho （the Ministry of Education, Science and Culture） reported to the Minister of Education, Science and Culture that two institutes for scientific research of biological sciences, namely, the Institute for Physiological Sciences and the Institute for Basic Biology, should be established as early as possible.

**May, 1976**

The Preparing Office and the Research Council for the establishment of Institutes for Biological Sciences were opened in the Monbusho.

**May, 1977**

The Institute for Physiological Sciences （Director-General: Prof. UCHIZONO K.） was officially established which, together with the Institute for Basic Biology, constituted the National Center for Biological Sciences （President: Prof. KATSUKI Y.）. Constituents of the Institute for Physiological Sciences at the time of inauguration were as follows.

Department of molecular physiology
  Division of Ultrastructure Research
Department of Cell physiology
  Division of Membrane Biology
Department of Information physiology
  *Division of Neurobiology and Behavioral Genetics
Special Facilities for Physiological Research
  Technical Division

**Apr., 1978**

In the second year the following laboratories were added:

Department of Molecular physiology
  *Division of Intracellular Metabolism
Department of Information physiology
  Division of Neural Information
Department of Biological Control System
  Division of Neural Control

**Apr., 1979**

In the third year the following laboratories were added:

Department of Cell physiology
  Division of Correlative Physiology
  *Division of Active Transport
Department of Biological Control System
  *Division of Cognitive Neuroscience

**Apr., 1980**

The following were added in the fourth year:

Department of Information physiology
  Division of Humoral Information
  *Division of Learning and Memory Research

Research Facilities
Division of Experimental Animals

**Apr., 1981**

A new organization, Okazaki National Research Institutes, comprised of three independent institutes (Institute for Molecular Science, Institute for Physiological Sciences, and Institute for Basic Biology) was established. Previously, these institutes had been managed independently. However, on 14 Apr. 1981, they were administratively amalgamated into one organization, and thereafter referred to collectively as the Okazaki National Research Institutes.

**Apr., 1982**

The following was added:
Department of Molecular physiology
Division of Neurochemistry

**Apr., 1984**

The following was added:
Department of Biological Control System
Division of System Neurophysiology

**Apr., 1985**

Prof. EBASHI S. was elected the Director-General of the Institute.

**Oct., 1988**

The Graduate University for Advanced Studies was founded and in the Institute the School of Life Sciences, Department of Physiological Sciences was established.

**Jun., 1990**

The following were added:
Department of Integrative Physiology
Sensory and Motor Function Research Project
Higher Brain Function Project
*Autonomic Function Research Project

**Dec., 1991**

Prof. HAMA K. was elected the Director-General of the Institute.

**Apr., 1997**

Prof. SASAKI K. was elected the Director-General of the Institute.

**Apr., 1998**

The following were added:
Department of Cerebral Research
Division of Cerebral Structure
Division of Cerebral Circuitry
Division of Cerebral Integration

A part of facilities in the complex of Physiological Research Facilities was reformed to the Center for Brain Experiment.

**Apr., 2000**

Division of Experimental Animals was transferred to the Research Facilities as shown below. Center for Integrative Bioscience
- Department of Strategic Methodology
- Department of Development, Differentiation and Regeneration
- Department of Bio-Environmental Science

Research Center for Computational Science
Center for Experimental Animals
Center for Radioisotope Facilities

**Apr., 2003**

Prof. MIZUNO N. was elected the Director-General of the Institute.

The following were added:
Department of Developmental Physiology
Division of Behavioral Development
Division of Homeostatic Development
Division of Reproductive/Endocrine Development
Division of Adaptation Development

**Apr., 2004**

Established National Institutes of Natural Sciences (NINS). National Astronomical Observatory of Japan (NAOJ), National Institute for Fusion Science (NIFS), National Institute for Basic Biology (NIBB), National Institute for Physiological Sciences (NIPS) and Institute for Molecular Science (IMS) were integrated and reorganized into NINS by reason of enforcement of the National University Corporation Law.

In NIPS, Division of Neurochemistry in Department of Molecular Physiology was renamed to Division of Biophysics and Neurobiology, Division of Humoral Information in Department of Information Physiology was renamed to Division of Neural Signaling, Department of Biological Control System was renamed to Department of Integrative Physiology, Division of Cognitive Neuroscience was renamed to Division of Computational Neuroscience, and Center for Integrative Bioscience was renamed to Okazaki Institute for Integrative Bioscience, respectively.

The Administration Bureau turned into Okazaki Administration Office of NINS.

**Nov., 2005**

Division of Neurobiology and Behavioral Genetics was reformed to the Center for Genetic Analysis of Behavior.

**Apr., 2007**

Prof. OKADA Y. was elected the Director-General of the Institute.

The following were added:
Department of Molecular Physiology
Division of Nano-Structure Physiology
Department of Cell Physiology
Division of Cell Signaling
Department of Information Physiology

Division of Developmental Neurophysiology

**Apr., 2008**

Division of Active Transport in Department of Cell Physiology was renamed to Division of Neural Systematics.

The following were abolished:

Division of Learning and Memory Research

Center for Brain Experiment

The following were added:

Center for Multidisciplinary Brain Research

Supportive Center for Brain Research

Center for Communication Networks

**Apr., 2009**

Division of Int r acellular Metabolism was abolished.

**Apr., 2011**

The following was added:

Section of Health and Safety Management

**Apr., 2013**

Prof. IMOTO K. was elected the Director-General of the Institute.

**Oct., 2013**

Research Enhancement Strategy Office was established.

**Jan., 2014**

The following were added:

Department of Information Physiology

Division of Cardiocirculatory Signaling

Center for Multidisciplinary Brain Research

Research Strategy for Brain Sciences Office

**Apr., 2014**

Division of Developmental Neurophysiology in Department of Information Physiology was renamed to Division of Visual Information Processing.

The following were abolished:

Department of Molecular Physiology

Division of Nano-Structure Physiology

Department of Cell physiology

Division of Correlative Physiology

Center for Communication Networks

Section of Communications and Public Liaison

**Apr., 2016**

The following were abolished :

Department of Molecular Physiology

Department of Cell Physiology

Department of Information Physiology

Department of Integrative Physiology

Department of Cerebral Research

Department of Developmental Physiology

Center for Multidisciplinary Brain Research

Division of Computational Neuroscience

Division of Adaptation Development

The following were renamed :

Division of Cerebral Structure to Division of Cell Structure

Division of Sensori-Motor Integration to Division of Integrative Physiology

Division of Homeostatic Development to Division of Homeostatic Development

The following were added :

Department of Molecular and Cellular Physiology

Division of Biophysics and Neurobiology

Division of Neurobiology and Bioinformatics

Division of Membrane Physiology

Division of Neural Systematics

Division of Neural Development and Regeneration

Department of Homeostatic Regulation

Division of Cell Structure

Division of Cell Signaling

Division of Cardiocirculatory Signaling

Division of Endocrinology and Metabolism

Department of Fundamental Neuroscience

Division of Neural Signaling

Division of Cerebral Circuitry

Division of Homeostatic Development

Division of Visual information processing

Department of System Neuroscience

Division of Sensory and Cognitive Information

Division of Behavioral Development

Division of System Neurophysiology

Division of Integrative Physiology

Division of Cerebral Integration

Center for Research Collaboration

Section of Collaboration Promotion

Section of Advanced Research Support

Section of Visiting Collaboration Research Project

Section of International Collaborative Research Project

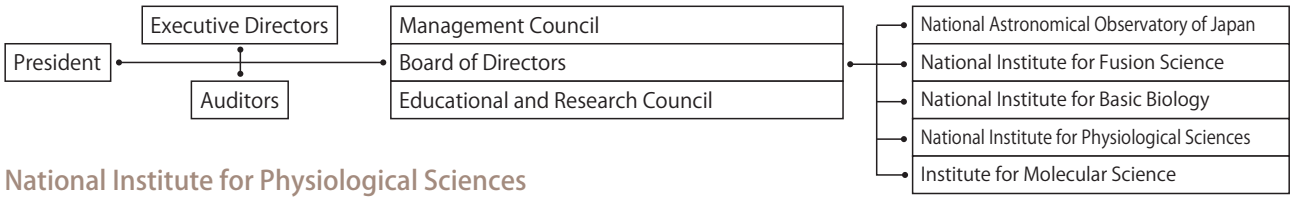
Regarding Supportive Center for Brain Research, Section of Viral Vector Development and Section of Primate Model Development have reorganized to Center for Genetic Analysis of Behavior and Center for Research Collaboration, respectively. Section of Primate Model Development has been renamed to NBR Project.

Section of Evaluation and Collaboration in Center for Communication Networks has also been renamed to Section of Research Archives.

Asterisk (*) denotes adjunct division.

# Organization of the Institute

## National Institutes of Natural Sciences




## National Institute for Physiological Sciences


※ Adjunctive divisions/sections
★ Okazaki Instititue for Integrative Bioscience

## Okazaki Research Facilities

# Advisory Committee for Research and Management

Chairman ◎ , Vice-Chairman ○

Advisory Committee for Research and Management shall advise the Director-General of the Institute, upon his request, on important matters in management of the Institute.

(Outside)

| | |
|---|---|
| OKABE, Shigeo | Professor, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo |
| KATO, Fusao | Professor, Department of Neuroscience, Jikei University School of Medicine |
| ○KADOMATSU, Kenij | Professor, Graduate School of Medicine, Nagoya University |
| FUJITA, Ichiro | Proffessor, Graduate School of Frontier Biosciences, Osaka University |
| ASAI, Kiyofumi | Professor, Graduate School of Medical Sciences, Nagoya City University |
| INOUE, Ryuji | Professor, Faculty of Medicine, Fukuoka University |
| TAKUWA, Noriko | Professor, Faculty of Nursing, Ishikawa Prefectural Nursing University |
| NAGAMINE, Takashi | Professor, School of Medicine, Sapporo Medical University |
| MUSHIAKE, Hajime | Professor, School of Medicine, Tohoku University |
| YAMAGUCHI, Yoko | Director, Neuroinformatics Japan Center, RIKEN Brain Science Institute |

(Inside)

| | |
|---|---|
| IKENAKA, Kazuhiro | Professor, NIPS |
| KAKIGI, Ryusuke | Professor, NIPS |
| KAWAGUCHI, Yasuo | Professor, NIPS |
| ◎KUBO, Yoshihiro | Professor, NIPS |
| KOMATSU, Hidehiko | Professor, NIPS |
| SADATO, Norihiro | Professor, NIPS |
| TOMINAGA, Makoto | Professor, NIPS |
| NABEKURA, Junichi | Professor, NIPS |
| NAMBU, Atsushi | Professor, NIPS |
| FUKATA, Masaki | Professor, NIPS |
| MINOKOSHI, Yasuhiko | Professor, NIPS |

# Director General/Vice Director General/Chief Researcher

| | |
|---|---|
| Director General | IMOTO, Keiji |
| Vice Director General | NABEKURA, Junichi |
| Chief Chairperson | KUBO, Yoshihiro |
| Chief Researcher / Chairperson for Cooperative Studies | SADATO, Norihiro |
| Chief Researcher / Chairperson for Animal Experiment Problem | MINOKOSHI, Yasuhiko |
| Chief Researcher /Chairperson for Safety and Research Ethics Problems | FUKATA, Masaki |
| Chief Researcher / Chairperson for News and Public Affairs | KAKIGI, Ryusuke |
| Chief Researcher / Chairperson for Educational Problem | KOMATSU, Hidehiko |
| Chief Researcher / Chairperson for Special Project | FURUSE, Mikio |

# Emeritus Professors

| | |
|---|---|
| OOMURA, Yutaka | KANEKO, Akimichi |
| HAMA, Kiyoshi | SASAKI, Kazuo |
| WATANABE, Akira | MIZUNO, Noboru |
| YAMAGISHI, Shunichi | NAGAYAMA, Kuniaki |
| MORI, Shigemi | OKADA, Yasunobu |
| OBATA, Kunihiko | OHMORI, Harunori |

# Emeritus Technical Staff

OHIRA, Hitoo

# Deceased Emeritus Professors

| | |
|---|---|
| IRISAWA, Hiroshi | KUNO, Motoy |
| UCHIZONO, Koji | TSUKAHARA, Nakaakira |
| EBASHI, Setsuro | YANAIHARA, Noboru |
| KATSUKI, Yasuji | WATARI, Hiroshi |

# Division of Biophysics and Neurobiology


KUBO, Yoshihiro
Professors
Biophysics
Neurobiology

TATEYAMA, Michihiro
Associate Professor
Pharmacology
Physiology

SHIMOMURA, Takushi
Assistant Professor
Molecular Physiology
Biophysics

CHEN, I-Shan
Project Assistant Professor
Molecular Physiology
Biophysics


## Functioning mechanisms and dynamic structure- function relationship of ion channels, receptors and G proteins

Ion channels, receptors and G proteins play critical roles for the excitability and its regulation of neurons. We focus on these molecules which enable brain function. From the biophysical point of view, we study structure-function relationships, regulation mechanisms and dynamic structural rearrangements of ion channels and receptors. We also study the functional significance of specific features of ion channels and receptors in the brain function by making gene manipulated mice and by studying their abnormalities in the synaptic transmission and whole animal behavior. Specific themes of research projects currently running are as follows.

Major target molecules are KCNQ $K^+$ channel complex, Kv4.2 $K^+$ channel complex, Two Pore $Na^+$ channel (TPC), hERG $K^+$ channel, P2X2 ATP receptor channel and various G protein coupled receptors including orphan receptor Prrt3. We also work on TRPA1 channels and Melanopsins as cooperative research projects.

One of the characteristic features of our experimental approaches is that we utilize heterologous expression systems such as Xenopus oocytes which enable high through-put recordings and precise biophysical analyses. Another is that we perform simultaneous recordings of electrophysiology and optophysiology to approach the dynamic aspects of the function and structural rearrangements, which is beneficial towards the understanding of the functioning images. Taking advantages of these facilities and methodologies, we would like to promote our research as well as cooperative research projects further.


* M. Kitazawa, Y. Kubo, K. Nakajo, *J. Biol. Chem.* **289**, 17597 (2015).
* B. Keceli, Y. Kubo, *J. Physiol.* **592**, 4657 (2014).
* K. Nakajo, Y. Kubo, *Nature Commun.* **5**, 4100 (2014).
* B. Keceli, Y. Kubo, *J. Gen. Physiol.* **143**, 761 (2014).
* M. Tateyama, Y. Kubo, *Neuropharmacol.* **65**, 173 (2013).
* K. Nakajo, A. Nishino, Y. Okamura, Y. Kubo, *J. Gen. Physiol.* **138**, 521 (2011).

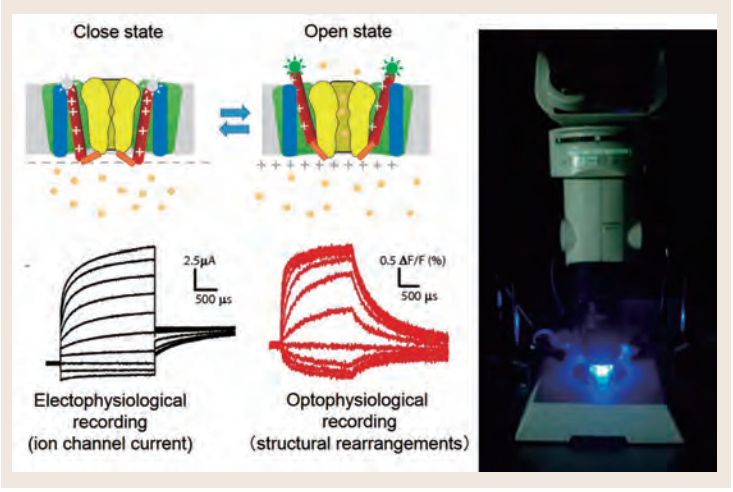




Fig. 1. Analyses of the function and dynamic structural rearrangements of the KCNQ1/KCNE1 $K^+$ channel cpmplex by simultaneous recordings of electrophysiology and optophysiology under voltage clamp condition using Xenopus oocyte expression systems. (Nakajo and Kubo, Nature Commun (2014))

# Division of Neurobiology and Bioinformatics

IKENAKA, Kazuhiro
Professor
Molecular Neurobiology

OHNO, Nobuhiro
Project Associate Professor
Histology
Cell Biology
Celluar and Molecular
Neuroscience

SHIMIZU, Takeshi
Assistant Professor
Molecular Developmental Biology

YOSHIMURA, Takeshi
Assistant Professor
Neuroscience
Molecular Biology

## Development and function of glial cells, and glial diseases.

We have been clarifying the roles of glial cells in the expression of brain function, and thereby the significance of glial cells is now recognized widely.

At present we are trying to prove that glial cells are forming giant net work, which we termed glial assembly, through which glial cells are actively regulating brain function. Below is the list of on-going projects.

1) Analysis of brain morphology and behavioral changes in astrocytic function-modified mice.
2) Clarifying the principle of axon selection for myelin formation by oligodendrocytes.
3) Mechano-modulation of oligodendrocyte during development.
4) Roles of cystatin F and cathepsin C in the formation of chronic demyelinated lesion.
5) Roles of proteoglycans during oligodendrocyte development.

## Function of glycans on glycoproteins expressed in the nervous system.

Significance of glycans harbored on glycoproteins has been recognized for a long time, however, their actual function has not been elucidated, because of the delay in the development of glycan analytical methods. We have finely tuned the classical N-glycan analytical method and developed a highly sensitive method, and clarified the function of N-glycans. There are three projects going on in our laboratory.

1) Exploring the function of a novel N-glycan whose expression level increases during brain development.
2) Clarifying the function of sulfate group on N-glycans harbored on P0 protein of peripheral nervous system.
3) Application of N-glycan profiling to the diagnosis of neuropsychiatric diseases.

* Lee HU et al (2013) Increased astrocytic ATP release results in enhanced excitability of the hippocampus. Glia, 60:210-24
* Ma J et al ( 2011) Microglial cystatin F expression is a sensitive indicator for ongoing demyelination with concurrent remyelination. J Neurosci Res 89:639-49
* Yoshimura T et al (2012) Detection of N-glycans on small amounts of glycoproteins in tissue samples and SDS-polyacrylamide gels. Analytical Biochem, 423:253-60

# Division of Membrane Physiology


FUKATA, Masaki
Professor
Neuroscience
Biochemistry
Cell Biology

FUKATA, Yuko
Associate Professor
Neuroscience
Biochemistry
Cell Biology

YOKOI, Norihiko
Assistant Professor
Neuroscience
Biochemistry
Bioinorganic Chemistry
Structural Biology


## Fundamental mechanisms for synaptic transmission and synaptic disorders

We will elucidate the core regulatory mechanisms for synaptic transmission and finally address the fundamental question, "How does our brain physiologically function and how is the system disrupted in brain diseases?". We have focused on the regulatory mechanisms for AMPA-type glutamate receptor (AMPAR) as AMPAR plays a central role in learning and memory formation. Based on our specific and quantitative biochemical methods, we discovered two types of AMPAR regulatory proteins: the DHHC palmitoylating enzymes and the epilepsy-related ligand/receptor, LGI1/ADAM22. So far, we have elucidated the physiological functions of these two AMPAR regulatory proteins and the implication in the pathogenesis of brain diseases such as epilepsy and limbic encephalitis, by developing new methods to screen the palmitoyl enzyme-substrate pairs and to specifically visualize the palmitoylated protein, and by integrating many methods such as super-resolution imaging, mouse genetics, and electrophysiology. We will elucidate the molecular basis in which these AMPAR regulatory proteins regulate synaptic plasticity and cognitive functions of mouse and human brains using the following our developed or cutting-edge approaches and resources.

1) Analyses of in vivo protein-protein interactions
2) Screening of palmitoylating enzyme library
3) Live cell imaging with palmitoylated protein-specific probes
4) Observation of synapses with super-resolution microscopy
5) Mouse models of human epilepsy with the LGI1 mutation


* N. Yokoi et al., Nat. Med. **21**, 19 (2015)
* T. Ohkawa et al., J. Neurosci. **34**, 8151 (2014)
* T. Ohkawa et al., J. Neurosci. **33**, 18161 (2013)
* Y. Fukata et al., J. Cell Biol. **202**, 145 (2013)
* Y. Fukata and M. Fukata, Nat. Rev. Neurosci. **11**, 161 (2010)

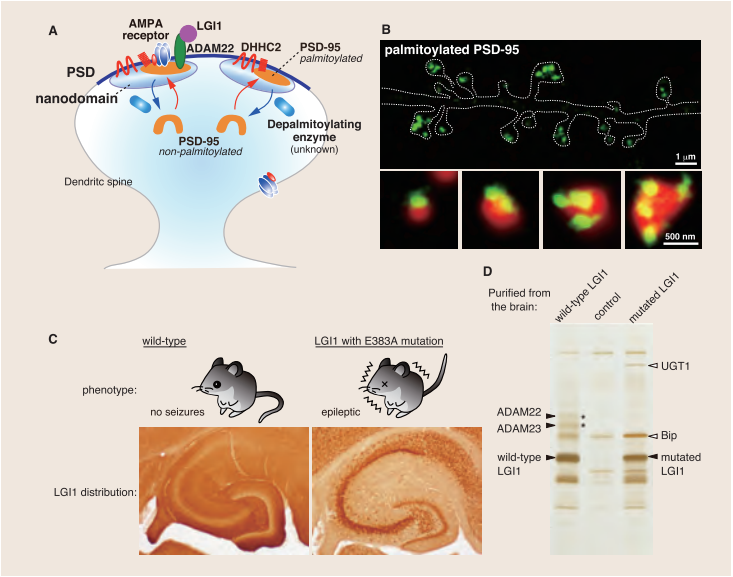




Figure (A) Two unique AMPA receptor regulatory proteins: DHHC palmitoylating enzymes and the epilepsy-related ligand/receptor, LGI1 and ADAM22. (B) Discovery of novel postsynaptic nanodomains by palmitoylated PSD-95-specific probe and super-resolution microscopy: a synaptic DHHC protein locally regulates the formation and reorganization of nanodomains. (C) Generation and analyses of mouse models of human epilepsy with the LGI1 mutation: Distribution (left) and protein interactions (right) of the LGI1 E383A mutant protein compared with the wild-type LGI1. This LGI1 mutant protein is misfolded and does not bind to its receptor, ADAM22.

# Division of Neural Systematics

SETOU, Mitsutoshi
Adjunct Professor
Neuroscience
Cell Biology

## Imaging mass spectrometric analysis of molecular machineries underlying the establishment and disruption of neuronal cell polarity

## Control of neuronal cell polarity by manipulation of lipid localization

Our group aims to elucidate molecular mechanisms that underlie the establishment and disruption of cell polarity and micro domains in neurons. We have been investigating spatiotemporal information about a huge number of molecular species that include lipids and post-translational modifications by means of imaging mass spectrometry. We have combined the multi-dimensional data with statistical analyses and bioinformatics to seek out new molecules that account for the establishment and disruption of neuronal polarity or small compartment. In addition, we are tackling a new challenging research topic for controlling neuronal cell polarity through manipulating localization of lipids that were shown to have unique intracellular distribution in imaging analyses including IMS. A high-priority issue is to manipulate lipid localization spatiotemporally by light stimulation, which we named “opto-lipidomics”.

* M. Setou, Imaging Mass Spectrometry (Springer, 2010).
* Y. Konishi, M. Setou, Tubulin tyrosination navigates the kinesin-1 motor domain to axons. Nat. Neurosci. 12, 55 (2009).
* H. J. Yang, et al., Axonal gradient of arachidonic acid-containing phosphatidylcholine and its dependence on actin dynamics. J. Biol. Chem. 287, 5290 (2012).
* D. Yuki, et al., DHA-PC and PSD-95 decrease after loss of synaptophysin and before neuronal loss in patients with Alzheimer’s disease. Sci. Rep. 4, 7130 (2014).
* H. Arima, et al., Blockade of IL-6 signaling by MR16-1 inhibits reduction of docosahexaenoic acid-containing phosphatidylcholine levels in a mouse model of spinal cord injury. Neuroscience 269, 1 (2014).

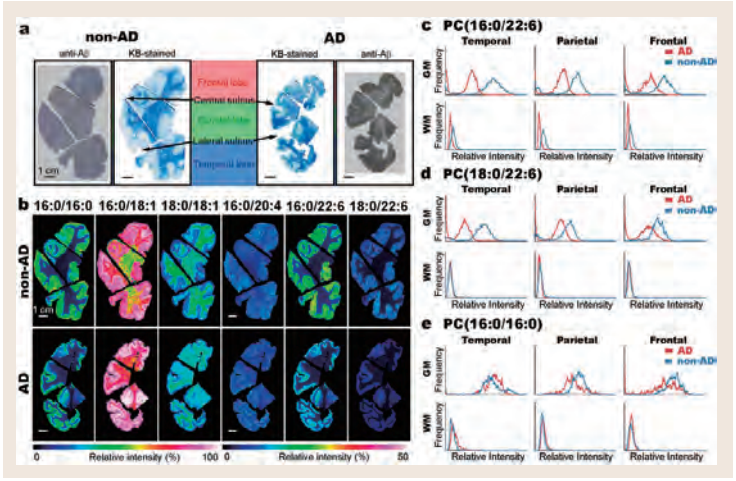



Fig. 1. Distribution of phosphatidylcholine in the cerebrum of Alzheimer’s disease patients. DHA-containing PC is decreased in the grey matter of AD patient cerebrum. (Yuki et al., Sci. Rep., 2014)

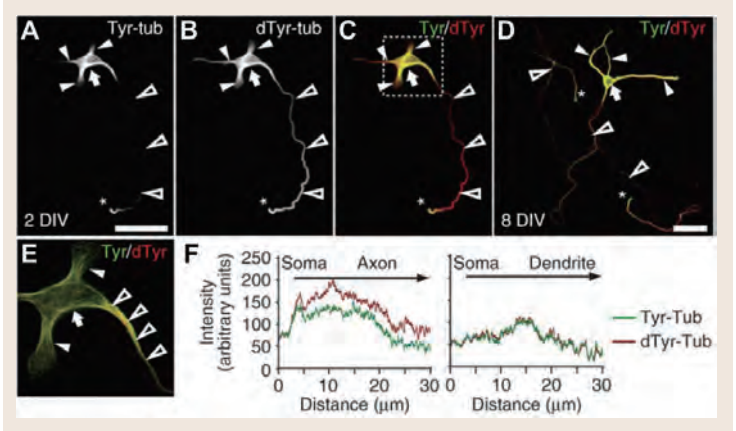



Fig. 2. Distribution of Tyr- and dTyr-tubulin in hippocampal neurons. The level of detyrosinated tubulin (red in panel F) is increased in the axon. (Konishi and Setou, Nat. Neurosci., 2009)

# Division of Neural Development & Regeneration

SAWAMOTO, Kazunobu
Adjunct Professor
Neuroscience
Development and
Regenerative Biology

## Mechanisms and functional significance of neurogenesis in the postnatal brain

## Endogenous regenerative mechanisms of injured brain and new therapies for brain diseases

New neurons and glial cells are continuously generated throughout life, not only at the embryonic and neonatal stages. Recent studies using experimental animals indicate that several regions of the adult brain have the capacity to regenerate injured neural tissues. In collaboration with researchers at other laboratories in NIPS, we have been studying the mechanisms for cell migration and regeneration in the postnatal brain. Our group aims to study the endogenous repair mechanisms in the brain and develop a new strategy to promote neuronal and glial cell regeneration after injury.

* H. Ota, et al., Speed control for neuronal migration in the postnatal brain by Gmip-mediated local inactivation of RhoA. Nat Commun 5: 4532 (2014)
* L.S. Zheng, et al., Mechanisms for interferon-alpha-induced depression and neural stem cell dysfunction. Stem Cell Rep 3: 73-84 (2014)
* E. Kako, et al., Subventricular-zone derived oligodendrogenesis in injured neonatal white-matter in mice enhanced by a nonerythropoietic EPO derivative. Stem Cells 30: 2234-2247 (2012)
* M. Sawada, et al., Sensory input regulates spatial and subtype-specific patterns of neuronal turnover in the adult olfactory bulb. J Neurosci 31: 11587-11596 (2011)
* N. Kaneko, et al., New neurons clear the path of astrocytic processes for their rapid migration in the adult brain. Neuron 67: 213-223 (2010).

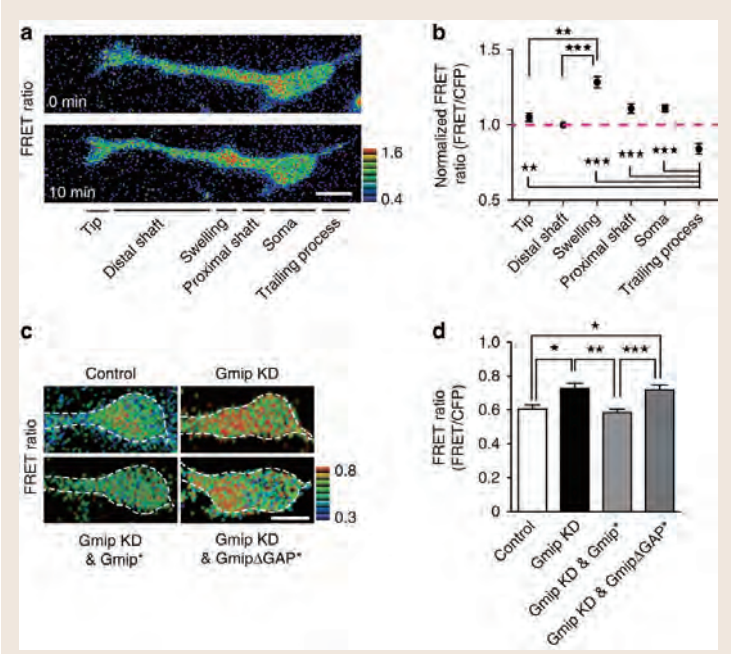



Fig.1. RhoA activity in migrating new neurons. (a,b) FRET imaging of RhoA acticity in cultured migrating new neurons. RhoA is activated at the proximal region of the leading process. (c, d) Effect of Gmip on the RhoA activity in new neurons. The RhoA activity at the proximal leading process is significantly decreased by overexpression of Gmip, and increased by knockdown of Gmip. (From Ota et al., Nat. Commun. 5:4532, 2014)

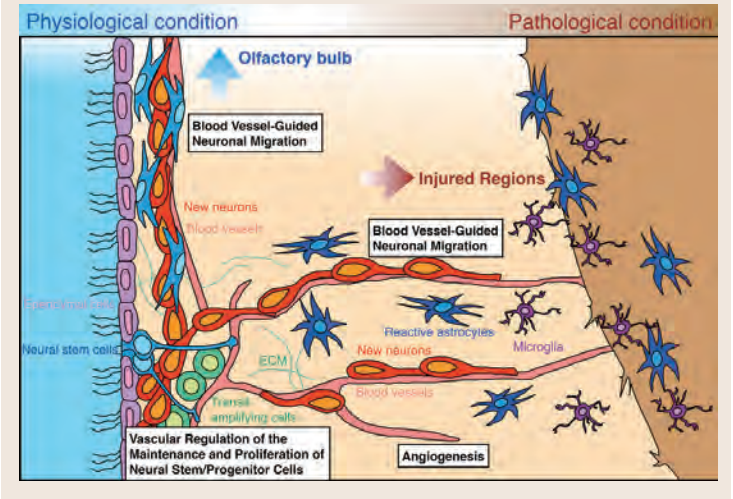



Fig. 2. Vascular regulation of adult neurogenesis in the ventricular-subventricular zone (V-SVZ) under physiological and pathological conditions. Neural stem cells (blue) continuously generate new neurons (red) that migrate towards the olfactory bulbs in the normal condition. These new neurons can also migrate towards injured regions using the blood vessel scaffold (pink). (From Sawada et al., Front. Neurosci. 8:53, 2014)

# Division of Cell Structure

FURUSE, Mikio
Professor
Cell Biology

IZUMI, Yasushi
Associate Professor
Cell Biology

OTANI, Tetsuhisa
Assistant Professor
Cell Biology

SUGAWARA, Taichi
Project Assistant Professor
Cell Biology

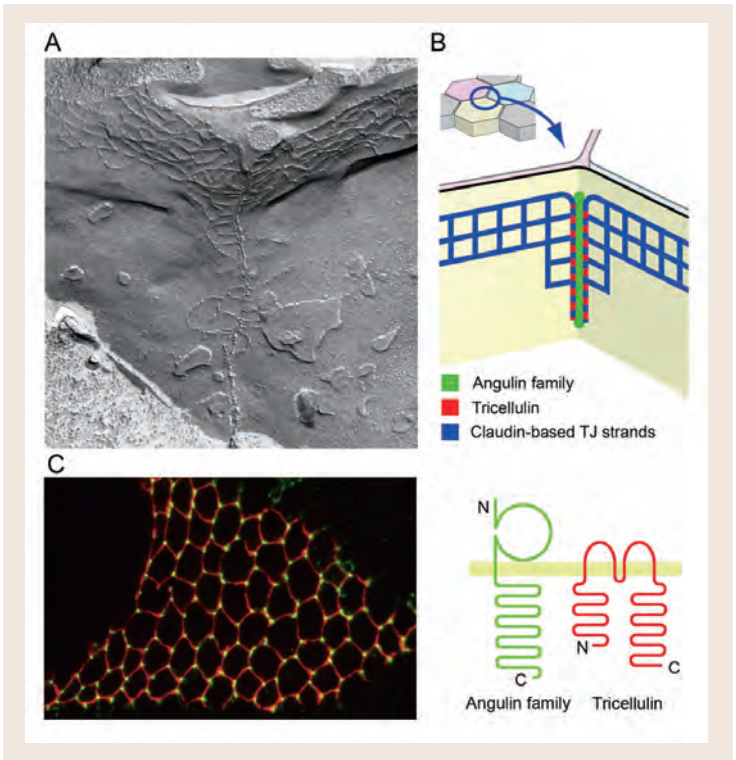
## Molecular basis of cell-cell junctions involved in epithelial barrier function

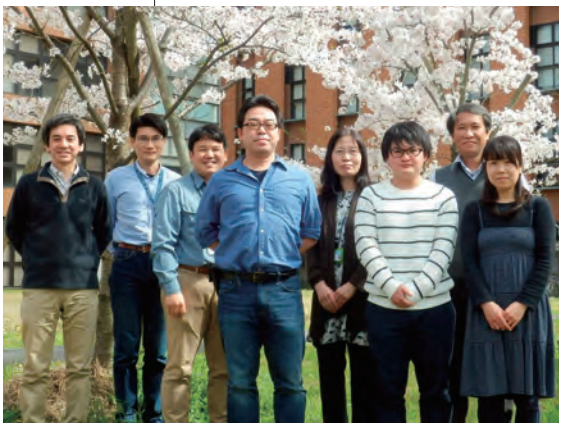
Epithelia separate body compartments as barriers and selectively transport various substances, thereby contributing to the functions of organs and homeostasis. Our laboratory aims to clarify the molecular bases of specialized cell structures that are responsible for these basic roles of epithelia. We focus on the cell-cell junctions involved in the regulation of paracellular transport (occluding junctions), including the tight junction and its related structures, and examine their molecular architectures, functions and dynamic behavior. One of the characteristic features of our research is that we identify structural or regulatory proteins of occluding junctions in our hands and characterize them. We take combined approaches of molecular biology, physiology and morphology including immunoelectron and freeze-fracture electron microscopy by using cultured epithelial cells and model organisms. For the study of cultured epithelial cells, we have recently introduced a system of gene disruption via genome editing. The following are ongoing projects.

1. Elucidation of the molecular mechanism behind the diversity of the morphology and function of tight junctions.
2. Molecular dissection of tricellular tight junctions and elucidation of their physiological functions.
3. Elucidation of the regulatory mechanism of cell-cell junction formation by using Drosophila genetics.
4. Analyses of the response of epithelial cells to the changes in the external environment.

* T. Higashi et al., J Cell Sci 126, 966 (2013)
* Y. Oda, et al., J Cell Sci 127, 4201 (2014)
* Y. Izumi and M. Furuse, Semin Cell Dev Biol 36, 186 (2014)
* T. Higashi et al., PLoS ONE 10: e0120674 (2015)

Morphology and molecular architecture of tricellular tight junctions. A. A freeze-fracture electron micrograph of tricellular tight junctions in mouse intestinal epithelial cells. B. A model of the molecular organization of tricellular tight junctions. C. Localization of angulin-1/LSR (green) and occludin (red) in a frozen section of the mouse epididymis by immunofluorescence staining.



# Division of Cell Signaling

## Department of Biosensing Research, Okazaki Institute for Integrative Bioscience


TOMINAGA, Makoto
Professor
Molecular and Cellular Physiology

OKADA, Toshiaki
Project Associate Professor
Molecular and Cellular Physiology

SUZUKI, Yoshiro
Assistant Professor
Molecular and Cellular Physiology

SAITO, Shigeru
Assistant Professor
Evolutionary Physiology
Molecular Evolution

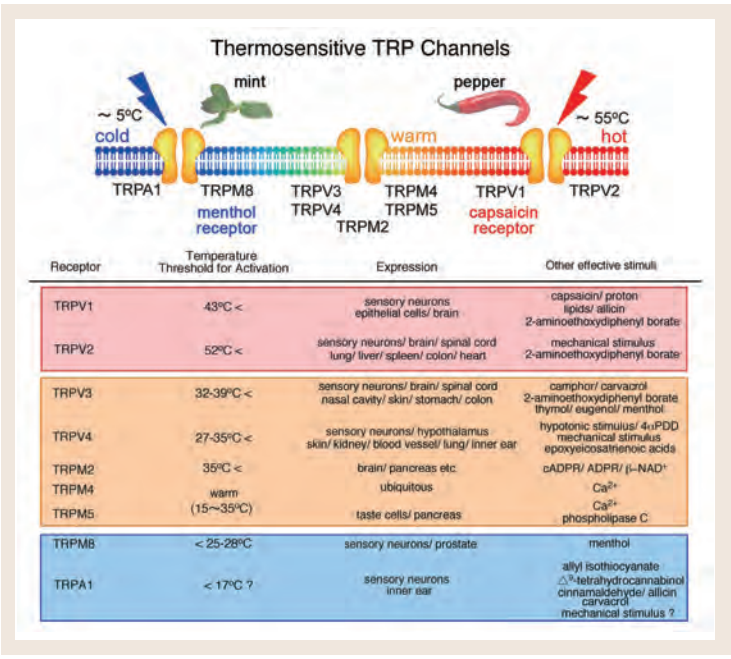
UCHIDA, Kunitoshi
Assistant Professor
Molecular and Cellular Physiology

TAKAYAMA, Yasunori
Project Assistant Professor
(Grant Project)
Molecular and Cellular Physiology


### Molecular Mechanisms of thermosensation and nociception

We mainly investigate molecular mechanisms of thermosensation and nociception by focusing on so called 'thermosensitive TRP channels'. Among the huge TRP ion channel superfamily proteins, there are nine thermosensitive TRP channels in mammals (TRPV1, TRPV2, TRPV3, TRPV4, TRPM2, TRPM4, TRPM5, TRPM8, TRPA1) whose temperature thresholds for activation range from cold to hot. Because temperatures below 15oC and over 43oC are known to cause pain sensation in our body, some of the thermosensitive TRP channels whose temperature thresholds are in the range can be viewed as nociceptive receptors. Indeed, TRPV1 and TRPA1 are activated by various nociceptive stimuli including chemical compounds causing pain sensation. Some of the thermosensitive TRP channels are expressed in the organs or cells which are normally not exposed to the dynamic temperature changes. We found that they contribute to the various cell functions under the body temperature conditions in the normal to febrile range. In addition, thermosensitive TRP channels expressed in the skin were found to detect the ambient temperature and transmit the temperature information to sensory neurons with ATP. Molecular and cell biological, biochemical, developmental and electrophysiological (patch-clamp and calcium-imaging methods) techniques are utilized to clarify the molecular mechanisms of thermosensation and nociception. In order to understand functions of thermosensitive TRP channels in vivo, we are also doing behavioral analyses using mice lacking the thermosensitive TRP channels. In the evolutionary process, organisms are thought to have adapted the changes in ambient temperature by altering the expression and functions of the thermosensitive TRP channels. Accordingly, we are characterizing the thermosensitive TRP channels from various species, which would help us to understand the mechanisms of thermosensation.


* Modulation of water efflux through functional interaction between TRPV4 and TMEM16A/anoctamin 1. FASEB J. 28: 2238-2248, 2014.
* Heat and noxious chemical sensor, chicken TRPA1, as a target of bird repellents and identification of its structural determinants by multispecies functional comparison. Molec. Biol. Evol. 31: 708-722, 2014.
* Identification of a splice variant of mouse TRPA1 that regulates TRPA1 activity. Nat. Commun. 4:2408, 2013.


Temperature thresholds, expression and properties of nine thermosensitive TRP channels

# Division of Cardiocirculatory Signaling

## Department of Biodesign Research, Okazaki Institute for Integrative Bioscience


NISHIDA, Motohiro
Professor
Cardiovascular Physiology

NUMAGA-TOMITA, Takuro
Assistant Professor
Molecular and Cellular Physiology

NISHIMURA, Akiyuki
Project Assistant Professor
Biochemistry

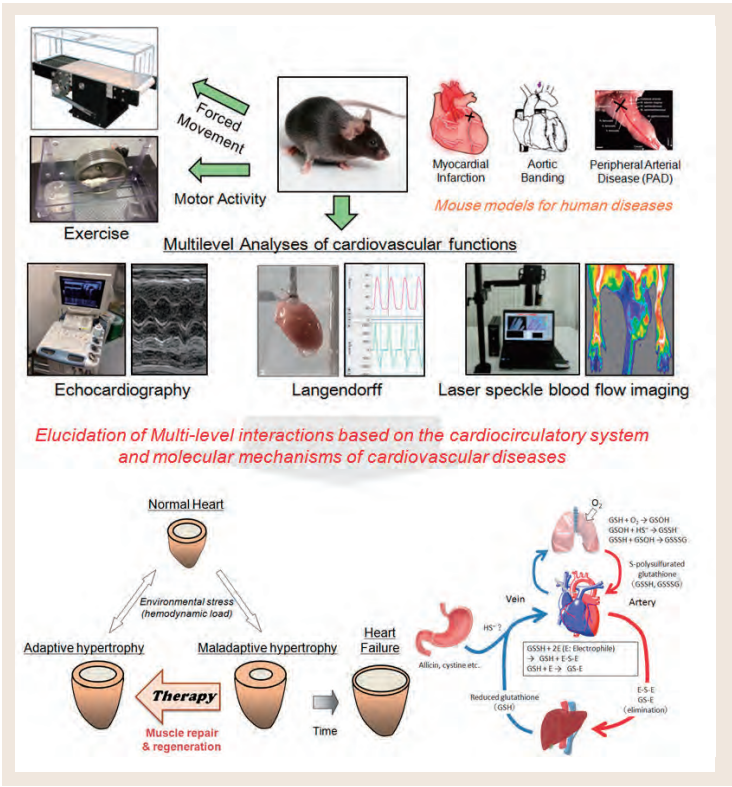

### Elucidation of biological functions using multilevel techniques to evaluate cardiovascular functions and its clinical application

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

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

1. Non-invasive measurements of muscular functions
   Echo-cardiography (mouse and rat), Laser Doppler flowmetry (mouse), Measuring devices of motor activity and forced movement (mouse), Tail-cuff (mouse and rat), blood pressure telementry (mouse)
2. Invasive measurements of cardiovascular functions
   Langendorff perfusion system (mouse and rat), Mouse millar catheter (for P-V loop measurement)
3. Isolation of primary-cultured cells and experiments
   mechanical stretching machine, $Ca^{2+}$ imaging, FRET imaging, Confocal laser microscopy, Patch-clamp recording, Plate reader (BRET assay, post-translational modification analyses)

Figure. Measuring systems for cardiovascualr functions and summary of our research using these systems




# Division of Endocrinology and Metabolism

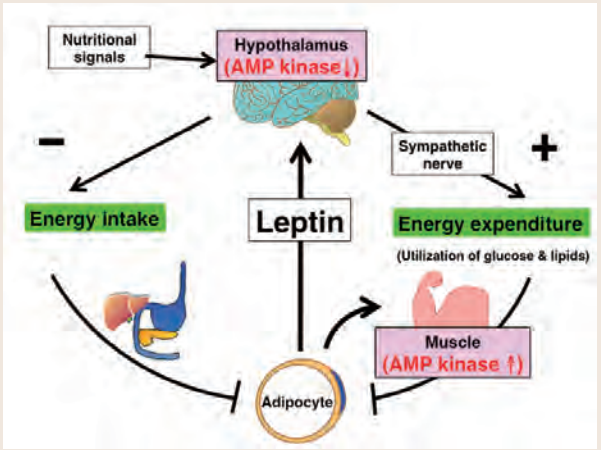
MINOKOSHI, Yasuhiko
Professor
Endocrinology and Metabolism

OKAMOTO, Shiki
Assistant Professor
Neuroimmunology
Stem Cell biology

## Molecular mechanism for the hypothalamic regulation of whole body energy metabolism
## Physiological and pathophysiological roles of AMPK in whole body metabolism

The animal body has an integrated-regulatory system for "homeostasis" that maintains a normal, constant internal state by responding to changes in both the external and internal environments. Within the central nervous system, the hypothalamus is a crucial center that regulates the homeostatic activities by integrating autonomic nervous system, endocrine system and immune function. This division is intensively investigating the role of hypothalamus in body energy balance in mammals. These studies are now important for better understanding the molecular mechanisms behind pathophysiology of obesity and diabetes mellitus. The main subjects of our current research are as follows:

(1) Molecular mechanism of the hypothalamic regulation of food intake and glucose and lipid metabolism.
(2) Signaling pathway for metabolic action of leptin and adipokines.
(3) Physiological and pathophysiological roles of AMPK in whole body metabolism.
(4) Development of novel analytical method for glucose and lipid metabolism.




＊Y. Minokoshi, et al., Nature 415, 339, 2002
＊Y. Minokoshi, et al., Nature 428, 569, 2004.
＊T. Shiuchi, et al., Cell Metab 10, 466, 2009.
＊C. Toda, et al., Diabetes 62, 2295, 2013.
＊L. Tang, et al., Endocrinology 156, 3680, 2015.

Fig.1 Leptin controls body energy metabolism by reciprocally regulating AMP kinase in the hypothalamus and skeletal muscle.
Leptin activates AMP kinase (AMPK) in skeletal muscle directly at the muscle level and indirectly through the hypothalamic-sympathetic nervous system. Leptin also inhibits food intake by suppressing AMPK activity in the hypothalamus. Reciprocal regualtion of AMPK activity in the hypothalamus and skeletal muscle is necessary for the leptin's effect on energy metabolism. We are studying the molecular mechanism for the reciprocal regulation of AMPK activity in the hypothalamus and skeletal muscle.

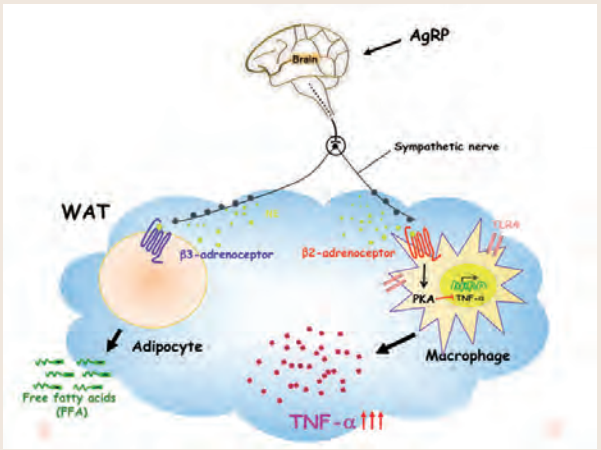



Fig.2 Sympathetic nerve activity maintains an anti-inflammatory state in adipose tissue in mice byinhibiting TNF-α gene expression in macrophages.
Adipose tissue macrophages (ATMs) play an important role in the inflammatory response in animals. We found that brain AgRP and sympathetic nervous system (SNS) are necessary to maintain the abundance of the mRNA for the proinflammatory cytokine TNF-α at a low level in ATMs of lean mice.

# Division of Neural Signaling

FURUE, Hidemasa
Associate Professor
Neurophysiology

YAMAGATA, Yoko
Assistant Professor
Neurochemistry
Neuroscience

SATAKE, Shinichiro
Assistant Professor
Neurophysiology

## Electrophysiological analysis of mechanisms underlying the neural information processing in the central nervous system

## Comprehensive study of genetically-modified pathological model animals

Using electrophysiological techniques (e.g. patch clamp recordings *in vivo* and brain/spinal cord slices *in vitro*) our laboratory focuses on the molecular and cellular mechanisms underlying the transduction and integration of neural information in local networks. We combine the use of genetically-modified animals with electrophysiological, biochemical and behavioral approaches to uncover the molecular basis of pathophysiological symptoms such as deficits in learning and memory. Recently, we have begun to use photo-release/optogenetic tools and computational methods. The following are currently ongoing projects.

(1) *In vivo* patch-clamp recording analysis of spinal synaptic responses elicited by optogenetic activation of locus coeruleus neurons (Fig. 1A)
(2) Analyses of nociceptive transmission and autonomic control of the lower urinary tract[1,2]
(3) Transmitter diffusion-dependent inter-synaptic crosstalk: Role of glia and transporters[3] (Fig. 1B)
(4) Computational simulation of neuronal network function
(5) Molecular basis of memory: Behavioral analysis of learning and memory using genetically modified mice[4] (Fig. 1C)
(6) Mechanisms underlying the diseases of the nervous system

* 1. D. Sugiyama *et al., J. Physiol.* **590**, 2225 (2012).
* 2. Y. Funai *et al., Pain* **155**, 617 (2014).
* 3. S. Satake, K. Imoto, *J. Neurosci.* **34**, 1462 (2014).
* 4. Y. Yamagata *et al., J. Neurosci.* **29**, 7607 (2009).

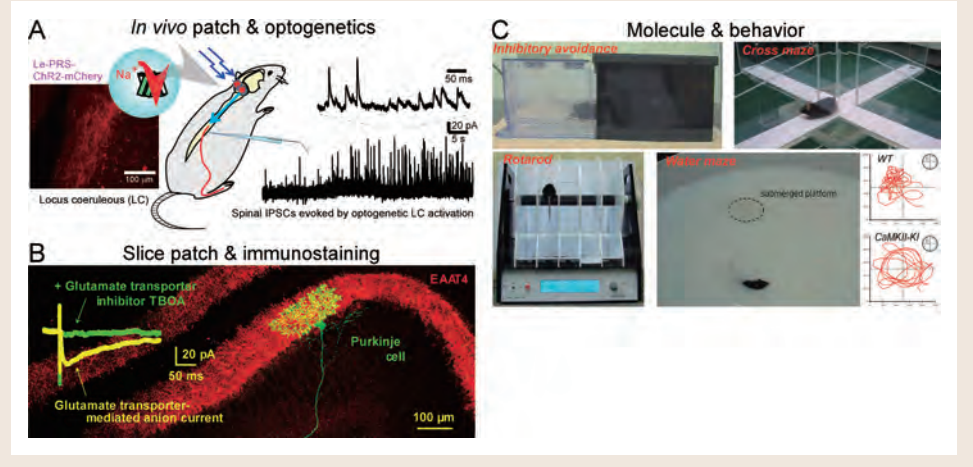
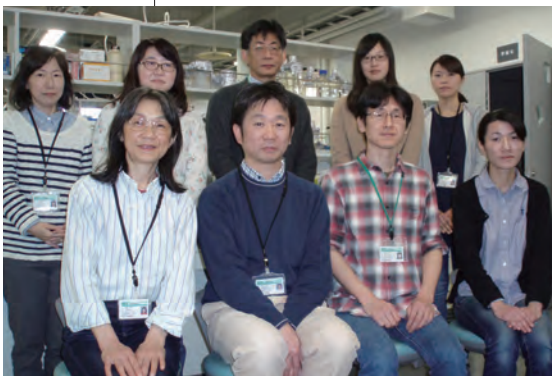



Fig. 1. Multilevel studies of the mechanisms underlying information processing in neural networks from the molecular level to whole animal physiology



# Division of Cerebral Circuitry

KAWAGUCHI, Yasuo
Professor
Neuroscience

KUBOTA, Yoshiyuki
Associate Professor
Neuroanatomy
Neuroscience

OTSUKA, Takeshi
Assistant Professor
Neuroscience

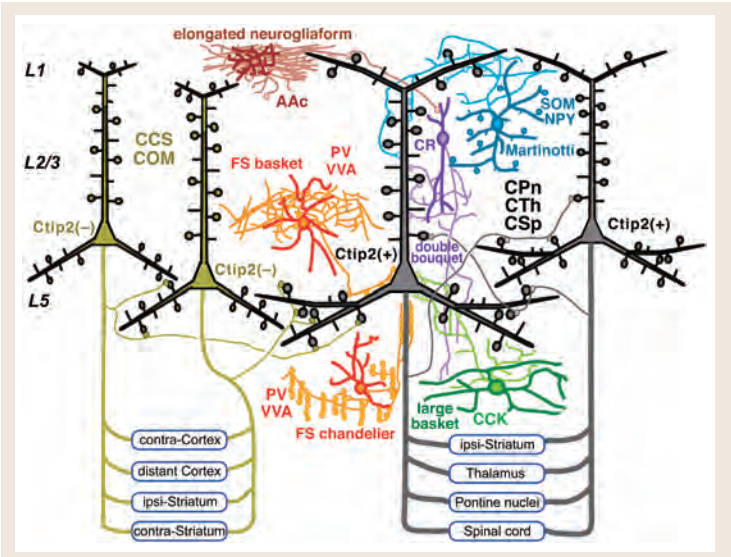
MORISHIMA, Mieko
Assistant Professor
Neuroscience

## Characterizing the neuronal organization and synaptic structure of the neocortex

## Mapping the micro- and macro-circuitry of the neocortex

The neocortex, especially the frontal cortex, is particularly interconnected with almost all other brain areas. Although early anatomical work revealed that cortical neurons are very diverse in their morphologies, a comprehensive understanding of neocortical structure has remained elusive. Cortical neurons are divided into excitatory glutamatergic pyramidal cells and inhibitory GABAergic cells. We first identified a subtype of GABAergic neuron called 'fast-spiking basket cells' based on their axonal morphology and selective expression of the calcium-binding protein 'parvalbumin'. Since then, we have identified many additional subtypes of cortical GABAergic cells by examination of their morphological, physiological, and chemical properties. We have followed this up by investigating their synaptic structures with pyramidal cells. Our findings have provided a framework for analysis of the structure and function of neocortical circuits under normal as well as pathological conditions. In addition to the GABAergic cells, we are now also investigating the organization and connectivity of cortical pyramidal cells projecting to diverse brain areas. Once we establish the organization of pyramidal and GABAergic cells in the neocortex, we would like to identify the developmental mechanisms that drive their differentiation and selective synaptic connectivity. To do this, we are using anatomical, molecular, and developmental techniques for identification of neocortical neuron groups, and electrophysiology and electron microscopy for circuit and synaptic transmission analysis. Our hope is that this new knowledge will provide insights into the function of the neocortex, as well as identify changes in cellular and circuit function that contribute to neurological and psychiatric disease.

* Y. Ueta et al., Cereb Cortex 24, 2362 (2014)
* M. Ushimaru and Y. Kawaguchi, J Neurosci 35, 11988 (2015)
* Y. Kubota et al., eLife 2015;10.7554/eLife.07919 (2015)




Basic subtypes and connections of GABA cells and layer 5 pyramidal cells in the frontal cortex. Molecules expressed in GABA cells: AAc, alpha-actinin-2; CCK, cholecystokinin; CR, calretinin; NPY neuropeptide Y; PV, parvalbumin; SOM, somatostatin; VVA, binding with *Vicia villosa*. Pyramidal cell groups: CCS, crossed-corticostriatal cell; COM, commissural cell; CPn, corticopontine cell; CTh, corticothalamic cell; CSp, corticospinal cell.

# Division of Homeostatic Development

NABEKURA, Junichi
Professor
Neuroscience

WAKE, Hiroaki
Professor
Neuroscience

ETO, Kei
Assistant Professor
Neuroscience

INADA, Hiroyuki
Project Assistant Professor
Neuroscience

## Remodeling of Neuronal Circuits in Development and Recovery, — *In vivo* Imaging — Remodeling of inhibitory neuronal circuits in development

Remodeling of neuronal circuits takes place during development, learning and recovery after brain damage. The main goal of our research is to understand the regulation of neural circuits remodeling. In details, we are focusing on

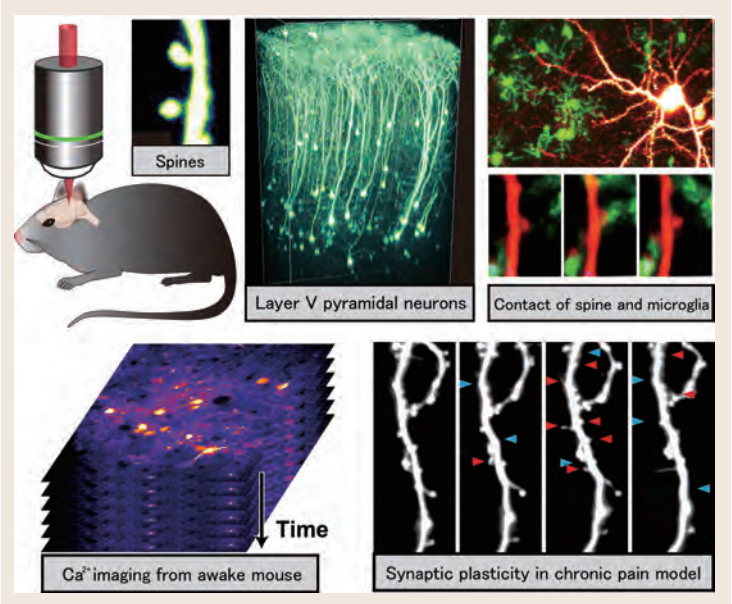
1. Glial contribution for the function of neuronal circuits.
2. Dynamic changes of GABA transmission.

Glia has been known as a key factor to regulate neural circuits through their physiological function. We are trying to determine their contribution onto the neural circuits in development and learning by visualizing fine structure, function of neuron and glia in living animals using multi-photon microscopy.

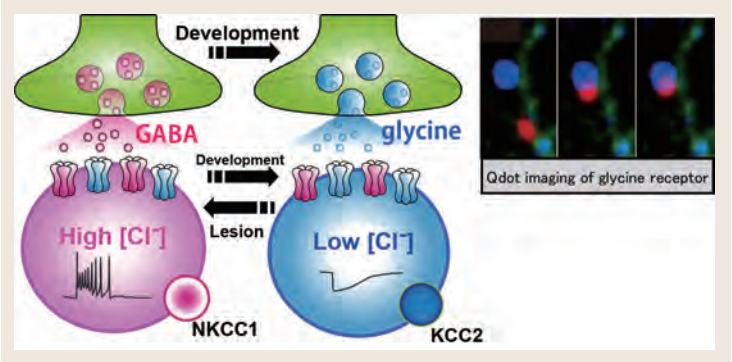
In addition, we also focus on the plastic change of GABA/glycine in development, e.g. GABA excitation-inhibition switch driven by a developmental expression of $Cl^-$ transporters, and its functional relevance to circuits development. The receptor dynamics associated with inhibitory transmitter has been investigated with an advanced single molecule-imaging.

* K. Eto et al., J. Neurosci. 32, 6552 (2012)
* H. Wake et al., Trends Neurosci. 36, 209 (2013)

Research of neuronal/glial remodeling by 2-photon *in vivo* imaging




Research of GABA/glicinergic circuits remodeling by electrophysiological and singl molecule imaging techniques




# Division of Visual Information Processing

YOSHIMURA, Yumiko
Professor
Neurophysiology

ISHIKAWA, Ayako
Assistant Professor
Neurophysiology

MIYASHITA, Toshio
Project Assistant Professor
Neuroscience

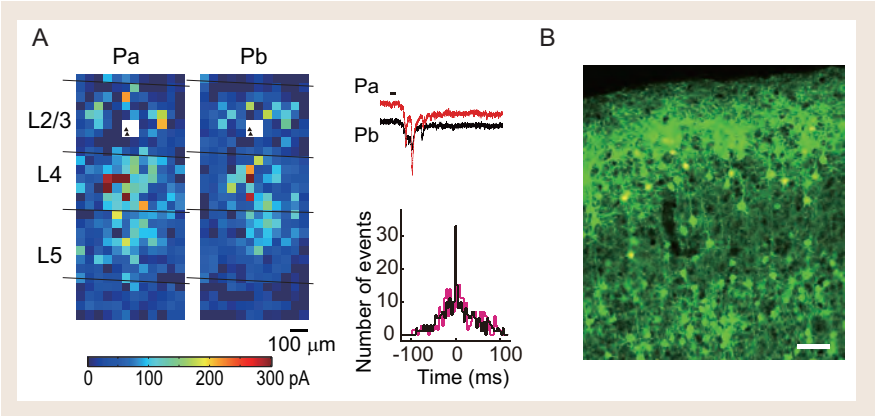
KIMURA, Rie
Project Assistant Professor
Neurophysiology

## Analysis of mechanisms underlying information processing and experience-dependent functional developments in neocortex

To elucidate the mechanisms underlying information processing in sensory cortex and the experience-dependent regulation of that processing, we are studying the relationship between visual functions and the signaling properties of neural circuits using rat and mouse visual cortex. We are also examining the development of neural circuits and functions based on neural activity or synaptic target recognition using specific molecules. To this end, we are analyzing the visual responses of cortical neurons using multi-channel electrodes or calcium imaging with 2-photon microscopy, neural circuit properties with a combination of laser scanning photostimulation and whole-cell recording methods in slice preparations, and neural connections morphologically using modern virus tracers. The following is a list of our main projects currently ongoing, including collaborative projects with researchers belonging to research organizations other than our institute.

1. The mechanisms that establish fine-scale networks in visual cortex and the role of these networks in visual information processing
2. Cell-lineage dependent establishment of neural connections and visual responsiveness
3. Synaptic plasticity and visual response plasticity in animals at different developmental stages and in animals subjected to the manipulation of visual inputs during postnatal development
4. Morphological analysis of neural circuits using trans-synaptic virus tracers
5. Neural activities in visual and motor cortex underlying visual cue-triggered behavioral tasks

* Ishikawa, A.W., Komatsu, Y., Yoshimura, Y. (2014) Experience-dependent emergence of fine-scale networks in visual cortex. J Neurosci. 34:12576-86




Electriphysiological and morphological analyses of cortical neural circuits
A. Cross-correlation analysis of photostimulation-evoked excitatory postsynaptic currents (EPSCs) simultaneously recorded from a pair of layer 2/3 pyramidal neurons that were synaptically connected. B. Visualization of neural circuits using a trans-synaptic virus tracer. Presynaptic neurons (green) providing synaptic inputs to some layer 2/3 pyramidal neurons (yellow) in neocortex.

# Division of Sensory and Cognitive Information

KOMATSU, Hidehiko
Professor
Neurophysiology

GODA, Naokazu
Assistant Professor
Visual Psychophysics
Neurophysiology

YOKOI, Isao
Assistant Professor
Neurophysiology

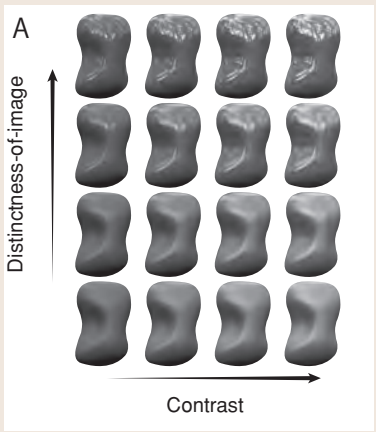
SANADA, Takahisa
Project Assistant Professor
Neurophysiology

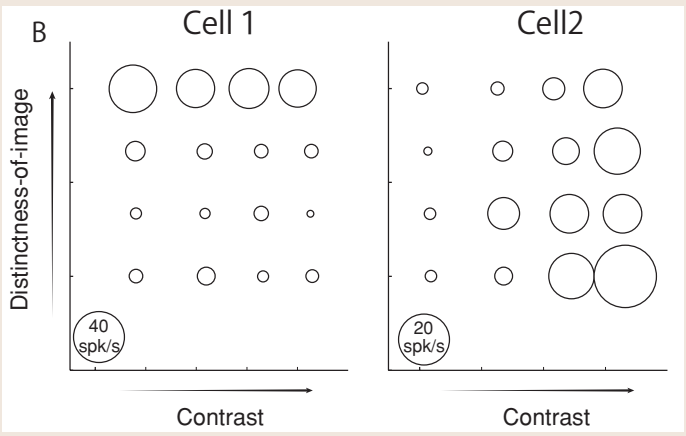
## Neural mechanisms of visual perception and cognition

The main purpose of this division is to study the neural mechanisms of visual perception and cognition. To understand the neural substrates of these abilities in our visual system, we are recording neuronal activities from the visual cortical areas of monkeys. We are analyzing the stimulus selectivity of neurons to determine the representation of various kinds of visual features, and their relationships to the perception and cognitive behaviors. We are also using functional magnetic resonance imaging (fMRI) in awake monkeys and humans to study brain activities evoked by visual stimuli and to analyze how various cortical areas encode stimulus information. In addition, to explore the ways in which various visual features contribute to visual perception, psychophysical experiments are conducted in this laboratory. We are mainly targeting higher visual areas, but we also target other areas when needed. Main themes of our recent research include color information processing and neural representation related to Shitsukan (perception of material and surface quality). With regard to the color processing, our main topic is to study functional organization of the inferior temporal cortex of the macaque in relation to color vision and the correlation between neuron activities and color perception. With regard to the Shitsukan research, we are analyzing brain activities related to gloss perception as well as those related to visual discrimination of materials. So far, we found neurons distinguishing a variety of gloss in the inferior temporal cortex of the macaque monkey, and precise nature of the information carried by these neurons. With regard to the material perception, we found that visual discrimination of mateirals is carried out mainly along the ventral visual pathway in both humans and macaque monkeys by using fMRI techniques.

* G. Okazawa, N. Goda, H. Komatsu, Neuroimage, 63,1321-1333 (2012).
* N. Goda, A. Tachibana, G. Okazawa, H. Komatsu H, J Neurosci, 34, 2660-2673 (2014).
* A. Nishio, T. Shimokawa, N. Goda, H. Komatsu, J Neurosci, 34,11143-11151 (2014).
* T. Namima, M. Yasuda, T. Banno, H. Komatsu, J Neurosci, 34,14934-14947 (2014).
* G. Okazawa, S. Tajima, H. Komatsu, Proc Natl Acad Sci USA 112 : E351-360, (2015)

Neuron activities recorded from the inferior temporal cortex of the monkey that were selective for gloss of objects. (A) Examples of stimuli to test gloss selectivity. Stimuli were generated by varying the contrast and sharpness of highlight. (B) Activities of two examples of gloss-selective neurons. They selectively responded to the change in the sharpness (left) and contrast (right) of highlight, respectively.




# Division of Behavioral Development（Isa Group）

ISA, Tadashi
Professor
Neurophysiology

NISHIMURA, Yukio
Associate Professor
Neuroscience

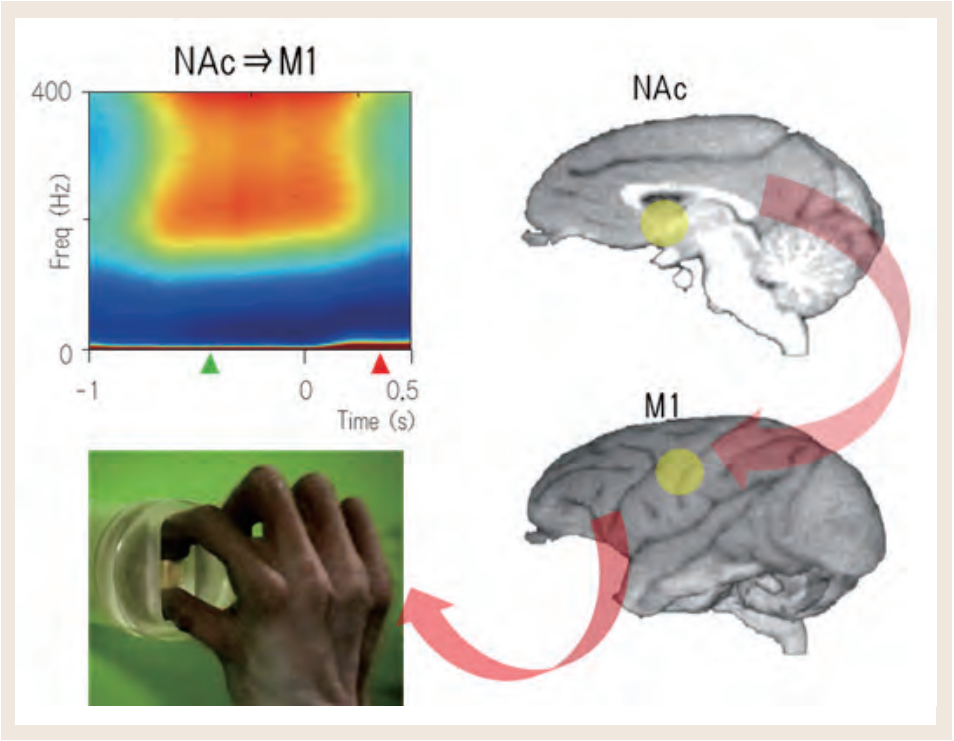
## Neural control of hand movements and functional recovery after brain/spinal cord injury

## Local circuits of the superior colliculus and neural mechanism of blindsight

Dexterous hand movements are supposed to be controlled by the corticospinal tract（CST）, which directly connects with spinal motor neurons. However, we have recently shown that the CST indirectly controls the activity of motoneurons also via indirect pathways, mediated by the propriospinal neurons (PNs) and that the PNs are responsible for the normal hand movements and functional recovery by a new technique of pathway-selective blockade with viral vectors in monkeys. Moreover, we are developing the brain computer interfaces with the concept of "artificial neural connection" to enable the subject with brain/spinal cord injury to control their own hands. In addition, we are also studying the neural mechanism of blindsight using monkeys with lesion of V1 by combining electrophysiology, brain imaging and psychophysics. We also study the local

circuit of the superior colliculus (SC), which plays a pivotal role in the control of attention and saccadic eye movements, especially in the blindsight, by adopting the electrophysiology in rodent SC slices preparations and imaging with 2-photon laser scanning microscope in vivo.

* Sawada et el Science2015




The NAc up-regulates the high-frequency activity of the motor cortex and is directly involved in the control of finger movements after spinal cord lesion.

# Division of Behavioral Development（Isoda Group）

ISODA, Masaki
Professor
Neurophysiology

GO, Yasuhiro
Project Associate Professor
Comparateive Genomics
Neurogenomics

YOSHIDA, Masatoshi
Assistant Professor
Cognitive Neuroscience
Neurophysiology

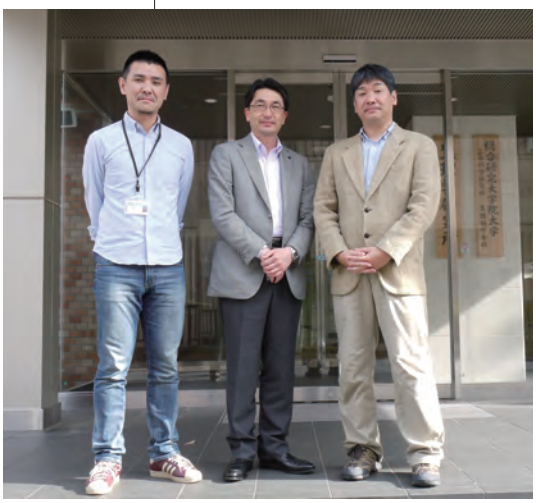
## Physiological understanding of social cognitive functions

## Neural mechanism of blindsight

In order to understand neural mechanisms underlying social cognition at the cellular and network levels, we have developed novel, experimental paradigms in which two monkeys monitor each other's behavior for making their own decisions, while activity of individual neurons is recorded from various brain regions. Our data suggest that the primate brain contains dedicated circuits for processing behavioral information about the self and others.

We are also interested in the neural mechanism underlying blindsight, i.e., a phenomenon known as "vision without awareness." Using monkeys with lesion of the primary visual cortex, we have carried out multidimensional analyses combining psychophysics, electrophysiology, and brain imaging.

* Yoshida K et al. (2011) Curr Biol, 21: 249-253.
* Yoshida K et al. (2012) Nat Neurosci, 15: 1307-1312.
* Yoshida M et al. (2012) Curr Biol, 22: 1429-1434.
* Yoshida M et al. (2015) Sci Rep, 5:10755.



# Division of System Neurophysiology

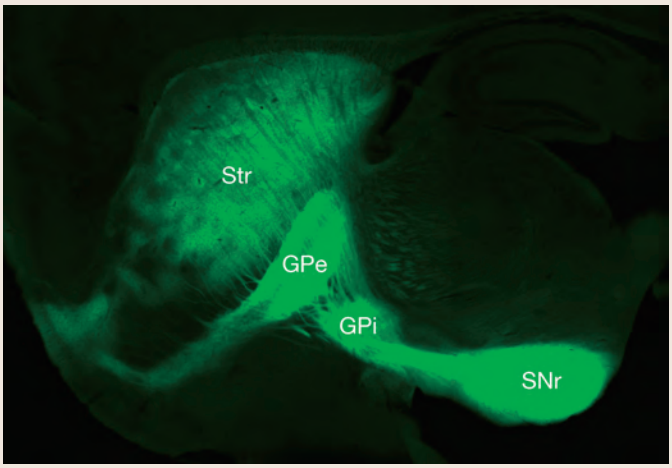
## Mechanism of voluntary movements
## Pathophysiology of movement disorders

The brain areas, such as the cerebral cortex, basal ganglia and cerebellum, play a major role in controlling voluntary movements. On the other hand, malfunctions of these structures result in movement disorders, such as Parkinson's disease and dystonia. The major goal of our research project is to elucidate the mechanisms underlying higher motor functions and the pathophysiology of movement disorders. To explore such intricate brain functions, we apply a wide range of neurophysiological and neuroanatomical techniques to rodents and subhuman primates.

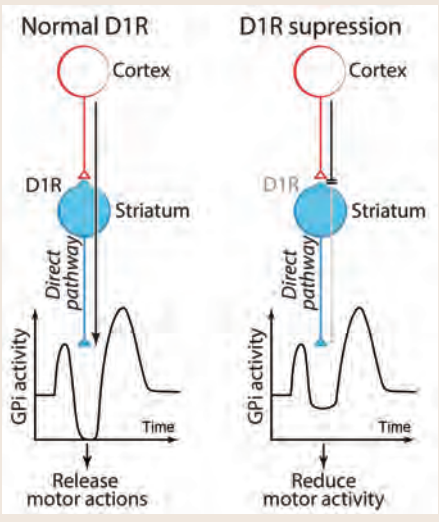
The current topics under study are as follows:

1) Elucidation of information flows through the neuronal networks by electrophysiological and anatomical methods.
2) Understanding the mechanism how the brain controls voluntary movements and higher brain functions by electrophysiological recordings of neuronal activity from animals performing motor tasks, combined with local injection of neuronal blockers or optogenetics.
3) Elucidation of the pathophysiology of movement disorders by applying electrophysiological methods to animal models.


* S. Takara, N. Hatanaka, M. Takada, A. Nambu, *J. Neurophysiol.* **106**, 1203 (2011).
* S. Chiken et al., *Cereb Cortex* **25**: 4885-4897 (2015).
* H. Sano, H. Murata, A. Nambu, *J Neurochemi* **134**: 371-381 (2015).


A sagittal section of the mouse brain showing selective expression of channelrhodopsin-2 (C128S) in striatal projection neurons as visualized by enhanced yellow fluorescent protein signals. Strong fluorescence was observed in the striatum (Str) as well as the its targets, such as the external (GPe) and internal (GPi) segments of the globus pallidus and the substantia nigra pars reticulata (SNr).




Functions of dopamine D1 receptors (D1R) reveled by conditional D1R knock-down mice. Under normal D1R expression (left), signals through the cortico-striato-GPi *direct* pathway induce inhibition in the GPi and release motor actions by disinhibiting the thalamus. During D1R suppression (right), the information flow through the *direct* pathway is strongly suppressed and fails to induce inhibition in the GPi, resulting in the reduced motor activity. GPi, internal segment of the globus pallidus.


NAMBU, Atsushi
Professor
Neurophysiology

HATANAKA, Nobuhiko
Assistant Professor
Neurophysiology
Neuroanatomy

CHIKEN, Satomi
Assistant Professor
Neurophysiology
Neurobiology

SANO, Hiromi
Assistant Professor
Molecular Neurobiology

KONDO, Hideki
Project Assistant Professor
(Grant Project)
Neuroanatomy
Neuroscience

# Division of Integrative Physiology


KAKIGI, Ryusuke
Professor
Neurophysiology

INUI, Koji
Associate Professor
Neurophysiology
Psychiatry

OKAMOTO, Hidehiko
Associate Professor
Neuroscience
Auditory Neurophysiology

KIDA, Tetsuo
Project Associate Professor
(Grant Project)
Cognitive Neuroscience
Exercise Physiology
Psychophysiology

SAKAMOTO, Kiwako
Assistant Professor
Neurophysiology


## Non-invasive measurement of human brain function

We investigate human brain functions non-invasively mainly using magnetoencephalography (MEG) and electroencephalography (EEG), but recently we have also used functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS) and near-infrared spectroscopy (NIRS). Integrative studies using various methods are necessary to understand the advantages and disadvantages of each method.

(1) By recording brain responses to noxious stimuli using MEG and EEG, sensory processing in the nociceptive system is being investigated. For noxious stimulation, intra-epidermal electrical stimulation, which was developed in our department, is used.

(2) We newly developed an electrical stimulus method to cause itch sensation. It is very useful to investigate itch perception in humans, and we have reported many new findings using this method (Fig.1).

(3) Auditory system: We are investigating the neural mechanisms of auditory perception in normal and hearing impaired people by measuring the brain activity. We are conducting joint researches to establish a new treatment strategy against hearing disorders such as tinnitus and sudden hearing loss (Fig. 2).

* H. Mochizuki et al., *J Neurophysiol* 111,488 (2014)
* H. Okamoto et al., *Sci Rep* 4, e3927 (2014)

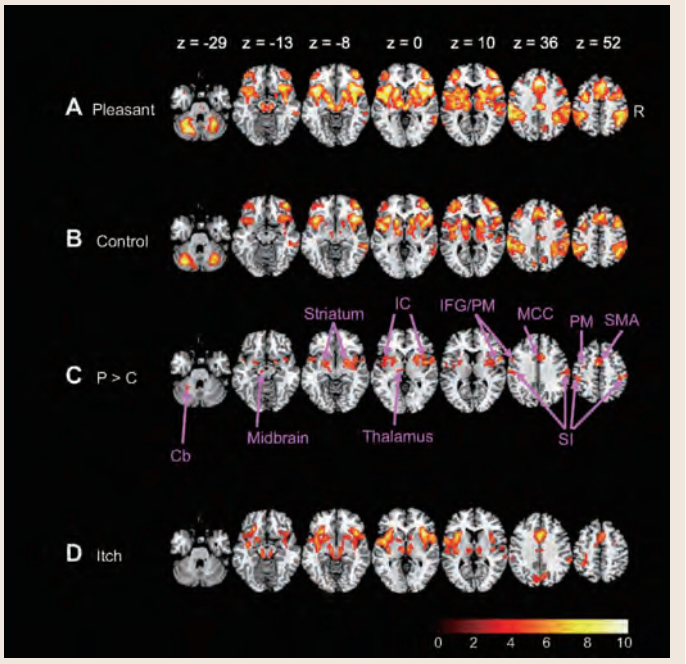



Figure 1. Brain activation during scratching and itch stimuli. *A* and *B*: brain regions significantly activated while scratching stimuli were applied in the pleasant (*A*) and control (*B*) conditions. R, right hemisphere. *C*: brain regions that showed significantly higher activity in the pleasant condition compared with the control condition within the brain regions significantly activated in the pleasant condition. *D*: brain regions significantly activated during itch stimuli. P > C, pleasant > control; Cb, cerebellum; IC, insular cortex; IFG, inferior frontal gyrus; PM, premotor cortex; MCC, medial cingulate cortex; SMA, supplementary motor area; S1, primary somatosensory cortex.
(Mochizuki et al. J Neurophysiol 111:488-498, 2014)

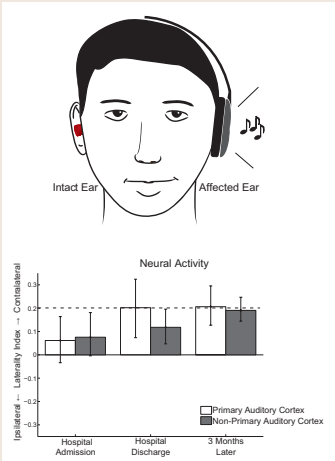



Figure 2. The canal of the intact ear was plugged. Sounds were only presented to the affected ear (upper panel). The auditory responses demonstrated the small laterality indices at entering hospital but became almost normal (= 0.2) at three months after discharge (lower panel). (Okamoto et al. *Sci Rep* 4, e3927, 2014)

# Division of Cerebral Integration

## Studies on Higher Function in Human Brain Using Neuroimaging Techniques

The goal of Division of Cerebral Integration is to understand the physiology of human voluntary movement and other mental processing including language and social interaction using noninvasive functional neuroimaging technique, mainly fMRI. In particular, neural mechanisms of the social interaction is the main interest is the main focus of our research activities. Hyper-scanning fMRI (3T) has been installed to evaluate two individuals as one neural network during social interaction, and 7T MRI is now being installed to evaluate the detailed structures of the neural network . Multimodal approach including EEG , MEG , TMS , and NIR is considered when appropriate.

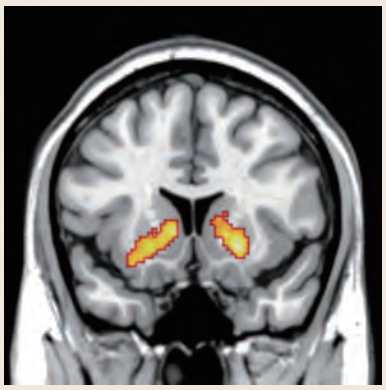


Figure 1. Brain areas commonly activated by social and monetary rewards. Why are we nice to others? One answer provided by social psychologists is because it pays off. A social psychological theory stated that we do something nice to others for a good reputation or social approval just like we work for salary. Although this theory assumed that social reward of a good reputation has the same reward value as money, it was unknown whether it recruits the same reward circuitry as money in human brain. In this study, we found neural evidence that perceiving one's good reputation formed by others activated the striatum, the brain's reward system, in a similar manner to monetary reward. Considering a pivotal role played by a good reputation in social interactions, this study provides an important first step toward neural explanation for our everyday social behaviors.

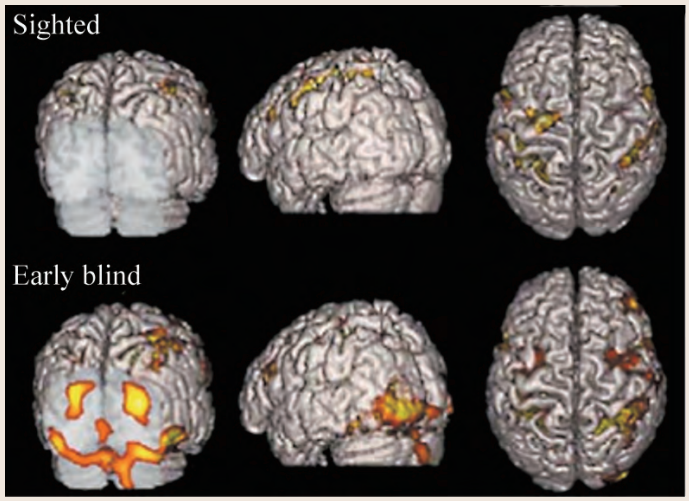



Figure 2. Activation in a sighted (upper row) and blind subject (bottom row) during tactile discrimination tasks similar to reading Braille. The primary and association visual cortices of the blind are activated bilaterally (bottom row) whereas no such activation in the sighted. Only pixels with significant increase in cerebral blood flow during the task were superimposed on surface-rendered high resolution MRI. This is an example of cross-modal plasticity of human brain due to early visual deafferentation and/or long-term training of Braille reading. Depicted by functional MRI using high Tesla (3T) machine.

SADATO, Norihiro
Professor
Functional Neuroimaging
Neuroscience

FUKUNAGA, Masaki
Associate Professor
Magnetic Resonance
Neuroimaging
Neuroscience

KITADA, Ryo
Assistant Professor
Cognitive Brain Science
Psychophysics

HARADA, Tokiko
Project Assistant Professor
Cognitive Neuroscience

KOIKE, Takahiko
Project Assistant Professor
(Grant Project)
EEG-fMRI Recording
Neural Network Modeling

* R. Kitada et al., J Neurosci 34, 10096 (2014).
* H. C. Tanabe et al., Front Hum Neurosci 6, 268 (2012).
* D. N. Saito et al., Front Integr Neurosci 4, 127 (2010).
* K. Izuma, D. N. Saito, N. Sadato, Neuron 58, 284 (2008).
* N. Sadato et al., Neuroimage 16, 389 (2002).

# Individual Researches

MURAKAMI, Masataka
Associate Professor
Physiology of Exocrine Glands
Energy Metabolism and Transport of Electrolyte and Water
Paracellular Transport

## Morpho-physiological basis of paracellular transport in exocrine glands

Murakami's group estimated the size of paracellular route①, and that the transcellular fluid secretion is dominant within 30 sec of stimulation, and that the paracellular fluid transport is more than 60% of whole secretion during sustained stimulation, using isolated perfused salivary gland②. This group is now going on confocal microscopic observation of paracellular transport of fluorescent dye and electron microscopic 3D observation of tight junction, to clarify the control of tight junction.

*① J Physiol 537: 899-906, 2001.
*② Eur J Molphol 40: 241-246, 2002.
*③日本生理誌 76: 43-57, 2014
*④日本唾誌 55: 19-19, 2014
*⑤日本歯科評論 75: 135-142, 2015

# Individual Researches

OHASHI, Masato
Assistant Professor
Molecular Cell Biology
Biochemistry
Developmental Biology

## The roles and mechanisms of membrane traffic

Not only does membrane traffic perform intracellular cargo logistics, but it also works as a dynamic integration system of cellular signaling in various physiological aspects including developmental regulation. We currently study the roles and the mechanisms of membrane traffic in developmental morphogenesis, the main theme being the mechanisms of planar cell polarity (PCP) formation. In developmental tissue morphogenesis, membrane traffic may work as an interface for integrating spatiotemporal information, between the intracellular level and the tissue level.

* R. H. K. Lee et al., XRab40 and XCullin5 form a ubiquitin ligase complex essential for the noncanonical Wnt pathway. EMBO J. 26, 3592-3606. (2007).
* I. Miwako, A. Yamamoto, T. Kitamura, K. Nagayama, M. Ohashi, Cholesterol requirement for cation-independent mannose 6-phosphate receptor exit from multivesicular late endosomes to the Golgi. J. Cell Sci. 114, 1765-1776 (2001).
* M. Ohashi et al., A role for phosphatidylinositol transfer protein in secretory vesicle formation. Nature 377, 544-547 (1995).

# Individual Researches

## Study on the mechanism of fertilization, egg activation, and oocyte maturation

MOHRI, Tatsuma
Assistant Professor
Cell Biology
Cell Physiology

Fertilization is a pivotal event that the sperm approaches, enters, and activates the egg. In many organisms, it is extremely important phenomenon that brings a new generation. However, the physiological molecular mechanism of fertilization or egg activation is still unsolved. Thus, it is not clear how sperm approaches, activates the egg, and invades or enters the egg. Furthermore, how oocytes mature and acquire the competence of fertilization remains unclear. I have been studied changes in intracellular $Ca^{2+}$ ($[Ca^{2+}]_i$), nitric oxide, $Zn^{2+}$, and organelles at fertilization using eggs of sea urchin and mice. I am presently studying the electrical changes in the egg membrane, the intracellular $[Ca^{2+}]_i$, the sperm entry, and those relationships among them in echinoderm oocytes such as sea urchins and starfishes using the techniques of Ca-imaging and the single electrode switched voltage clamp method. Furthermore, I am investigating the mechanism of the intracellular release of $[Ca^{2+}]_i$ during oocyte maturation using starfish oocytes. If you are interested in egg/oocyte activation in any organism, please contact me.

* T. Mohri, K. Kyozuka, "*Sexual Reproduction in animals and plants*" pp.187-197, Springer, Japan (2014).
* T. Mohri, M. Sokabe, K. Kyozuka, *Dev Biol 322*, 251 (2008).
* Mohri, T., Yoshida S. (2005). *Biochem Biophys Res Comm 326*: 166-173.

# Center for Research Collaboration

KUBO, Yoshihiro
Professor
Director

## Outline

Center for Research Collaboratiion was newly established in April 2016. The center consists of 5 sections of Collaboration Promotion, Advanced Research Support, National BioResource (NBR) Project, Visiting Collaborative Research Project and International Collaborative Research Project. (1) As a mission of the inter- university research institute, NIPS promotes and conducts collaborative researches. The "Collaboration Promotion" section serves as a sort of "Concierge" of joint research with NIPS. (2) NIPS, in cooperation with NIBB, starts to conduct "Supporting Platform for Advanced Bio-Imaging" project supported by JSPS KAKENHI from April 2016. In this framework, the "Advanced Research Support" section serves to promote support for advanced imaging techniques using optical microscope, electron microscope and fMRI. (3) The National Bio-Resource (NBR) Project Section is responsible for management of National BioResource Project "Japanese monkeys". (4) The aim of the "Visiting Collaborative Research Project" section is to facilitate collaborative researches with researchers staying in NIPS using a sabbatical leave. (5) The "International Collaborative Research Project" section is a laboratory run by a visiting professor from abroad who stays for a significantly long time in NIPS. The laboratory is run up to for 3 years.

Thus, the new "Center for Collaborative Research" plays a critical role in the promotion of various collaborative research activities, including inter-university research, advanced bio-imaging support, supply of monkeys for experiments, and domestic as well as international research collaborations.

## ▶ Section of Collaboration Promotion

## ▶ Section of Advanced Research Support

## ▶ Section of NBR Project

## ▶ Section of Visiting Collaborative Research Project

## ▶ Section of International Collaborative Research Project

# Supportive Center for Brain Research

SADATO, Norihiro
Professor
Director

## Outline

This center has been called as the "Center for Brain Experiment" until the end of March 2008. Then, to expand its role in supporting brain research at NIPS, the center was reorganized as the "Supportive Center for Brain Research" in April 2008. This center was initially comprised of six sections: Section of Brain Structure Information, Brain Function Information, Multiphoton Neuroimaging, Electron Microscopy, Instrument Design, and Ine Marine Laboratory. The latter three sections were combined with this center in 2008. In 2010, Ine Marine Laboratory has been closed. In 2012 two new sections opened: Section of Viral Vector Development and Section of Primate Model Development. The former section will distribute developed viral vectors to researchers and the latter will distribute Japanese Macaques to researchers. Effective in April 2016, Section of Viral Vector Development is transformed into the Center for Genetic Analysis of Behavior without changing the section name. At the same time, Section of Primate Model Development is reorganized as NBR Project in the Center for Research Collaboration.

Brain research is one of the hottest scientific topics worldwide, of course including Japan, and recent progress in the brain research has been very impressive and attractive. Brain research is one of the main themes at NIPS and recently NIPS has been recognized as one of the most advanced centers for brain research in Japan. The main objective of this center is to support brain research performed at NIPS. The reorganization of this center allowed better support to the brain research in various fields. This center plays a central role in the neuroscientist network in Japan to facilitate interaction among multidisciplinary research fields.

# ▶ Section of Brain Structure Information

MURATA, Kazuyoshi
Associate Professor
Electron Microscopy

## Ultrastructural analysis of cells by high voltage electron microscopy

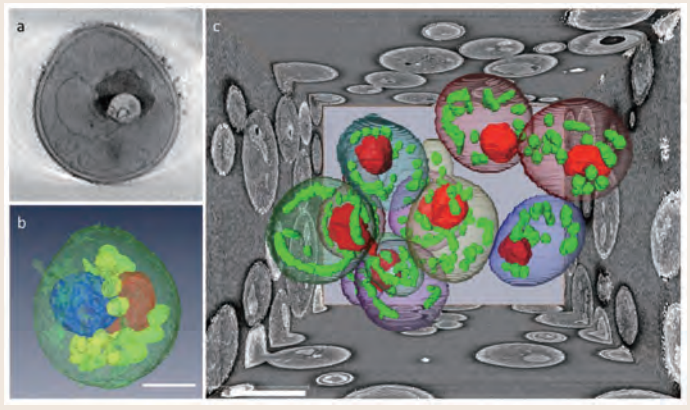
## High-resolution structural analysis of biomolecules by phase-contrast electron cryomicroscopy

Our research goal is to reveal the relatonship between biological functions and the structures. For this purpose, we use differnet types of electron microscopes. One is the high voltage electron microscope (HVEM) for biologcal research (H-1250M: 1MV), which equips with a digital camera. The other is the phase-plate electron cryomicropscope with energy filter (JEM-2200FS: 200kV), which is used for high resolution structural analyses of non-stained biological samples. By using these microscopes, we visualise biological fine structures from molecules to cells. Recent studies are shown in the figures.

* K. Satoh *et al.,* Neurosci Let, 599, 86–91 (2015).
* K. Ichimura *et al.,* Sci Rep 5, 8993 (2015).
* K. Murata *et al.,* Ultramicroscopy 146, 39–45 (2014).
* N. Miyazaki *et al.,* J Struct Biol 187, 187–193 (2014).
* M. Yoshioka-Nishimura *et al.,* Plant Cell Physiol 55, 1255–1265 (2014).
* Y. Wu *et al.,* J. Physics D 46, 494008 (2013).
* K. Kumoi *et al., PLoS ONE* 8 (3), e60294 (2013).
* T. Oti *et al., Histochem. cell biol.*138, 693 (2012).
* G. S. Hansman *et al., J. Virol,* 86, 3635 (2012).

Flg. 1 1M High-voltage electron microscope (HVEM) for biological research: H-1250M (left) and 200kV Phase-contrast cryo electron microscope with energy filter: JEM2200FS (right).

Flg. 2 A tomographic slice of S. cerevisiae visualized by 1MV HVEM (a) and the 3D reconstruction (b). Scale 1 μ m . (Murata *et al.* 2014).
3D reconstruction revealed by serial block face scaning electron microscopy (c). Scale 5 μ m . (Miyazaki *et al.* 2014).



# ▶ Section of Multiphoton Neuroimaging

## Imaging activation of signaling molecules in living cells by 2-photon fluorescence lifetime imaging microscopy

NABEKURA, Junichi
Professor
Neuroscience

MURAKOSHI, Hideji
Associate Professor
Biophysics
Neuroscience

Our state of the art two-photon fluorescence lifetime imaging microscopes allow us to image protein activity and protein-protein interaction in living cells in deep tissue such as brain slice and brain of living mouse. We accept the collaborative research using the fluorescence lifetime imaging microscope for imaging the activity and interaction of various signaling proteins. We also accept students to pursue the PhD degree, especially, the students who are interested in molecular imaging.

In addition to the cutting-edge microscope techniques, we try to develop novel fluorescent proteins and light-controllable signaling proteins. By far, we succeeded in visualizing the activities of signaling proteins in dendritic spine of hippocampal neuron by using two-photon microscopy by combining the photo-activatable probes, new fluorescent proteins, electrophysiology. These techniques will enable us to reveal the system of neural networks and underlying molecular mechanisms in a living mouse neuron.

Our mission is to reveal "missing-links" underlying between molecular functions and physiological functions in a living body. We believe that the development & application of optical imaging methods will reveal the biological system at the cellular level.

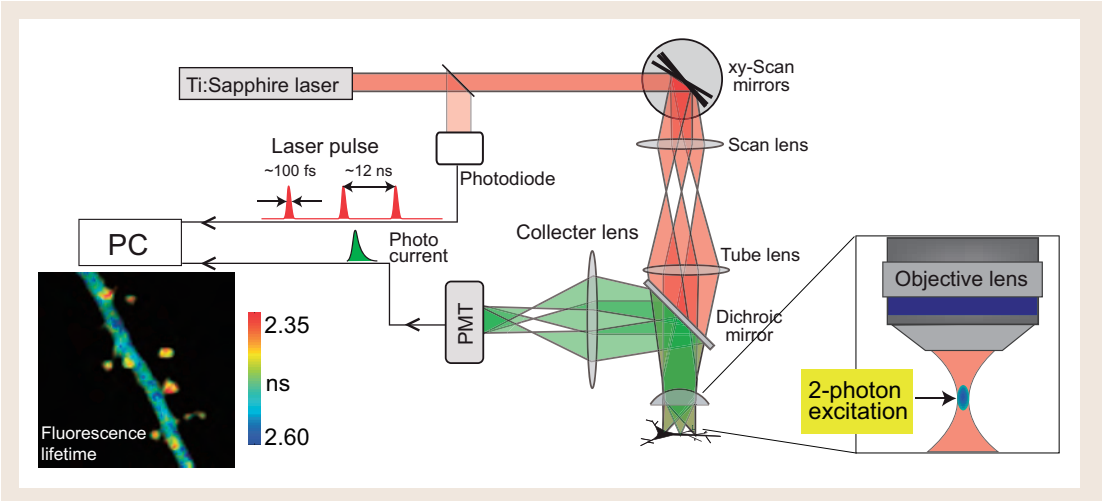



Figure 1. Two-photon excitation is a phenomenon that two photons of half energy than needed for one photon excitation can excite a fluorescent molecule. The advantages of 2-photon excitation are 1) Because infrared light is used for excitation, it minimizes excitation-light scattering in the tissue 2) Because 2-photon excitation happens only at the focal point of an objective lens, the background signal is strongly suppressed. These effects enable us to image cells and subcellular structures in deep tissue with high spatial resolution. Recently, the combination of 2-photon excitation and fluorescence lifetime imaging method enabled us to image the protein-protein interaction or structural change of protein in deep tissue such as brain slice. The fluorescence lifetime is measured by counting the arrival time of signal photon at the detector upon a laser pulse. After making histogram of lifetimes at each pixel by repeating this measurement, the pixel-by-pixel lifetime image is constructed in a pseudocolor format.

# ▶ Section of Electron Microscopy

FURUSE, Mikio
Professor
Cell Biology

KUBOTA, Yoshiyuki
Associate Professor
Neuroanatomy
Neuroscience

MURATA, Kazuyoshi
Associate Professor
Electron Microscopy

## Support for electron microscopy

Ultrastructures of tissues, cells and macromolecules are observed using transmission or scanning electron microscopes. The facility also provides instruments for their sample preparations, i.e. ultra-microtome, high-pressure freezing device, and freeze fracture and replica machine, vaccuum evaporator, etc. For digital image analysis, high-resolution film scanner, image processing software, and volume rendering software are available. Serial block-face SEMs (Gatan 3view/Zeiss Σ IGMA/VP & MARLIN; Fig. 1) and Array tomography SEM (Zeiss Σ IGMA) have opened since 2013, which reveal 3D structures of biological thick specimens.

Fig. 1 Serial block-face SEM (SBF-SEM) Gatan 3view - Zeiss S Σ IGMA/VP


Fig. 2 Transmission electron microscope (TEM) JEOL JEM1010 equipped with 2kx2k CCD camera

# ▶ Section of Brain Function Information

## Research on functional-anatomical mapping of the primate brain

SADATO, Norihiro
Professor
Functional Neuroimaging Neuroscience

CHIKAZOE, Junichi
Associate Professor
Neuroscience

The mission of the Section of Brain Function Information is to support collaborative studies using high field magnetic resonance imaging (3T and 7T) and to promote research on functional-anatomical mapping of the primate brain. We are actively promote collaborative studies ranging from basic research and development of MRI to clinical applications as well as studies on establishing standards for MRI procedures, including safety, applications, and quantitative analyses of the images. We are now trying to develop an algorithm to quantitatively and statistically handle image data of the brain generated by MRI. In addition to collaborative research, training junior researchers in MRI applications and basic neuroscience research are promoted.

# Center for Genetic Analysis of Behavior

IKENAKA, Kazuhiro
Professor
Director

## Outline

This center produces gene modified rat/mouse and analyzes their behavior using multiple parameters under normal and various stressful conditions. The facilities in this center are open for the collaboratory use from researchers all over Japan.

# ▶ Section of Viral Vector Development

NAMBU, Atsushi
Professor
Neurophysiology

ISA, Tadashi
Professor
Neurophysiology

KOBAYASHI, Kenta
Associate Professor
Molecular Neurobiology

① Production and provision of viral vectors in response to the requests from other laboratories.

② Developing new useful viral vectors in cooperation with collaborators.

③ Providing a technical guidance for handling of viral vectors and gene introduction methods, in response to requests. In addition, providing guidance for document works required for the handling of recombinant DNA to help the applicants to use viral vectors for their researches.

④ Test of gene introduction into animals using viral vectors.

⑤ Storage of plasmids to produce useful viral vectors.

National Institute for Physiological Sciences is an inter-university research institute, and has an obligation to facilitate collaborative studies for physiology and brain sciences in Japan. Recently, the gene introduction using viral vectors is becoming a very important technique for the analysis of brain function, and the development of a variety of new viral vectors is rapidly progressing. However, it is difficult for individual laboratories to produce high quality viral vectors in a large scale. Therefore, the laboratory plays a role as a Vector Core, and promotes the collaboration by providing useful viral vectors for the brain science studies. Moreover, the technical assistance is provided in response to requests.

*① K. Kobayashi et al., Methods. Mol. Biol. 1382, 175 (2016).
*② A. Ishida et al., J. Neurosci. 36, 455 (2016).
*③ AS. Wahl et al., Science. 344, 1250 (2014).
*④ S. Kato et al., J. Neurosci. Methods. 227, 151 (2014).
*⑤ M. Hirano et al., PLoS One. 8, e75896 (2013).

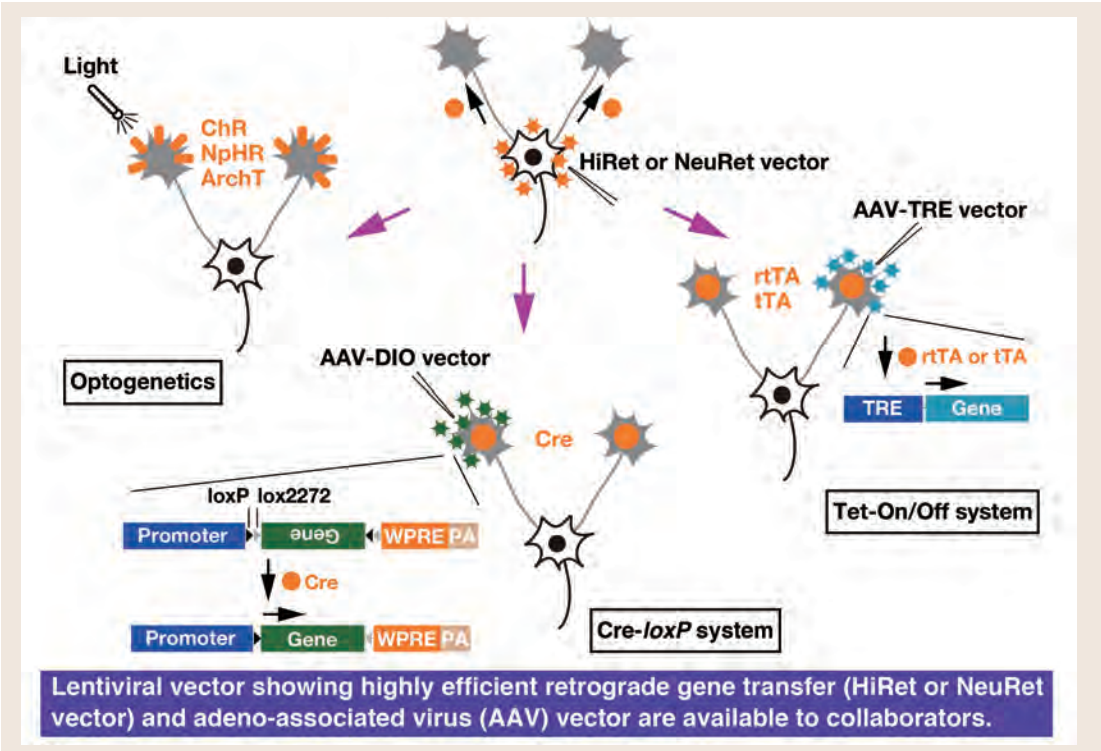



Figure 1. Application of viral vectors to brain research. For example, the optogenetical analysis and conditional gene expression in the specific neural pathway become possible by using newly developed lentiviral vector showing highly efficient retrograde gene transfer (HiRet or NeuRet vector) and adeno-associated virus (AAV) vector. These useful viral vectors are available to collaborators.

HIRABAYASHI, Masumi
Associate Professor
Laboratory Animal Science

TARUSAWA, Etsuko
Project Associate Professor
(Grant Project)
Neuroanatomy

## Development of Advanced Reproductive / Transgenic Technologies in Laboratory Animals

We have focused on the reproductive biotechnology to understand gamete interactions during fertilization and the development of novel methodology to produce transgenic animals. Among them, we have a special interest in the increasing demand for production of gene-targeted (KO: knock-out) rats because use of rats rather than mice is advantageous in aspects of microsurgery and mapping of brain functions. Generation of functional organs with a 3D structure using transgenic/KO rat individuals will offer model system and open a new window for regenerative medicine in humans. Embryonic stem (ES) cell lines and induced pluripotent stem (iPS) cell lines have been established in rats, and they will contribute to the progress of research regarding not only the brain function but also the regenerative medicine. Recently, new technologies such as Zinc Finger Nucleases (ZFNs), TAL Effector Nucleases (TALENs) and the clustered regularly interspaced short palindromic repeat (CRISPR)/Cas9 system have been shown to be very effective for gene- modification in rats. At present, we devote all our skills (e.g., in vitro fertilization, intracytoplasmic sperm injection; ICSI, establishment of ES/iPS cell lines) to explore the possibility of producing KO rats, and also provide collaborative services to produce conventional and conditional KO mice, and transgenic mice and rats by pronuclear DNA microinjection or ICSI-mediated DNA transfer. Our recent attempts at establishing the ES cell lines and the iPS cell lines in the rat were successful and expanded to the generation of gene-modified rat individuals. Somatic cell nuclear transplantation in the rat is still one of the challenging subjects in our laboratory.

∗ T. Goto *et al.*, Mol Reprod Dev. 82, 116 (2015).
∗ M. Hirabayashi *et al.*, Stem Cell Dev. 23, 107 (2014).
∗ M. Hirabayashi *et al.*, J Reprod Dev. 60, 78 (2014).

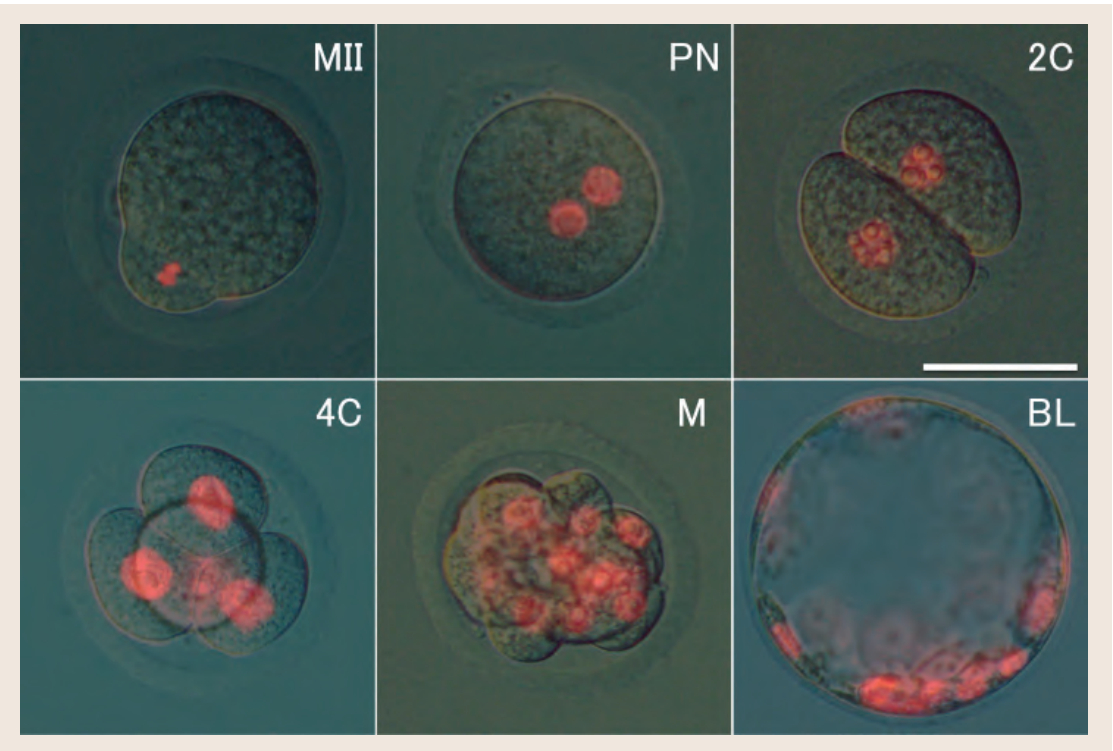



Fig. 1 Images of Rosa26-H2B/tdTomato knock-in rat zygotes, following 560-nm excitation.
MII: Metaphase-II stage oocyte. PN: Pronuclear stage zygote. 2C: 2-cell stage embryo. 4C: 4-cell stage embryo. M: Morula. BL: blastocyst. Scale bar: 50 μ m.

## Comprehensive Behavioral Analysis of genetically engenieerd mice
## Investigation of endophenotypes in psychiatric disorders

MIYAKAWA, Tsuyoshi
Adjunct Professor
Experimental Psychology
Neuroscience

TAKAO, Keizo
Professor
(Concurrent post)
Behavioral Physiology
Neuroscience

Since 99% of mouse genes have homologous in humans, a large-scale project that is aimed to encompass knockouts of every gene in mice is in progress. Approximately 80% of all genes are expressed in brain and, to investigate their function in individual organisms, we should investigate their functions in the brain. We can identify the genes that have significant impact on the brain functions efficiently by examining the final output level of gene function in the brain, that is, behavior. The influence of a given gene on a specific behavior can be determined by conducting behavioral analysis of mutant mice lacking that gene. The test comprehensive behavioral battery covers sensori-motor functions, emotion, learning and memory, attention and so on. So far, we obtained behavioral data from 80 strains, 4243 mice. In those mice strains, we found some models of psychiatric disorders.

* Takao K, et al., Deficiency of schnurri-2, an MHC enhancer binding protein, induces mild chronic inflammation in the brain and confers molecular, neuronal, and behavioral phenotypes related to schizophrenia. *Neuropsychopharmacology*, 2013; 38（8）:1409-25.
* Takao K and Miyakawa T, Genomic responses in mouse models greatly mimic human inflammatory diseases., *Proc Natl Acad Sci U S A. 2014*; pii: 201401965.
* Hagihara H, Ohira K, Takao K, and Miyakawa T, Transcriptomic evidence for immaturity of the prefrontal cortex in patients with schizophrenia. *Mol Brain.* 2014; 7:41.
* Zheng LS, et al., Mechanisms for interferon- α -induced depression and neural stem cell dysfunction., *Stem Cell Reports*. 2014; 3（1）:73-84.
* Fujioka R, et al., Comprehensive behavioral study of mGluR3 knockout mice: implication in schizophrenia related endophenotypes., *Mol Brain*. 2014; 7:31.
* Yasumura M, et al., IL1RAPL1 knockout mice show spine density decrease, learning deficiency, hyperactivity and reduced anxiety-like behaviours., *Sci Rep*. 2014; 4:6613.
* Shibasaki K, et al., TRPV4 activation at the physiological temperature is a critical determinant of neuronal excitability and behavior. *Pflügers Archiv-European Journal of Physiology*, 2015; pp1-13.

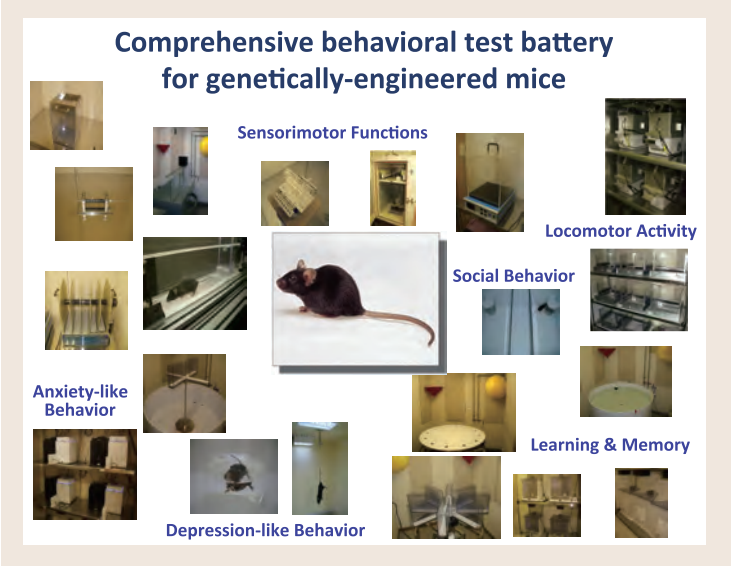



Figure 1. Apparatus for behavioral analysis of mice.

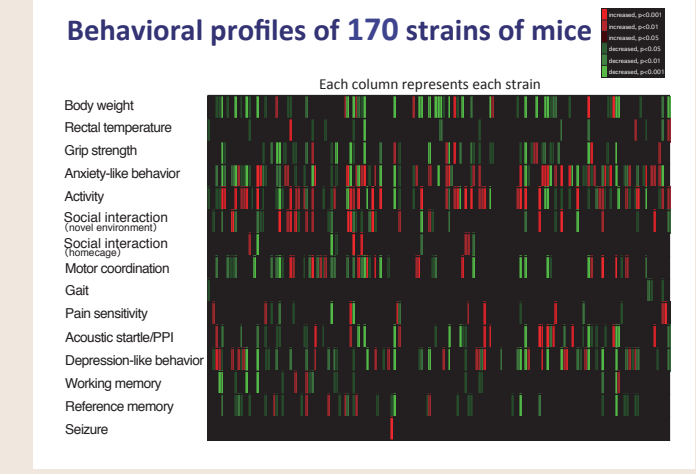



Figure 2. Heat map showing behavioral phenotypes of genetically engineered mice. Each column represents the strain of genetically-engineered mice that has been analyzed. Each row represents a category of behavior assessed by comprehensive behavior test battery. Colors represent an increase (red) or decrease (green) in a comparison between the wild-type and mutant strains.

# ▶ Section of Metabolic Physiology

MINOKOSHI, Yasuhiko
Professor
Endocrinology and Metabolism

SUZUKI, Yoshiro
Assistant Professor
Molecular and Cellular Physiology

## In vivo analysis of neuronal and metabolic activity in mice and rats

This section analyzes the in vivo neuronal and metabolic activity in mice and rats which were modifi ed their related genes and exposed with various environmental conditions. This section examines the following subjects and will be open for the collaboratory use of researchers all over Japan from April, 2011:

1) Single unit recording from motor related brain regions in awake state.
2) Neurotransmitter release in local brain regions in free-moving animals.
3) Regional neural activity detected as intrinsic signals with taking the advantage of light fl uorescent dynamics of fl avin or hemoglobin.
4) Energy intake and expenditure in free-moving animals.
5) Body temperature, heart rate and blood pressure in free-moving animals.
6) Measurement of cardiac functions using Langendorffperfused hearts and non-invasive measurement of cardiac functions and peripheral blood fl ow using anethetized mice.

# Center for Communication Networks

KAKIGI, Ryusuke
Professor
Director

## Outline

The center provides information of NIPS programs and activities to the public, scientific community, medical profession, and media through WEB, publication, conferences and symposium. Science education activities and Institutional review processes are also coordinated. The center maintains infrastructures of LAN as well as WEB-based services.

# ▶ Section of Research Archives

MURAKAMI, Masataka
Associate Professor
Physiology of Exocrine Glands
Energy Metabolism and Transport of Electrolyte and Water
Paracellular Transport

The Institute has made the self-evaluation and peer review every year since 1993. In addition, the institute started editing a volume of annual plans and annual reports every year since 2004. The section was opened in 2007 to perform more efficient evaluation processes. For efficient accumulation of historical events in the institute, this section also takes care of archiving the documents that describe the activities of the Institute.

Since Last year 2015, this section started to collect the interviews from the people who worked in the Institute. By accompanying the written record and interview we could understand the events with reality.

# ▶ Section of Physiology and Medicine Education

TOMINAGA, Makoto
Professor
Molecular and Cellular Physiology

NAKAGAWA, Eri
Project Assistant Professor
Psycholinguistics
Foreign Language Education

## Developing materials and system for 'step-by-step studies of human life sciences'

The material is presented in very small steps, pproximately 10-fold more steps than conventional materials. At each step, straight-forward images are presented, so that the learners 'get the image', as well as few-choice questions, to provide an immediate opportunity to use the learned information. To prevent a one-way flow of information, the learners are encouraged to share their questions, comments and suggestions. 'Active learning' is very much possible with this material, not only by answering questions, but the learners explaining the image to others. The rate of success is very high as the portion that the learners do originally is not very much. With this system, not only knowledge, but also confidence and motivation for further studying is shown to increase. This system was developed by the previous NIPS visiting professor, Dr. Masato Shibuya (a professor of Junior College of Kagawa Nutrition University).

## Developing materials and system for 'step-by-step studies of brain science'

The part about neuroscience of above 'step-by-step studies of human life sciences' is provided as 'step-by-step studies of brain science I' for the Brain Science Joint Program of SOKENDAI (The Graduate University fro Advanced Studies). 'step-by-step studies of brain science II', another e-learning subject, was also developed for the Brain Science Joint Program with Dr. Yoshihisa Kudo (a professor emeritus of Tokyo University of Pharmacy and Life Science). Students take the e-learning-based exams in the end of each semester. Upon taking both 'step-by-step studies of brain science I' and 'step-by-step studies of brain science II', students are supposed to learn basic brain science completely.

# ▶ Section of Network Management

Computer services and network supports are indispensable for research activity. In this section, we manage the "Computer System for Data Analysis in Physiology" for Numeric Computation, data analysis, visualization, mathematics, statistics, DNA analysis, and electronic design. Two technical staffs support high-speed and reliable network for intra-/internet services such as E-mail communication, Web services, and peripheral devices for in-house information network. Technological developments for the best use of these facilities are also underway（Fig. 1）.

Fig.1. Computer System for Data Analysis in Physiology & Network Servers

# Section of Health and Safety Management

## Outline

FUKATA, Masaki
Professor
Neuroscience
Biochemistry
Cell Biology

NIPS is sincerely trying to promote the security and health of researchers and workers, particularly considering the environments of laboratories and offices. Recently, NIPS has had to focus on resolving some serious problems, for example, storing several drugs such as narcotics properly, and safely maintaining several machines such as those using lasers. To avoid accidents caused by such drugs and machines, NIPS is conducting a regular annual medical examination for all researchers and workers. Considering how important this problem is, the Section of Health and Safety Management was founded in 2011 under the direct management of the Director-General. This section is mainly conducting the following four activities:

1. Work to prevent accidents and health problems of workers at NIPS.
2. Education related to safety and hygiene for workers.
3. Regular medical examinations.
4. Investigation of problems causing labor accidents in order to prevent them.

Monthly meetings are held to smoothly conduct the regulatory procedures.

# Research Enhancement Strategy Office


NABEKURA, Junichi
Professor
Neuroscience

KUBO, Yoshihiro
Professor
Biophysics
Neurobiology

KAKIGI, Ryusuke
Professor
Neurophysiology

MINOKOSHI, Yasuhiko
Professor
Endocrinology and Metabolism

YOSHIMURA, Yumiko
Professor
Neurophysiology

URANO, Toru
Project Professor
Loboratory Animal Science
Bacterial Infectious Disease

KAGAWA, Tetsushi
Project Professor
Neuroscience
Molecular Neurobiology

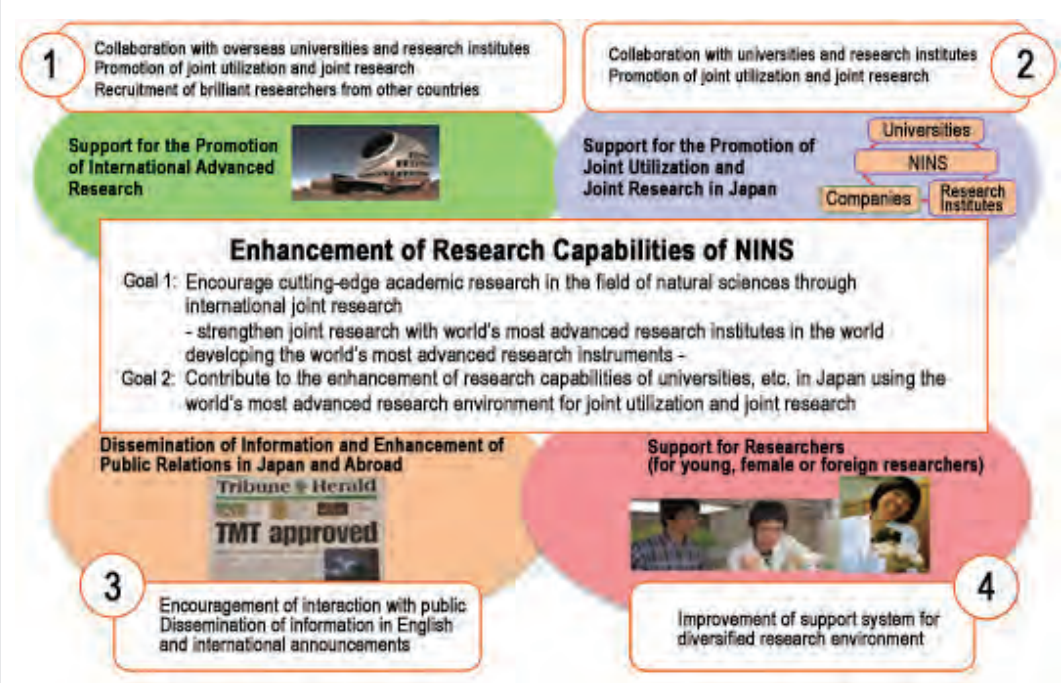
MARUYAMA, Megumi
Project Associate Professor
Neurophysiology
Environmental Physiology

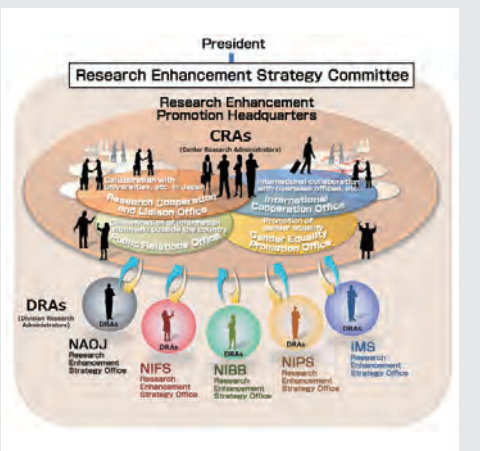
SAKAMOTO, Kiwako
Assistant Professor
Neurophysiology

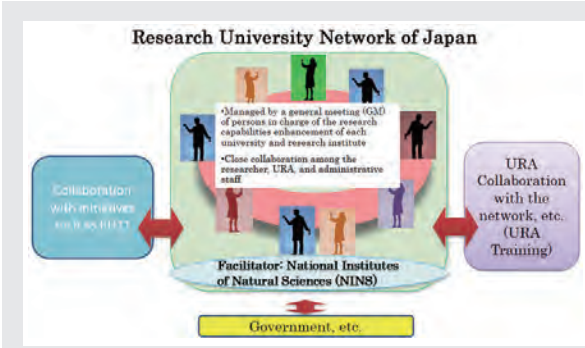

## Research Enhancement Promotion Project

National Institutes of Natural Sciences NINS) has been selected as one of 20 Universities and 3 Inter-University Research Institutes in the Program for Promoting the Enhancements of Research Universities funded by Monbukagakushou (MEXT), which started from September 2013. Reseach Enhancement Promotion Headquarters and Research Enhancement Strategy Office of this program have been settled at NINS, and each 5 Research Institutes, including NIPS, respectively. At NIPS, Research Enhancement Strategy Office (manager: vice director of NIPS) has been composed of by 5 units, 1) Research Surveillance and Analysis, 2) Evaluation, 3) Research Animal Management, 4) Promotion of gender equality, 5) Promotion of Outreach Activity. Projected Professors, Projected Associate and Assistant Professors were assigned to Research Surveillance and Analysis Unit, Evaluation Unit, Research Animal Management Unit and Promotion of Outreach Activity Unit. Each unit promotes its activity to facilitate own research and research collaboration to achieve NIPS mission.

http://www.nins.jp/english/ura/outline.php



# Okazaki Institute for Integrative Bioscience

## ▶ Department of Biosensing Research

- Cell Signaling—National Institute for Physiological Sciences (See P. 14)
- Bioregulatory Signaling—National Institute for Physiological Sciences (See P. 47)
- Bioinorganic Chemistry—National Institute for Basic Biology

## ▶ Department of Biodesign Research

- Cardiocirculatory Signaling—National Institute for Physiological Sciences (See P. 15)
- Plant Development and Physiology—National Institute for Basic Biology
- Molecular & Developmental Biology—National Institute for Basic Biology
- Nuclear Dynamics—National Institute for Basic Biology
- Behavioral Neurobiology—National Institute for Basic Biology

## ▶ Department of Bioorganization Research

- Biomolecular Science—Institute for Molecular Science
- Neuronal Cell Biology—National Institute for Basic Biology
- Constructive Biology—Institute for Molecular Science
- Molecular Machine Designing—Institute for Molecular Science
- Nano-Structure Physiology—National Institute for Physiological Sciences
- Quantitative Biology—National Institute for Basic Biology

# Orion Project
(Bioregulatory Signaling)

SATO, Koji
Project Associate Professor
(Grant Project)
Sensory Physiology

## Molecular mechanisms of signal transduction in chemical senses

The senses of olfaction and gustation are essential chemosensory systems to recognize the tens of thousands of chemical compounds in nature. These systems regulate both animal behavior and endocrine status. We focus on the molecular mechanism of signal transduction in chemical senses, which enable the complex neuronal coding of multiple of chemical information.

The genes of olfactory receptors (ORs) encode the large a large family of seven-transmembrane-domain G protein coupled receptors (GPCRs). However insect ORs possess the seven transmembrane topology with the intracellular amino terminus, and comprise the odor-gated ion channels (fig. 1). One of the insect gustatory receptor families also comprises the fructose-activated ion channels. These chemosensory receptors hardly wire the neural circuits related to the innate response. However their activation mechanisms are still unclear. One of the fundamental problems is that the behavior of functionally expressed ORs in heterologous cells is different from that of *in vivo*. Our goal is to elucidate the nature involving the chemical senses by using integrated research technique, such as physiology, single-molecule imaging and MEMS.

* Miura S et al. (2015) Fluid shear triggers microvilli formation via mechanosensitive activation of TRPV6. *Nature Communications* 6:doi: 10.1038/ncomms9871
* Ishii T et al. (2015) Light generation of intracellular $Ca^{2+}$ Signals by genetically encoded protein BACCS. *Nature Communications* 6:doi: 10.1038/ncomms9021
* Sato K and Takeuchi S (2014) Chemical vapor detection using a reconstituted insect olfactory receptor complex. *Angewandte Chemie International Edition* 53:11798-802
* Onoe H et al. (2013) Metre-long cell-laden microfibres exhibit tissue morphologies and functions. *Nature Materials* 12:584-90
* Sato K et al. (2011) Sugar-regulated cation channel formed by an insect gustatory receptor. *PNAS* 108:11680-685
* Iwabu et al. (2010) Adiponectin/AdipoR1 increase PGC-1a expression and activity via Ca2+ signaling and AMPK/SIRT1, leading to increased mitochondrial bioenergetics. *Nature* 464:1313-19
* Sato K et al. (2008) Insect olfactory receptors are heteromeric ligand-gated ion channels. *Nature* 452:1002-6

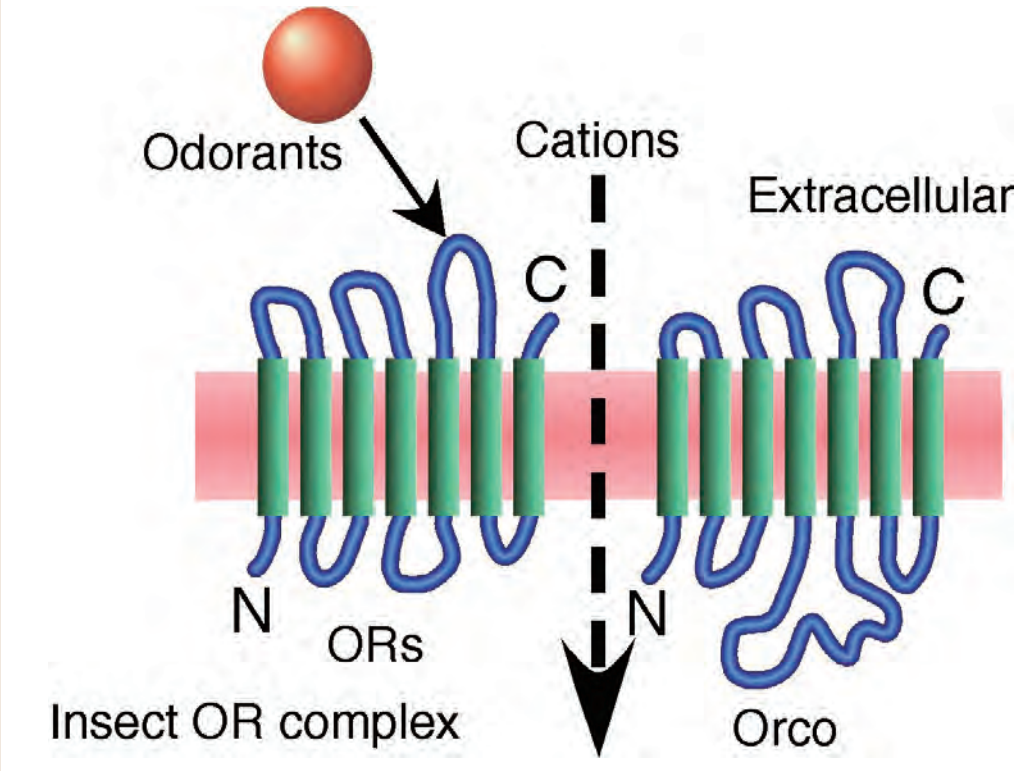



Fig. 1 Schematic model for ligand-gated channel properties of the insect conventional OR + co-receptor (Orco) complex.

# Center for Experimental Animals

MINOKOSHI, Yasuhiko
Professor (Director)

URANO, Toru
Project Professor
Loboratory Animal Science
Bacterial Infectious Disease

WANG, Chen-Chi
Assistant Professor
Laboratory Animal Science
Cell Biology

The Center for Experimental Animals was established in 1980 for communal use by both the National Institute for Physiological Sciences and the National Institute for Basic Biology. The facility consists of the terrestrial animal section and the aquatic animal section, where about 30 species including rat, mouse, monkey, and frog, are kept and supplied for experimentation.

For the highly reproducible experiments, it is important to use well-characterized and quality-proofed animals. For this purpose, it is necessary to provide air condition, care for animal health, and prevention of infectious diseases. Surgical rooms and experimental rooms are provided in the terrestrial animal section. In addition, an annex composed of special rooms for experimentation with transgenic animals was built in 1994.

In 2000, the structure of Okazaki National Research Institutes changed following establishment of Center of Integrative Bioscience. Currently, the Center for Experimental Animals is situated under Research Facilities of our institute complex. In 2002, another SPF animal facility building was built in the new campus in the "Yamate" area.

In recent years, the number of mutants or gene-modified animals has remarkably been increased, which raised technical problems to maintain or preserve these special animal strains. Staffs are now improving the method of freezing fertilized eggs or early stage embryos.

In 2007, novel animal experimentation was started on the basis of the guidelines of animal care and experiments of the NINS. In 2008, the aquatic facilities have been entirely improved and SPF facilities have also opened in the "Myodaiji" area.

# Research Center for Computational Science

Non-selection

# Division of Coordinator for Animal Experimentation

SATO, Hiroshi
Project Professor
Laobratory Animal Science
Zoonoses

This Division was established in 2008 under the IACUC covered with 3 Institutes at Okazaki.

The important role of animal-based research in the life science, especially physiological science field has been extensively increasing in the world. However, animal welfare and ethical problems are rising in the field.

This Division has three main missions as follows.

1. To educate and train researchers whom belong to 3 Okazaki Institutes concerning to 'Law for the humane treatment and management of animals', 'Standards relating to the Care and Management of laboratory animals and relief of pain', 'Fundamental guidelines for proper conduct of animal experiment and related activities in academic research institutions under the jurisdiction of MECSST' and domestic Standard.
2. To prepare a report of self-evaluation.
3. To disclose the data for animal-based research among 3 Institutes.

# NIPS Research Fellow

The NIPS Research Fellows are young researchers with advanced research capabilities through operational expense subsidies for a certain period in order to have them be engaged in specific joint research projects, and to develop and promote research activities.

OSANAI, Yasuyuki
Division of Neurobiology & Bioinformatics
**Neuroscience**

YOKOTA, Shigefumi
Division of Endocrinology & Metabolism
**Endocrinology and Metabolism**

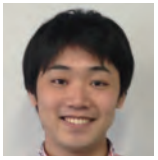
NISHIO, Akiko
Division of Sensory & Cognitive Information
**Neurophysiology**

DEROUICHE, Sandra
Division of Cell Signaling
**Molecular and Cellular Physiology**

YAMAURA, Hiroshi
Division of Visual Information Processing
**Neuroscience**

ITOU, Tomoya
Division of Cardiocirculatory Signaling
**Molecular Biology**

SOHN, Jaerin
Division of Cerebral Circuitry
**Neuroscience**
**Neuroanatomy**



HORIUCHI, Hiroshi
Division of Homeostatic Development
**Neurophysiology**
**Neuroimmunology**

# Technical Division

## Outline

The Technical Division is an organization of technical staffs to support research activities in National Institutie for Physiological Sciences（NIPS）. This organization is under the direction of the Director-General of NIPS. It is organized in a management system with Head, Assistant Head, Section Chief, Unit Chief, Assistant Unit Chief and Staff.

The division is composed of the technicians, who are covering a wide diversity of fields, such as electric circuitry, mechanical machine tooling, computing, gene engineering, biochemical analysis, cell culture, microscope, raising and reproduction of gene-implanted animals and so on.

The division is divided into two sections, one is for Departments and the other is for Research Centers. The personnel belonging to the Departments support mainly the researchers in the Departments. Those belonging to the Research Center or Laboratory are maintaining and controlling common research equipment for use in joint research projects by scientists of inside and outside of the institute.

In addition to these technical supports, the division is conducting common operations（maintenance and control of equipment, machinery and other installations, and management of research meeting and supply shops）.

Beside the division conducts self-study activities by organizing technical research meeting and by publishing technical reports, in order to improve the technical abilities of individual members. A technical committee is organized to allow the institute to obtain new technologies vital to the research and to dissolve technically challenging subjects.

Every year, "Operation Report Meeting" is held to promote the mutual understandings of technical operations and to exchange general information in the division.

The Annual Meeting of Technical Research is held for the purpose of exchanging technological information among technicians working in all universities and research institutes in the country. In the meeting, discussions are made through oral presentations, panel exhibitions and lectures with technical practice.

These study activities and technical research meetings conducted at the division are summarized and published in "Annual Report of Technical Division" and in "Annual Report of Technical Research Meeting."

Head :
OKAWARA, Hiroshi

Unit Chief :
YOSHIMURA, Nobuaki
Center for Communication Networks Technical Unit

Staff :
KANO, Yuichiro
Molecular & Cellular Physiology Technical Unit

Assistant Head :
OHARA, Masahiro
Research Centers Technical Section

Unit Chief :
ITO, Akimitsu
Center for Experimental Animals Technical Unit

Staff :
ISHIHARA, Hiromi
Homeostatic Regulation Technical Unit

Section Chief :
TOGAWA, Morio
Departments Technical Section

Assistant Unit Chief :
YAMAMOTO, Tomomi
Molecular & Cellular Physiology Technical Unit

Staff :
TAKAHASHI, Naoki
System Neuroscience Technical Unit

Unit Chief :
SAZI, Toshiyuki
Molecular & Cellular Physiology Technical Unit

Assistant Unit Chief :
FUKUTA, Naomi
Homeostatic Regulation Technical Unit

Staff :
YAMADA, Gen
Supportive Center for Brain Research Technical Unit

Unit Chief :
NAGATA, Osamu
Homeostatic Regulation Technical Unit

Assistant Unit Chief :
TAKAGI, Masahiro
Fundamental Neuroscience Technical Unit

Staff :
MURATA, Yasuhisa
Center for Communication Networks Technical Unit

Unit Chief :
YAMAGUCHI, Noboru
Fundamental Neuroscience Technical Unit

Assistant Unit Chief :
YOSHITOMO, Miki
Fundamental Neuroscience Technical Unit

Staff :
KAMIYA, Emi
Center for Experimental Animals Technical Unit

Unit Chief :
TAKESHIMA, Yasuyuki
System Neuroscience Technical Unit

Assistant Unit Chief :
SATO, Shigeki
System Neuroscience Technical Unit

Staff :
KUBOTA, Mitsuko
Center for Experimental Animals Technical Unit

Unit Chief :
MAEBASHI, Hiroshi
Center for Collaborative Research Technical Unit

Assistant Unit Chief :
SANBO, Makoto
Center for Genetic Analysis of Behavior Technical Unit

Staff :
MORI, Masahiro
Research Infrastructure Technical Unit

Unit Chief :
ITO, Yoshikuni
Supportive Center for Brain Research Technical Unit

Assistant Unit Chief :
HIROE, Takeshi
Center for Experimental Animals Technical Unit

Unit Chief :
SAITO, Kumiko
Center for Genetic Analysis of Behavior Technical Unit

Staff :
INAHASHI, Hiroki
Molecular & Cellular Physiology Technical Unit

# Large facilities and equipments for cooperative studies

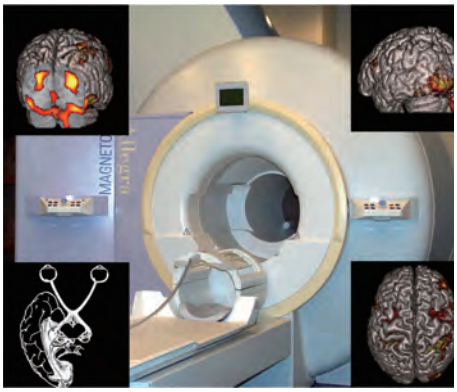
## Outline

As a mission to be the inter-university research institute, NIPS conducts joint studies with researchers from domestic or foreign universities and other research institutes. NIPS provides specialized equipments, large-scale equipments and research facilities, and develops new equipments for morphological and functional 4D imaging ｓ of various organs such as brain.

## ▶ High Voltage Electron Microscope (HVEM)

Hitachi H-1250M is the unique high voltage electron　microscope specially designed for biological and medical sciences. The microscope usually operates at an accelerating voltage of 1,000 kV. The column pressure is kept at less than $7 \times 10^{-6}$ Pa near the specimen position. The image acuisition is performed at the magnification ranges from 1k to 1,000 k. Projections of thick biological specimens up to 5 $\mu$ m are collected at tilt angles between $\pm 60°$ using the side entry specimen holder, which gives 3-dimentional ultra-structures of biological specimens at nanometer scales.

## ▶ Magnetic Resonance Imaging System



MRI is an imaging technique that utilizes the nuclear magnetic resonance of the hydrogen atom. Not only to image the anatomical details of the brain, MRI also allows to explore the neural substrates of human cognitive function by the visualization of the task-related changes in regional cerebral blood flow (functional MRI). For over a decade, we have been working on 3T MRI to investigate higher brain function of human. To simultaneously measure the neural activities of two participants during their social interaction,we have recently installed dual functional MRI system with two 3T MRI. Furthermore, ultra-high field (7T) MRI system has been installed. Thus NIPS is now equipped with three 3-Tesla MRIs and one 7-Tesla MRI (Allegra, Siemens in FY 2000, and Verio x 2, Siemens in FY 2009, Magnetom 7T, Siemens in FY 2014).

## ▶ Magnetoencephalography (MEG)

Magnetoencephalography (MEG) has a potential to measure brain activities with better temporal and spatial resolution in milliseconds and millimeter, respectively, compared with other methods such as functional magnetic resonance imaging. Event-related magnetic fields following various kinds of sensory stimulation are mainly analyzed. In addition, background brain activities (brain waves) in various conditions can be analyzed.

## ▶ Phase Contrast Electron Cryomicroscope

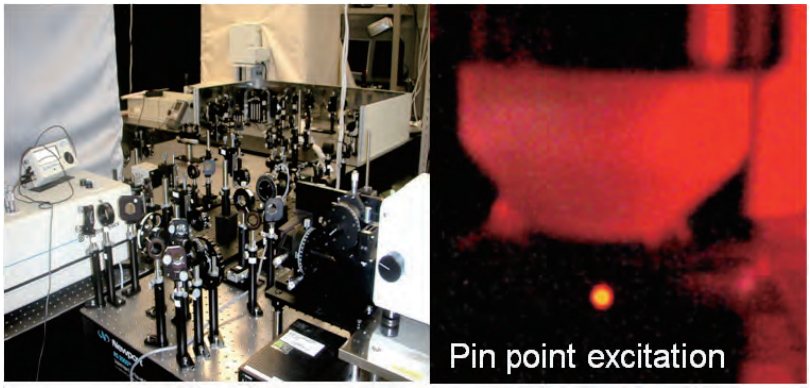
Phase contrast electron cryomicroscope is an electron microscope developed for observing close-to-life state biological samples with a combination of rapid freezing and ice embedding sample preparation methods. Biological specimens up to 200 nm thicknesses can be observed with high-resolution and high-contrast. Ultrastructure analyses of protein molecules, viruses, bacteria, cultured cells and frozen tissue sections are performed with this novel microscopic system.

## ▶ Serial Block-Face Scanning Electron Microscope (SBF-SEM)

Serial block-face scanning electron microscope (SBF-SEM) is an advanced 3-D nano-imaging equippment. Two different types of SBF-SEM are available; high-resolution and wide-area types. Resin-embedded biological specimens are trimed by a diamond knife prepared inside the chamber, and the block-face images are acquired by scanning electron microscope (SEM). 3-D structure of the specimen is finally rebuilt from the serial block-face images. 3-D structures of large biological specimens like a brain tissue can be visualized at nanometer resolution.


## ▶ Multiphoton excitation microscopy

Multi-photon excitation is a method to visualize living tissue by exciting the fluorescence molecules with the tightly focused near-infrared femtosecond pulse laser. Since the longer wavelength is used for multi-photon excitaton, it has a superior deeper tissue penetration and reduced phototoxicity than single-photon excitation. Current projects are the imaging of neurons, glial cells in deep tissues such as mouse brain. Our 2-photon microscopes have top level specification for deep tissue imaging. As new projects, we recently started to image protein-protein interaction and the activation of signaling molecules by using a 2-photon fluorescence imaging microscope.



## ▶ A comprehensive behavioral test battery

We conduct various kinds of behavioral tests for genetically engineered mice, including wire hang, grip strength, light/dark transition, open field, elevated plus maze, hot plate, social interaction, rotarod, prepulse inhibition/startle response, Porsolt forced swim, gait analysis, beam test, eight-arm radial maze, T maze, Morris water maze, Barnes maze, object recognition test, cued and contextual fear conditioning, passive avoidance, tail suspension, and 24 hour home cage monitoring.

The primary goal of our research group is to reveal functional significances of genes and their involvement in neuropsychiatric disorders by conducting a comprehensive behavioral test battery on genetically engineered mice.

eight-arm radial maze

Morris water maze

## ▶ Analytical equipment for in vivo neuronal, metabolic and physiological parameters in mice and rats

We analyze the following physiological parameters in mice and rats:

1) Single unit record ingfrom motor related brain regions in awake state , 2) Neurotransmitter release in local brain regions in freemoving animals, 3) Regional neural activity detected as intrinsic signals with taking the advantage of light fluorescent dynamics of flavin or hemoglobin, 4) Energy intake and expenditure in free-moving animals, 5) Body temperature, heart rate and blood pressure in free-moving animals, 6) Measurement of cardiac functions using Langendorff-perfused hearts and non-invasive measurement of cardiac functions and peripheral blood flow using anethetized mice.

# Facilities Shared by the Two Institutes

## Outline

National Institute for Physiological Sciences and National Institute for Basic Biology are sharing facilities which are innovative for conducting biological researches, but rather expensive to be supported only by one institution.

## ▶ Section of Electron Microscopy

See P. 33

## ▶ Instrument Design Room

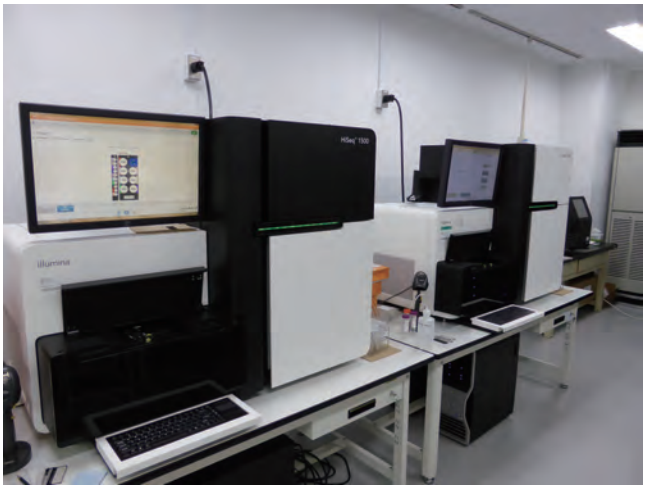
Custom-designed equipments, which are not commercially available, can be constructed in this room. The machine shop is equipped with various types of machines such as milling machines and drill presses. The electronic shop is equipped with various types of test instruments used for construction and measurement calibration of electronic devices.

Machine shop equipments（Instrument Design Room）

## ▶ Functional Genomics Facility

The Functional Genomics Facility is a division of NIBB Core Research Facilities and organized jointly by NIBB and NIPS for promoting DNA and protein studies. The facility maintains a wide array of core research equipments, from standard machinery like ultracentrifuges to cutting edge tools such as next generation DNA sequencers, which amount to 40 different kinds of instruments. Our current focus is supporting functional genomics works that utilize mass spectrometers and DNA sequencers.

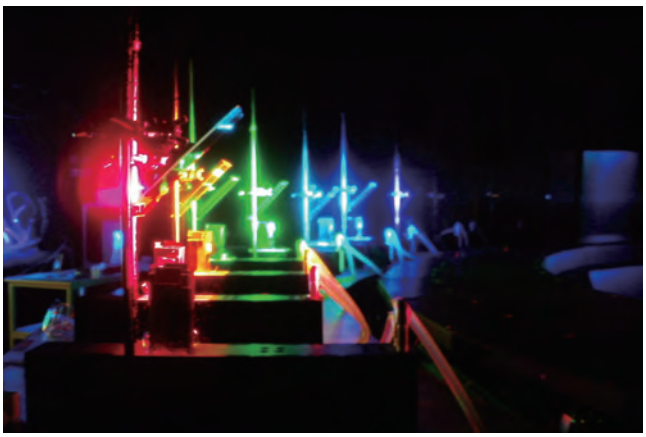
Next generation DNA sequencers (Functional Genomics Facility)



## ▶ Spectrography and Bioimaging Facility

Spectrography and Bioimaging Facility is a division of NIBB Core Research Facilities. It assists both collaborative and core research by managing and maintaining research tools that use “Light”, such as the Okazaki Large Spectrograph, confocal microscopes, two–photon microscopes, and other imaging equipments. We also hold technical seminar and training session about microscopes and bioimaging to provide useful information to users.

Okazaki Large Spectrograph（Spectrography and Bioimaging Facility）



# Joint Researches

## Outline

The National Institute for Physiological Sciences（NIPS）, an inter-university research institute, carries out general collaborative research, planned collaborative research that focuses on the most important theme at the time, and cooperative research using large facilities.
As the following table shows, many collaborative studies are conducted each year and have produced promising results. In 2016, the institute plans to carry out 98 cooperative research projects, and 39 cooperative experiments.

Another one of principal pillars of the corporative studies at NIPS is the NIPS research meeting. Unlike normal academic meetings, here, most of these meetings include oral presentations, giving plenty of time for Q&A.

The small number of participants also allows detailed discussions to take place. Nineteen meetings were held last year, and 19 meetings are planned for this year. The number of NIPS research meetings greatly outnumbers those hosted by the other two research institutes in Okazaki, and in fact, they have become a highly important base organization. In the past, the meetings have helped establish new scientific research funded study groups, and have even established activities such as academic conferences. The NIPS International Workshop has been running since 2008. Research meetings inviting overseas researchers, who present their work in English, have shown positive potential for the future of science. In 2014, two International Workshops are scheduled.

### 1. General collaborative project

The general collaborative projects and planned collaborative projects involve studies carried out by researchers from outside universities or research institutes, and professors or associate professors from within NIPS. About a total of 30 to 40 projects have been selected in the past, but in 2015, 115 projects had been selected as part of a move to raise the number of cooperative studies.

### 2. Planned collaborative project

Planned collaborative project themes are selected by NIPS, which are based on requests from researchers. Until 2007, there were two themes, "Physiological and neuroscientific studies into genetically modified model animals" and "Biomolecular sensors and physiological function". Additional themes were added in 2008, with "Functional and morphological analyses of cells and tissues by multi-photon microscopy" and "Medical and biological applications of phase-contrast cryo electron microscopy"（name changed to "Medical and biological applications of cutting edge electron microscopy" in 2011）, and in 2009 with, "Behavioral analysis of mouse and rat". Also, "Analysis of metabolic physiology for mouse and rat" began in 2011, while "Transfection study with primates", "Analysis of fluctuations in function research in life science", and "Multidisciplinary study of neural information" began in 2012. In addition, "Transfection study with viral vector neurological system" was started in 2013. Furthermore, "Purification of supra molecular complexes and analyses of their constituents by mass spectrometry" was started in 2016. Two projects, "Analysis of fluctuations in function research in life science" and "Multidisciplinary study of neural information" were closed in 2015, due to the finish of the related NINS projects. All these themes cover the most talked about scientific topics today, and are areas where NIPS is considered to be a frontrunner in Japan.

We expect to receive many new proposals. In regards to the proposal agenda, long discussions had been carried out at both faculty meetings and work meetings in 2012. The agreed requirements are as follows.

1) Proposals should clearly state the aim and experimental design of the research project, and should be completed within five years. However, depending on the state of the research, an extension period may be granted after the initial five years.
2) Proposals should specifically state the research area of interest. Broad themes will not be accepted.
3) There will be a limit to the number of proposals accepted. Each general collaborative research area category and research facility will accept five projects each at most, in principle.

The details of the planned collaborative research are as follows.

#### "Physiological and neuroscientific analysis of genetically modified model animals"

Genetically modified model animals help researchers studying physiology and brain science, where progress can only be made through studying individuals. The engineering required to create such model animals has taken huge leaps forward in recent years. Compared to other institutes, the Section of Mammalian Transgenesis at the Center for Genetic Analysis of Behavior in NIPS has made a large contribution to physiology and brain science, and reproductive biotechnology, by providing researchers all across the country with technology to produce genetically modified model animals. To support our cooperative studies, we provide the means

to develop adoptive models such as transgenic or knock-out mice and rats. Genetically modified rats have been particularly difficult to produce in the past, but the recently accepted use of embryonic stem（ES）cells and induced pluripotent stem（iPS）cells have made it possible to create knock-out rats. Researchers at our lab have already been successful in establishing ES and iPS germ cell lines from rats, from which they and then created three strains of knock-out rats and one strain of knock-in rats. In a calendar year of 2015, we have created a total of 37 transgenic or knock-out lines in mice and rats under five collaborative research projects. Successful application of artificial restriction enzymes to create knock-out/knock-in animals will facilitate our future contribution to requested task in NIPS.

### "Behavioral analysis of mouse and rat"

Today it has become possible to associate genes to particular behaviors, thanks to genetically modified animals. However, such research requires a large number of different behavioral tests that are also reproducible. Having individual laboratories conduct these tests individually is both complicated and produces a lot of waste. The Section for Behavior Patterns was set up in the Center for Genetic Analysis of Behavior at NIPS to provide analytical information on animal behavior to all the researchers involved in our cooperative research studies. As an expert in mouse behavior, Adjunct professor Tsuyoshi Miyakawa was invited to the section,and in 2009 started the planned cooperative research on"Behavioral analysis of mouse and rat". Currently, mouse analysis is being carried out, but the group plans to start rat analysis soon.

In 2015, Section for Behavior Patterns carried out 11 planned collaborative projects with outside research institutes, and 1 projects within NIPS. Seven strains of genetically modified mice were analyzed using comprehensive behavioral test battery. Additionally, eight strains including mutant mice and mice treated with drug were anlayzed by behavioral tests in the section. Raw data of behavioral test examined are disclosed in the mouse phenotype database (http://www.mouse-phenotype.org/). We promote standardization and effective use of behavior tests for mice, by publishing protocols of behavioral tests in *the Journal of Visualized Experiments*. So far, we published four protocols. Softwares used in those protocols are freely avaialble at the following URL: http://www.mouse-phenotype.org/software.html

In 2016, NIPS will perform only the collaborateive experiments carried over from last year, as the closure of the lab is scheduled in near future

### "Analysis of metabolic physiology for mice and rats"

The Section of Metabolic Physiology was set up in 2010, and the planned collaborative research project, "Metabolic physiology analysis of mice and rats", had started in 2011. Since then, researchers from within and outside NIPS have been looking at the following topics concerning genetically modified animals.

1) Measuring neural activity of individual neurons associated with motor function while awake.
2) Measuring the discharge of neurotransmitter substance in specific areas of the brain during freemovement.
3) Circuit behavior imaging of flavin and haemoglobin intrinsic signals in the brain using voltage sensitive dyes.
4) Measuring food intake and energy consumption during free movement.
5) Measuring body temperature, pulse rate, and blood pressure
6) Measuring the cardiac functuon and blood flow volume of mice *in vivo* or in vitro.

Nine collaborative research projects with researchers outside NIPS were conducted in 2015.

### "Ultrastructure analysis of biological specimens by cutting edge electron microscopy"

One phase-contrast electron microscope (PC-TEM) and two serial block-face scanning electron microscopes (SBF-SEMs) are mainly used for this joint research program. PC-TEM developed by NIPS shows the best performance when combined with a rapid-freezing sample preparation method. Under this condition, it is possible to study three-dimensional structures of unstained biological specimens, including isolated proteins, viruses, bacteria, cultured cells and tissues, to more or less their true state with 1 nm spatial resolution. On the other hand, SBF-SEMs are used for the studies of ultrastructural analysis of thick biological specimens, like a brain tissue. The specimens embedded in plastic resin are sliced by a diamond-knife and imaged by SEM continuously. Finally, the three-dimensional ultrastructure of the specimens is rebuild at dozens of nanometer resolution. The program support studies by using these state of the art electron microscopes. In 2015, five projects using PC-TEM and 25 projects using SBF-SEMs were carried out.

### "Functional and morphological analyses of cells and tissues by multi-photon excitation microscopy"

Two-photon excitation fluorescence microscope is a less invasive method for studying the microscopic structure and functions of cells in deep tissues of biological organisms. Currently, our institute has three upright two-photon excitation microscopes, and these allows us to observe the structure in depth of one millimeter with a spatial resolution of micrometer. Since the maintenance of two-photon microscope is complicated, NIPS is the only institute which can provide the opportunity of collaborative research with the high quality experience. Furthermore, we recently

build the two-photon fluorescence lifetime microscope system which enable us to observe the intermolecular interactions and the activity of signaling protein in living cell in deep tissue. We also working on single-molecule imaging using quantum dot in combination of fluorescence microscope. Using these "cutting-edge methods", we have conducted the collaborative researches. Recent successes are particularly in vivo $Ca^{2+}$ imaging, and long-term imaging of neurons in living mice.

In 2014, four planned collaborative projects was carried out. We also discussed about collaborative research with over ten groups, and introduced our multi-photon excitation microscopes to over ten groups.

### "Development and supply of viral vectors and gene-transfer to primates"

Advances in technology to control molecular functions or change neural activity by inserting certain genes into primate brains using virus vectors can lead to major possibilities. Getting to do such research, however, requires a long list of equipment and facilities to enable researchers to develop do things such as develop vectors, or insert vectors. A planned collaborative research project "Transfection study with primates" was launched in 2012 so that researchers could share their resources, and work together to unravel mysteries about higher brain functions and pathological conditions. In 2013, five projects were carried out and five projects were carried out in 2014.

The key point of the experiments is the development of suitable viral vectors. Also, viral vectors are useful not onlny for primates but also for other animals. Thus, a planned collaborative project "Gene transfer into nervous system using viral vectors" was started in 2013. In Section of Viral Vector Development, we promote the collaboration with many laboratories by providing various serotypes of AAV vectors, conventional lentiviral vectors, and highly efficient retrograde gene transfer vectors. Moreover, we proceed with the collaboration to exploit the more advantageous viral vectors. Up to 2014, we provided more than 100 viral vectors for other laboratories, and performed 2 planned collaborative research in 2013, and 4 in 2014. At present, very intriguing research results are being obtained.

In 2015, the two projects were merged as "Development and supply of viral vectors and gene-transfer to primates" and 14 planned collaborative research was performed in total.

The three examples of the achievements are as follows. The first study looked at whether virus vectors could help find out how compensatory motor system circuits in macaque monkey brains causes a monkey with a damaged motor cortex to recover its function. The second study used virus vectors and immunotoxins to look at how the basal ganglia functioned and its pathological condition. The team was then able to selectively eliminate the hyperdirect pathway in the neural pathway of the basal ganglia. The last study used virus vectors in RNA interference to suppress gene expression in primates, all of which was observed using PET molecular imaging.

In 2016, 13 research are planned.

### "Purification of supra molecular complexes and analyses of their constituents by mass spectrometry"

To understand the function of proteins in vivo, it is necessary to identify the constituents of supra molecular complexes pricisely. Therefore, there are gradually increasing needs for the support to perform purification of protein complexes from tisses and cells, and to identify constituents of the complex and the target antigens in auto- immune diseases by mass spectrometry. This project was newly started in 2016 to respond to the needs.

## 3. NIPS research meeting

In 2015, more than 1000 researchers took part in a total of 19 meetings, and the numbers keep growing each year. In 2016, 19 meetings are being planned. At each meeting, the country's best researchers gather to take part in serious discussions about the meeting's theme.

The discussions often lead to new collaborative research project ideas both within and outside the institute, or even new researching funding. For example, the Glial Young Researcher Meeting in 1994 – 1996 had lead to the priority area (B) "Glial cell role in the neural transmission regulation mechanism" discovery, and later on the became the priority area" Glial Neural Network". Another example would be the Biomolecular sensor related NIPS research meeting held in 2008, which lead to the Grant-in-Aid for scientific research on priority area "Cell Sensor". The establishment of two priority areas in 2015, "Thermal biology" and "Oscillology" was also triggered by the activity of NIPS research meeting. In addition, synapse research meetings, and research meetings on pain, have all helped progress in research communities across Japan, and have lead to the establishment of new fields.

More recently, there have been a number of debates going on about whether it was useful or not to hold researching meetings on the same topic every year.

As a result, the meeting application guidelines were revised, and put into use from 2013. The revised guidelines are as follows.

1) Research meetings: This research debate meeting will aim to create a new research field or develop a new technology, and will only involve up to 100 participants, one of which must be a Professor or

Associate Professor from NIPS. NIPS will provide some financial support to pay for travel expenses.

2) Meeting duration: Up to three days.
3) Meeting venue: Meetings will take place within the Okazaki area, where the National Institutes for Natural Sciences is based. The Okazaki Conference Center is available for use, and reservations can be made by contacting the International Research Support division（TEL: 0564-55-7138）.
4) Research report: The organizer is required to submit a report to the institute head within 30 days after the meeting has ended.
5) Other: Researching meeting themes may only be repeated for three consecutive years. If you wish to continue research meetings on a theme for more than three years, please submit an agenda that has included new points of discussion.

### 4. NIPS International Workshop

To promote the international efforts at NIPS, the NIPS International workshop was launched in 2008. The workshop invites renowned scientists from around the world, and a wide-range of participants from around the country. All presentations and discussions are held in English. In 2015, one International Workshop was held. The themes was TRPs and SOCs --Unconventional $Ca^{2+}$ Physiology--". In 2016, two NIPS international workshops are scheduled.

### 5. Cooperative study by high voltage electron microscopy

NIPS is the unique organization running the high voltage electron microscope（H-1250M）that is only used for medical and biological researches. Worldwide researchers who are working on collaborative research projects use the microscope every year. The accelerating voltage of 1000 kV allows researchers to take a look into a deep area of the cell at higher resolution. Therefore, it is possible to study the conformations and connections of neurons in brain tissues, or rebuild three-dimensional ultrastructure of cellular components using electron tomography. Currently, the microscope is being used in collaborative studies of biological specimens involving 1) three-dimensional analysis, 2) high-resolution observation, and 3) observation in near native conditions. Since the program was started, the majority of users have come from outside of the institute. This emphasizes the role of NIPS as a resource provider. In 2015, 9 projects had been carried out. A digital camera was installed in 2012, which accelerates three-dimensional structural analysis by high-voltage electron tomography. In 2016, 10 projects will be carried out.

### 6. Cooperative study by functional imaging（combined study of 2011's cooperative study by functional magnetic resonance imaging and cooperative study by magneto- encephalography）

Until 2011, NIPS had been conducting two individual cooperative studies on its large-scale functional imaging machines, the magnetic resonance imaging machine, and the magnetoencephalography machine. However, as it became apparent that many researchers used both machines, it would be more efficient for everyone if the two studies were combined into one in 2012.

Magnetic resonance imaging involves two research themes, "non-destructive three-dimensional observation of living organisms" and "structure and energy state observation of organic activity, including brain activators". Currently, the institute has a 3 Tesla machine in 2000, which is twice as powerful as the standard 1.5 Tesla machine, and has a considerable advantage when measuring cerebral blood flow in brain activator tests. Another characteristic is that it is capable of running primate brain activator tests. On top of this, it systematically processes all experimental designs, image data, and statistical image analysis, making it more than just a high-resolution image machine, but something that produces high quality data that researchers need. In 2010, the two machines were interlocked, becoming a dual system capable of analyzing brain function related to social communication. A new 7 Tesla magnetic resonance imaging machine for human was introduced in 2014, and the operation was started in 2015. In 2016, 3 cooperative study projects using 7T machine will be performed for the purpose of technical assessment and development. After confirming stable operation, it will be fully provided for cooperative studies.

In 1991, the first 37 channel magnetoencephalography（MEG）machine in Japan was installed at NIPS, and has since been a pioneer for MEG studies, even getting recognition from the international community. At the same time, researchers from universities and institutes without a MEG machine took part in collaborative studies with NIPS, many of who discovered fascinating results. Even today, NIPS is the only institute providing outside researchers the opportunity to use the MEG machine in cooperative studies using large facilities. In 2002, a new whole-head type MEG machine was installed, allowing clinical test measurements impossible at other universities to be made at NIPS. Cooperative MEG study themes either come under, "higher brain function investigations such as judgment, memory, and learning" or, "sensory and motor function investigations". A significant problem that is likely to come up in the near future is how to use the MEG machine simultaneously with other techniques such as functional magnetic resonance imaging（fMRI）, transcranial magnetic stimulation（TMS）and near infrared spectroscopy（NIRS）.

# NIPS International Workshop

## TRPs and SOCs ～Unconventional $Ca^{2+}$ Physiology～

The conference was held at Okazaki Conference Center on June 4th and 5th. We had 96 participants of wide range of research fields including physiology, pharmacology, structural biology, biotechnology, pharmaceutical science, and clinical science (http://www.nips.ac.jp/circulation/TRP2015workshop/). The purpose of this conference was to create a new unitary framework for understanding the molecular diversities of transient receptor potential (TRP) and store-operated $Ca^{2+}$ (SOC) channels and their functional relevance of unconventional $Ca^{2+}$ signalings required for various physiological and pathophysiological processes. The conference consisted of 19 oral presentations by top-class investigators including 6 foreign speakers, 16 poster presentations by young investigators and graduate students, and one Keynote Lecture entitled 'Role of TRP channels in respiratory control' by Dr. Yasumasa Okada of Murayama Medical Center, and one Technological Lecture entitled 'Mechanomedicine: Applications of mechanobiology to regenerative and reproductive medicine' by Dr. Keiji Naruse of Okayama University. All presentations were well discussed, and we also considered possibilities of future international collaborations and cooperations.

# The 46th NIPS international Symposium

## The 46th NIPS International Symposium, "Homeostatic mechanisms among interacting organ systems - Key to understanding obesity" October 2- 3, 2015, Nagoya Congress Center, Nagoya, Aichi, Japan

The 46th NIPS International Symposium held at Nagoya Congress Center in Nagoya City from October 2nd to 3rd, 2015. This symposium was co-held with the 36th Annual Meeting of Japan Society for the Study of Obesity (JASSO) and the 8th Asia-Oceania Congress of Obesity (AOCO) with 159 participants including 7 oversea speakers (total 20 speakers). All speakers presented their recent studies with high quality level in science. Prof. Joseph S. Takahashi and Richard Palmiter who are special lecturers of the 36th Annual Meeting of JASSO and leading authorities on biological clock system and food intake regulation, respectively, also participated in this symposium as a discussant. This was the first NIPS symposium co-held with clinical scientific meetings. All participants enjoyed intensive and fruitful discussion about their common scientific interests regarding "Obesity".

## Program

### Oct 2 (Fri) 2015

**Opening remarks**

**Yasuhiko Minokoshi** (National Institute for Physiological Sciences)

**Session 1**

**Chair:** Toshihiko Yada, FeiFan Guo

**16:50-17:20**

The neurobiology of homeostatic hunger

**Scott M. Sternson** (Janelia Research Campus, HHMI, Ashburn, Virginia, USA)

**17:20-17:38**

Pathophysiological roles of adipokine and epigenome dysregulation in obesity

**Toshimasa Yamauchi** (University of Tokyo)

**17:38-17:56**

Inter-organ neural network mediate the regulation of systemic energy metabolism

**Tetsuya Yamada** (Tohoku University)

**17:56-18:14**

Regulation of skeletal muscle mass and fat mass by myokines and origin of ectopic fat accumulation in skeletal muscle

**Kunihiro Tsuchida** (Fujita Health University)

**18:14-18:32**

Hepatokine selenoprotein P and skeletal muscle receptor LRP1 induce exercise-insensitivity by inhibition of ROS and AMPK

**Hirofumi Misu**[1,2] ([1]Kanazawa University, [2]PRESTO, Japan Science and Technology Agency)

**18:32-18:50**

Role of novel variants of PGC-1α in the regulation of energy metabolism

**Kazuhiro Nomura** (Kobe University)

### Oct 3 (Sat)

**Session 2**

**Chair:** Shin-Ichiro Imai, Michihiro Matsumoto

**8:10-8:28**

AMP-activated protein kinase in CRH neurons in the

PVH controls food selection behavior

**Shiki Okamoto**[1,2], Tatsuya Sato[2], Yasuhiko Minokoshi[1,2]

([1]National Institute for Physiological Sciences, [2]SOKENDAI)

**8:28-8:58**

Discovery and characterization of a novel class of endogenous lipids

**Alan Saghatelian** ,Mark M. Yore, Ismail Syed, Pedro M. Moraes-Vieira,Tejia Zhang, Mark A. Herman, Edwin A. Homan, Rajesh T. Patel, Jennifer Lee,Shili Chen, Odile D. Peroni, Abha S. Dhaneshwar, Ann Hammarstedt, Ulf Smith,Timothy E. McGraw, Barbara B. Kahn (The Salk Institute for Biological Studies, Peptide Biology Laboratory, USA)

**8:58-9:16**

Role of dsRNA-mediated immunometabolic regulation in obesity

**Takahisa Nakamura** (Divisions of Endocrinology and Developmental Biology, Cincinnati Children's Hospital Medical Center, USA)

**9:16-9:34**

The transcriptional coregulator CITED2 regulates adipose tissue mass by enhancing preadipocyte proliferation and PPARγ expression through Rb inactivation

**Michihiro Matsumoto** (National Center for Global Health and Medicine)

## Session 3

**Chair:** Shingo Kajimura, Takahisa Nakamura

**9:34-10:04**

Adipose tissue controls systemic $NAD^+$ biosynthesis through the secretion of extracellular nicotinamide phosphoribosyltransferase (eNAMPT)

**Shin-ichiro Imai** (Department of Developmental Biology, Department of Medicine (Joint), Washington University School of Medicine, USA)

**10:04-10:22**

Engineering fat cell fate to fight obesity and metabolic diseases

**Shingo Kajimura** (University of California, UCSF Diabetes Center and Department of Cell and Tissue Biology, USA)

**10:22-10:40**

Regulation of higher-order chromatin structure during thermogenesis in brown adipocytes

**Takeshi Inagaki**[1], Yohei Abe[1], Royhan Rozqie[1], Yoshihiro Matsumura[1],Shingo Kajimura [2], Juro Sakai[1]

([1]University of Tokyo, [2]UCSF Diabetes Department of Cell and Tissue Biology, University of California,USA)

## Session 4

**Chair:** Tetsuya Yamada, Takeshi Inagaki

**14:20-14:38**

Amino acid regulation of metabolism

**FeiFan Guo** (Institute for Nutritional Sciences, Shanghai Institute for Biological Sciences, Chinese Academy of Sciences, China)

**14:38-14:56**

Regulation of hepatic glucose production by central insulin action through vagus and kupffer cells

**Hiroshi Inoue** (Kanazawa University)

**14:56-15:14**

Mechanisms by which PTP1B affects energy balance

**Ryoichi Banno** (Nagoya University)

**15:14-15:32**

Impact of successful leptin replacement therapy in Japan on adult and child, systemic and partial lipodystrophy

**Kiminori Hosoda**, Toru Kusakabe, Daisuke Aotani, Ken Ebihara, Kazuwa Nakao (Kyoto University)

## Session 5

**Chair:** Masamitsu Nakazato, Hiroshi Inoue

**15:32-16:02**

Neural dynamics underlying hunger

**Zachary A. Knight** (Department of Physiology, University of California, USA)

**16:02-16:20**

Gut hormones regulating energy homeostasis

**Masamitsu Nakazato** (University of Miyazaki)

**16:20-16:38**

$Na^+$,$K^+$-ATPase in the arcuate nucleus senses systemic energy states to regulate feeding behavior

**Toshihiko Yada**, Hideharu Kurita, Masanori Nakata (Jichi Medical University)

## Closing remarks

**Keiji Imoto** (Director General, National Institute for Physiological Sciences)

In recent years, it has become necessary to train scientists, who are highly skilled and creative, to support the promotion of creative research and pioneer in leading scientific areas, which is a strong demand in our country.

According to the increasing internationalization of academic research, it is also necessary to take enormous effort to train international-minded researchers with broad outlook, particularly for interdisciplinary research in multiple fields.

The Graduate University for Advanced Studies (SOKENDAI) was established in 1988 to develop creative international researchers with wide-ranging vision capable of leading the latest streams of research under close cooperation with the inter-university research institutes. It has accepted graduate students since 1989.

SOKENDAI is composed of 6 schools; Cultural and Social Studies; Physical Sciences; High Energy Accelerator Science; Multidisciplinary Sciences; Life Science and Advanced Sciences.

School of Life Science is constituted three departments; Department of Genetics (based on NIG (National Institute of Genetics)), Department of Basic Biology (based on NIBB (National Institute for Basic Biology)), and Department of Physiological Sciences (based on NIPS (National Institute for Physiological Sciences)).

The outline of Department of Physiological Sciences.

The aim of this department is to promote researchers who mainly investigate underlying mechanisms the function of human body in a comprehensive manner.

Physiological Science plays a central role to combine various fields in basic medicine, as sharing the base with bioscience and maintains close connections with clinical medicine.

The policy is to promote educated researchers who have a broad knowledge of medicine and physiological science, and is to be able to find the function from the molecular, which is the basic organization of living bodies, to individual body from an original physiological scientific points of view.

**SOKENDAI Students（NIPS）as of 2016**

# International Exchanges

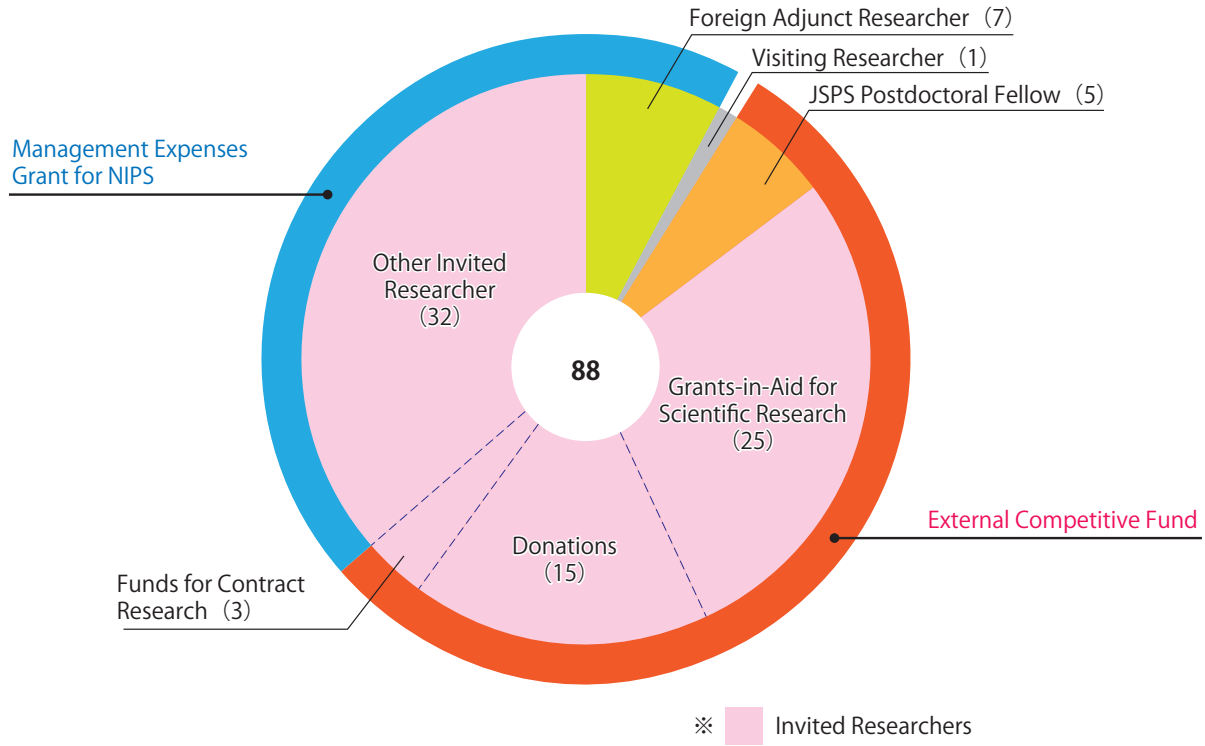
NIPS is an internationally recognized research center, and international exchanges are performed flourishingly. NIPS has the positions of foreign research staff (3 visiting professors and 3 visiting research fellows), and many world first-class researchers have made research collaboration using this system. Besides research collaboration, visiting professors contribute to education of young researchers. In 2014, NIPS started the International Collaboration Laboratory and Dr. Ravshan Sabirov, an adjunctive professor, was selected as the Principal Investigator to run the lab for 3 years. In addition, using the systems such as JSPS postdoctoral fellowship, foreign researchers and graduate students conduct research at NIPS. Recently, an increasing number of foreign students enter Department of Physiological Sciences of SOKENDAI graduate school.

One of the main international exchange activities at NIPS is the international symposium. It is held once or twice a year. A NIPS professor serves as an organizer, and usually 10-15 top researchers from abroad and a similar number of top domestic researchers are invited. The number of participants is around 100-150. In 2015, the 46th NIPS International Symposium entitled "Homeostatic mechanisms among interacting organ systems -Key to understanding obesity" was organized by Professor Minokoshi. It was co-held with the 36th Annual Meeting of Japan Society for the Study of Obesity (JASSO) and the 8$^{th}$ Asia-Oceania Congress of Obesity (AOCO) at Nagoya Congress Center from Oct 2nd to 3rd. There were 159 participants including 7 oversea speakers (total 20 speakers). In addition, the international workshop, which is an international version of NIPS research meetings, was started in FY2008 and is held once or twice a year. In 2015, one workshop entitled "TRPs and SOCs --Unconventional $Ca^{2+}$ Physiology--" was held to provide researchers with opportunities for intensive discussion and international communications.

NIPS has an academic contract or a memorandum of understanding for academic interaction with foreign institutions as follows, and is actively conducting joint academic activities including collaborative researches. The institutions are Uzbekistan Academy of Science, Research Institute for Physiology and Biophysics (Uzbekistan); Korea University, Faculty of Medicine and Yonsei University, Faculty of Medicine and Dentistry (Korea); Tübingen University, Werner Reichardt Center for Integrative Neuroscience (Germany); Chulalongkorn University Faculty of Pharmaceutical Sciences (Thailand); and University of New South Wales, Faculty of Medicine (Australia). Especially, NIPS has organized symposia focusing on higher brain function with Tübingen University CIN every year since 2012 either in Germany or in Japan.

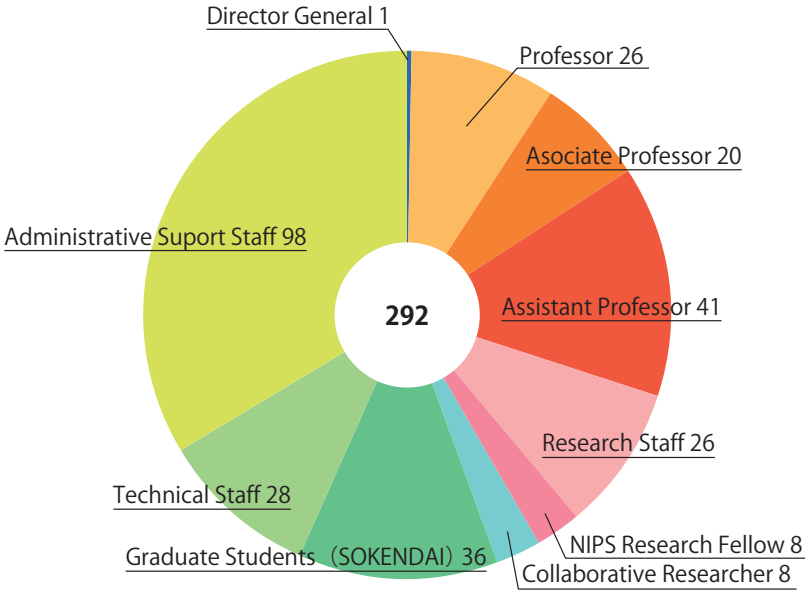
Besides these, many international research collaborations of high quality are performed at the individual researchers' level, supported by the budget of NIPS and also research grant from outside.

## Number of Foreign Researchers



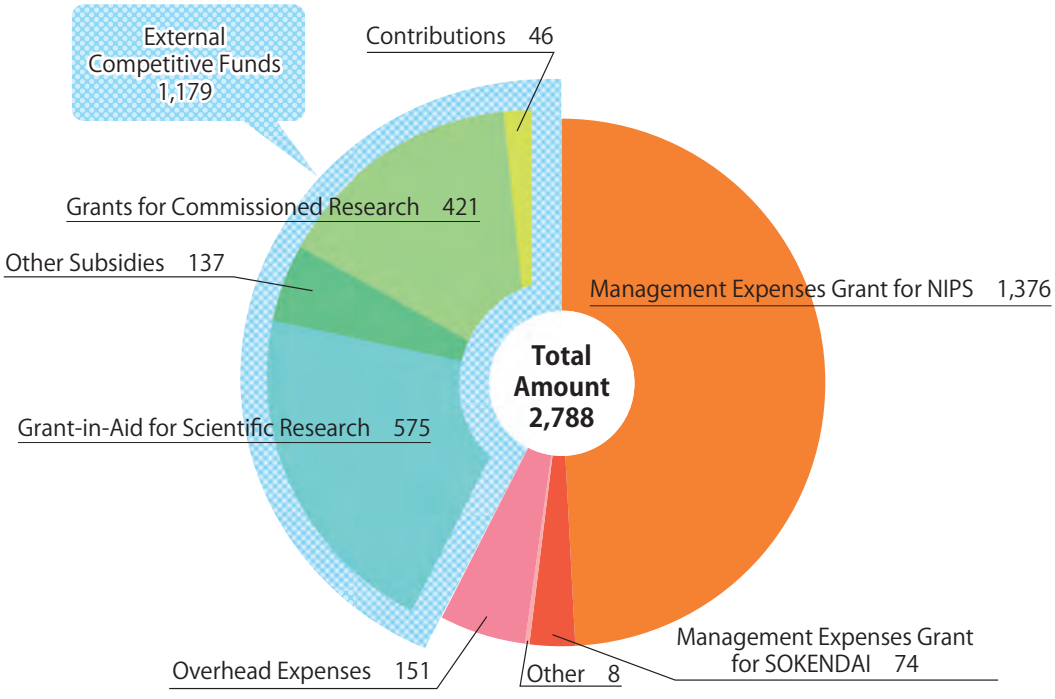
# Current State

## Staffs




## Budget

numbers are in million yen/As of May, 2016




The budget consists of grants from the government (Management Expenses Grants・SOKENDAI Research Grants) as well as many competitive funds (Grants-in-Aid for Scientific Research, Funds for Contract Research etc.) which are awarded by competitive selection process.

# Common Facilities in Okazaki

## ▶ Okazaki Library and Information Center

The Library collects, arranges and preserves journals and books of the three Institutes, and provides them for common use for the Institutes staff and their guests.
<main function>

1. 24hours use by a library card
2. Information retrieval service
（Web of Science, SCOPUS, SciFinder, etc）.

## ▶ Okazaki Conference Center

Okazaki Conference Center was founded on February, 1996 to promote international and domestic conference program of research and education.

Conferece Room A（capacity of 200）
Conferece Room B（capacity of 120）
Conferece Room C（2 rooms, capacity of 50 each）

Conferece Room

## ▶ Accommodation

The lodging houses（Mishima Lodge and Myodaiji Lodge）are provided for guests, both foreign and domestic, for the common use of the three Institutes（NIPS, NIBB and IMS）.

Myodaiji Lodge

The lodging capacities are as follows :

| | Single Room | Twin Room | Family Room |
|---|---|---|---|
| Mishima Lodge | 60 | 14 | 14 |
| Myodaiji Lodge | 17 | — | 3 |

## ▶ The Sakura Nursery School

The Sakura nursery school is the institutional child care facility established for supporting both research and child-rearing. The school accept a child from the 57th day of after the birth, and is supporting a researcher's smooth return to research activity.

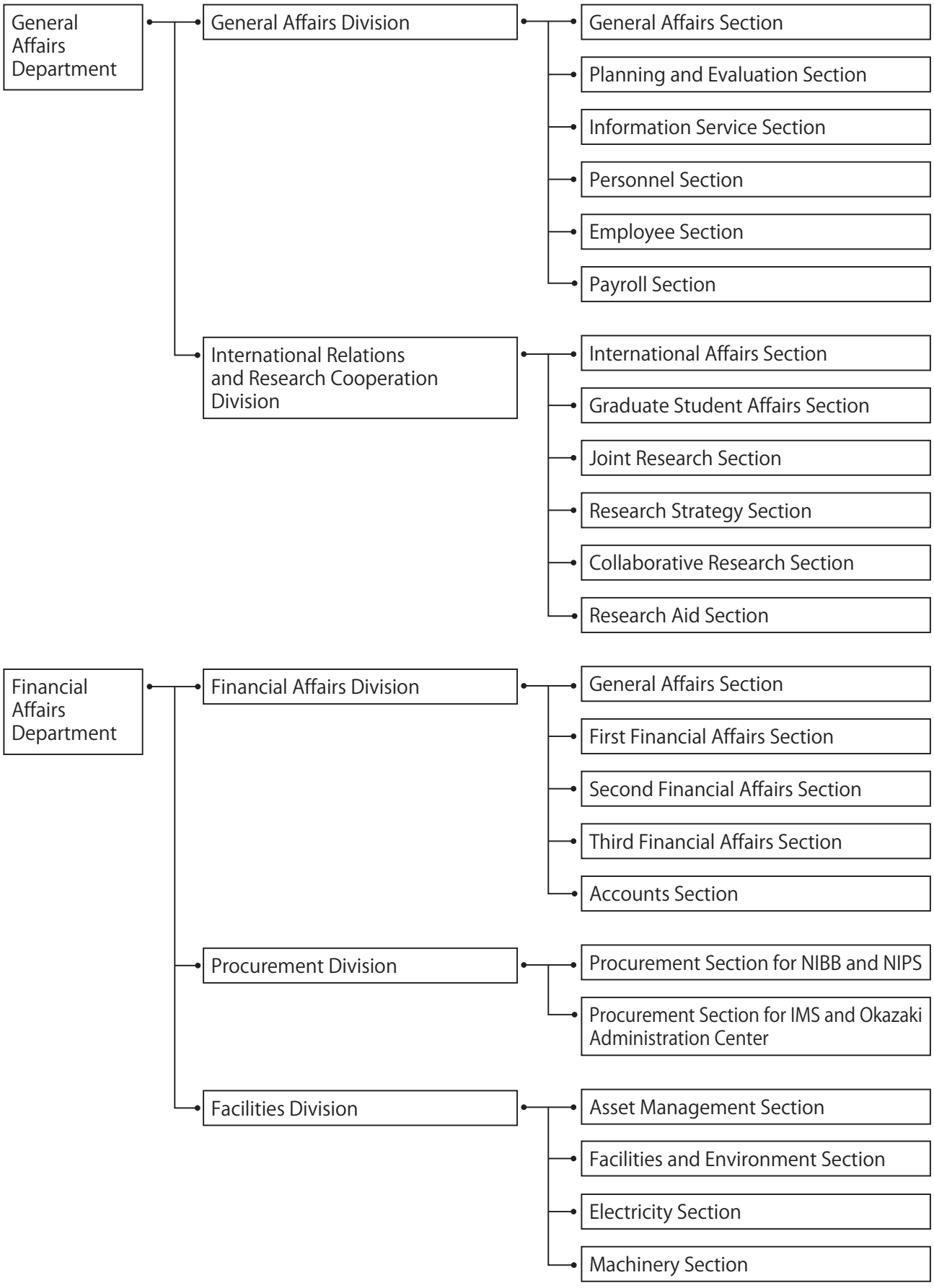
Age: From the 57th day of after the birth to 3 years old

Capacity: 18 persons

Use candidate: The officers, reserchers, visiting researchers, graduate students at Okazaki three institutes Opening day: From Monday to Friday

Opening time: From 8:00 to 19:00（maximum extension 20:00）Childcare form: Regular childcare, temporary nursery care

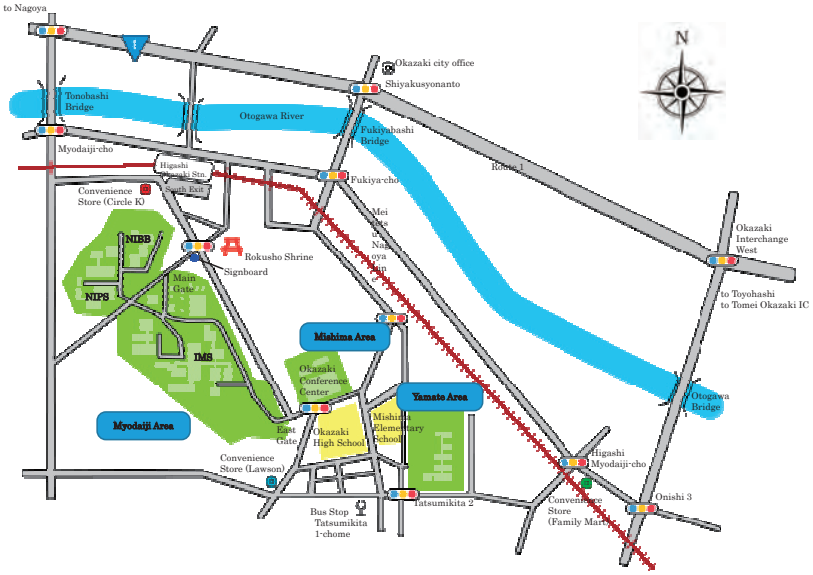
# Okazaki Administration Center

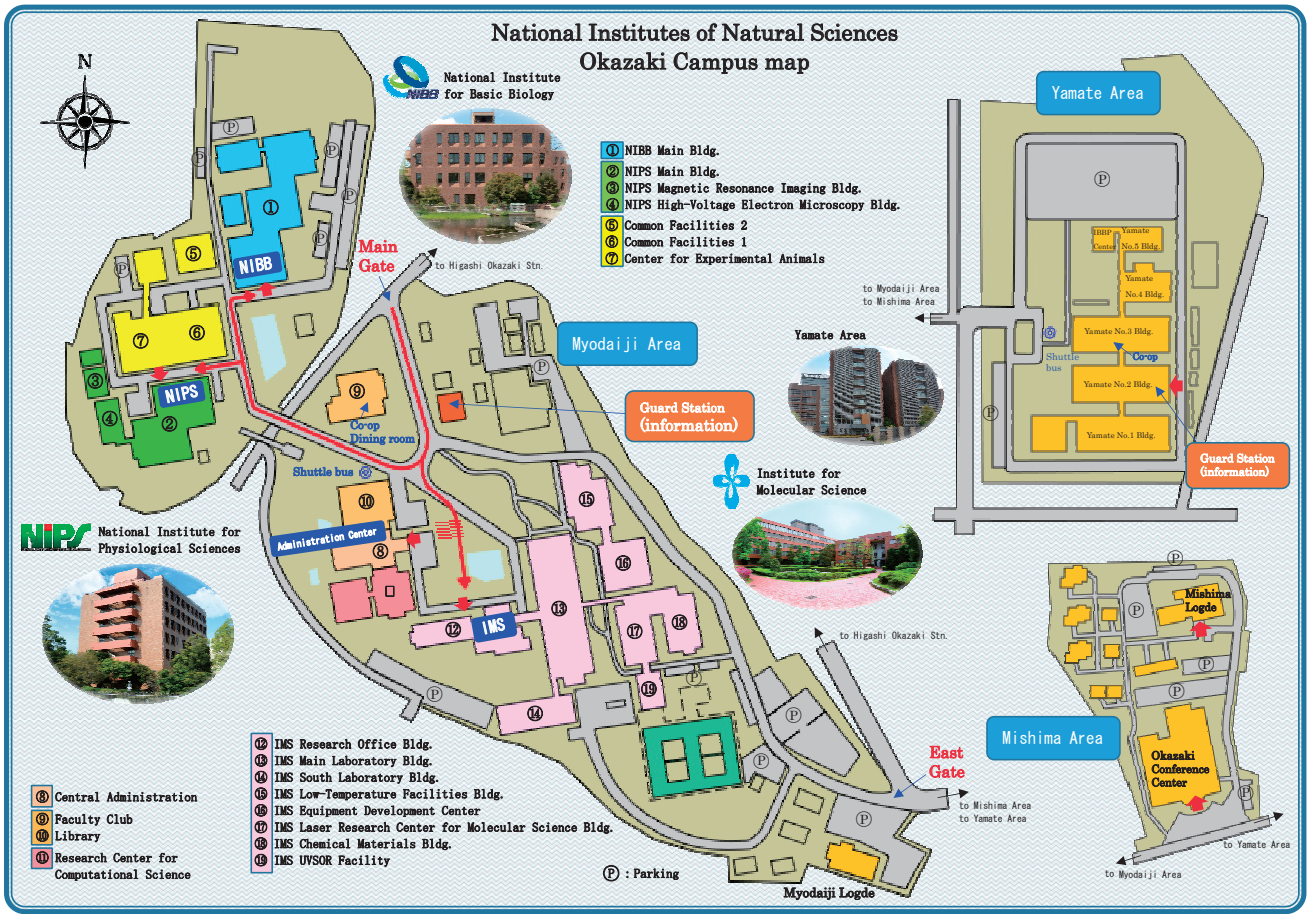



As of Apr., 2016

# Campus Map

| According to area | Use classification |
|---|---|
| Myodaiji Area | National Institute for Physiological Sciences / National Institute for Basic Biology / Institute for Molecular Science / Okazaki Administration Office / Staff hall / Lodging for staff / Myodaiji Lodge |
| Mishima Area | Okazaki Conference Center / Mishima Lodge |
| Tatsumi Area | Lodging for staff |
| Yamate Area | Okazaki Institute for Integrative Bioscience |



# Location

## From Central Japan International Airport

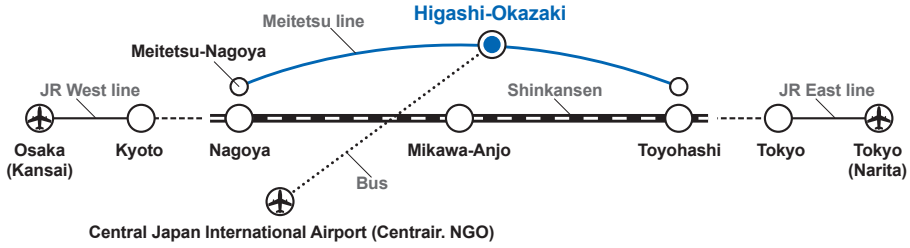
**A) By bus**
Get on the Meitetsu Airport Bus bound for Okazaki Station and get off at Higashi Okazaki Station

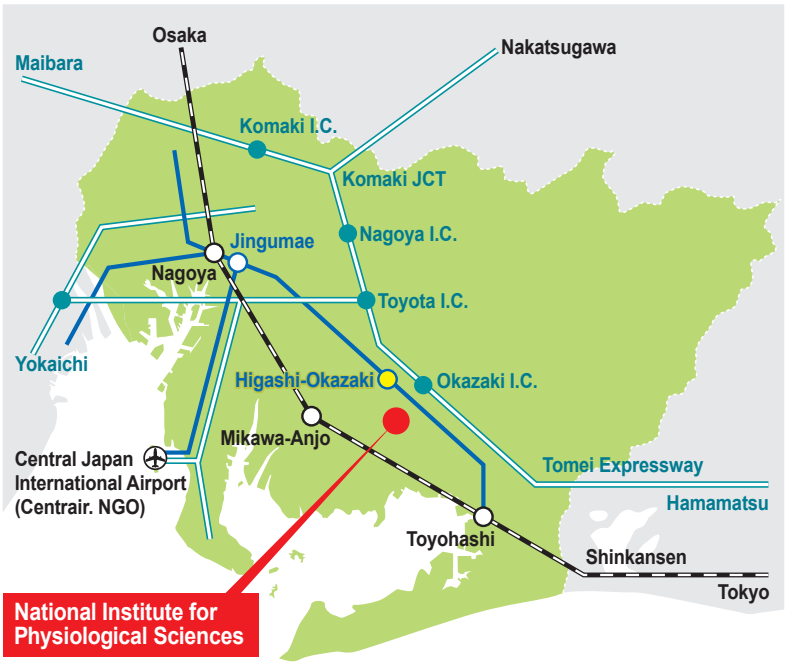
**B) By train**
Take the Meitetsu train from Central Japan International Airport to Higashi Okazaki Station. NIPS is a 7-minute walk up the hill on the south side of the station.

## From New Tokyo International Airport (Narita Airport)

**A) By plane (*Recommended)**
Transfer to Central Japan International Airport

**B) By train**
Take the JR Narita Express airport shuttle train from Narita to Tokyo Station (approximately 60 minutes) and change trains to the Tokaido shinkansen (bullet train).
At Toyohashi JR Station (approximately 2.5 hours from Tokyo), change trains to the Meitetsu Line's Limited Express train bound for Gifu. Get off at Higashi Okazaki Station (approximately 20 minutes from Toyohashi). Turn left (south) at the ticket gate and exit the station. NIPS is a 7-minute walk up the hill.

# Staff Index

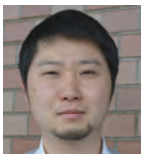
## C

CHEN, I-Shan
8
Project Assistant Professor
*Div. of Biophysics & Neurobiology

CHIKAZOE, Junichi
34
Associate Professor
*Sec. of Brain Function Information

CHIKEN, Satomi
24
Assistant Professor
*Div. of System Neurophysiology

## E



ETO, Kei
19
Assistant Professor
*Div. of Homeostatic Development

## F

FUKATA, Masaki
10 44
Professor
*Div. of Membrane Physiology
*Sec. of Health & Safety Management

FUKATA, Yuko
10
Associate Professor
*Div. of Membrane Physiology

FUKUNAGA, Masaki
26
Associate Professor
*Div. of Cerebral Integration

FURUE, Hidemasa
17
Associate Professor
*Div. of Neural Signaling

FURUSE, Mikio
13 33
Professor
*Div. of Cell Structure
*Sec. of Electron Microscopy

## G

GO, Yasuhiro
23
Project Associate Professor
*Div. of Behavioral Development

GODA, Naokazu
21
Assistant Professor
*Div. of Sensory & Cognitive Information

## H

HARADA, Tokiko
26
Project Assistant Professor
*Div. of Cerebral Integration

HATANAKA, Nobuhiko
24
Assistant Professor
*Div. of System Neurophysiology

HIGASHINO, Atsunori
29
Project Assistant Professor (Grant Project)
*Sec. of NBR Project

HIRABAYASHI, Masumi
37
Associate Professor
*Sec. of Mammalian Transgenesis

## I

IKENAKA, Kazuhiro
9 35
Professor
*Div. of Neurobiology & Bioinformatics
*Center for Genetic Analysis of Behavior

INADA, Hiroyuki
19
Project Assistant Professor
*Div. of Homeostatic Development

INUI, Koji
25
Associate Professor
*Div. of Integrative Physiology

ISA, Tadashi
22 36
Professor
*Div. of Behavioral Development
*Sec. of Viral Vector Development

ISHIKAWA, Ayako
20
Assistant Professor
*Div. of Visual Information Processing

ISODA, Masaki
23
Professor
*Div. of Behavioral Development

IZUMI, Yasushi
13
Associate Professor
*Div. of Cell Structure

## K

KAGAWA, Tetsushi
45
Project Professor
*Research Enhancement Strategy Office

KAKIGI, Ryusuke
25 40 45
Professor
*Div. of Integrative Physiology
*Center for Communication Networks
*Research Enhancement Strategy Office

KANO, Masanobu
29
Adjunct Professor
*Sec. of Advanced Research Support

KAWAGUCHI, Yasuo
18
Professor
*Div. of Cerebral Circuitry

KIDA, Tetsuo
25
Project Associate Professor (Grant Project)
*Div. of Integrative Physiology

KIMURA, Rie
20
Project Assistant Professor
*Div. of Visual Information Processing

KITADA, Ryo
26
Assistant Professor
*Div. of Cerebral Integration

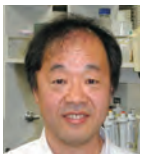
KOBAYASHI, Kenta
36
Associate Professor
*Sec. of Viral Vector Development

KOIKE, Takahiko
26
Project Assistant Professor (Grant Project)
*Div. of Cerebral Integration

KOMATSU, Hidehiko
21
Professor
*Div. of Sensory & Cognitive Information

KONDO, Hideki
24
Project Assistant Professor (Grant Project)
*Div. of System Neurophysiology

KUBO, Yoshihiro
8 29 45
Professor
*Div. of Biophysics & Neurobiology
*Center for Research Collaboration
*Research Enhancement Strategy Office



KUBOTA, Yoshiyuki
18 33
Associate Professor
*Div. of Cerebral Circuitry
*Sec. of Electron Microscopy

M

MARUYAMA, Megumi
45
Project Associate Professor
*Research Enhancement Strategy Office

MINOKOSHI, Yasuhiko
16 39 45 48
Professor
*Div. of Endocrinology & Metabolism
*Sec. of Metabolic Physiology
*Research Enhancement Strategy Office
*Center for Experimental Animals

MIYAKAWA, Tsuyoshi
38
Adjunct Professor
*Sec. of Behavioral Patterns

MIYASHITA, Toshio
20
Project Assistant Professor
*Div. of Visual Information Processing

MOHRI, Tatsuma
28
Assistant Professor
*Sec. of Individual Researches

MORISHIMA, Mieko
18
Assistant Professor
*Div. of Cerebral Circuitry

MURAKAMI, Masataka
27 41
Associate Professor
*Sec. of Individual Researches
*Sec. of Research Archives

MURAKOSHI, Hideji
32
Associate Professor
*Sec. of Multiphoton Neuroimaging

MURATA, Kazuyoshi
31 33
Associate Professor
*Sec. of Brain Structure Information
*Sec. of Electron Microscopy

N

NABEKURA, Junichi
19 32 45
Professor
*Div. of Homeostatic Development
*Sec. of Multiphoton Neuroimaging
*Research Enhancement Strategy Office

NAKAGAWA, Eri
42
Project Assistant Professor
*Sec. of Physiology & Medicine Education

NAMBU, Atsushi
24 29 36
Professor
*Div. of System Neurophysiology
*Sec. of Viral Vector Development
*Sec. of NBR Project

NISHIDA, Motohiro
15
Professor
*Div. of Cardiocirculatory Signaling

NISHIMURA, Akiyuki
15
Project Assistant Professor
*Div. of Cardiocirculatory Signaling

NISHIMURA, Yukio
22
Associate Professor
*Div. of Behavioral Development

NUMAGA-TOMITA, Takuro
15
Assistant Professor
*Div. of Cardiocirculatory Signaling

## O

OHASHI, Masato
27
Assistant Professor
*Sec. of Individual Researches

OHNO, Nobuhiko
9
Project Associate Professor
*Div. of Neurobiology & Bioinformatics

OKADA, Toshiaki
14
Project Associate Professor
*Div. of Cell Signaling

OKAMOTO, Hidehiko
25
Associate Professor
*Div. of Integrative Physiology

OKAMOTO, Shiki
16
Assistant Professor
*Div. of Endocrinology & Metabolism

OTANI, Tetsuhisa
13
Assistant Professor
*Div. of Cell Structure

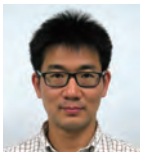
OTSUKA, Takeshi
18
Assistant Professor
*Div. of Cerebral Circuitry

## S

SADATO, Norihiro
26 30 34
Professor
*Div. of Cerebral Integration
*Supportive Center for Brain Research
*Sec. of Brain Function Information

SAITO, Shigeru
14
Assistant Professor
*Div. of Cell Signaling

SAKAMOTO, Kiwako
25 45
Assistant Professor
*Div. of Integrative Physiology
*Research Enhancement Strategy Office



SANADA, Takahisa
21
Project Assistant Professor
*Div. of Sensory & Cognitive Information

SANO, Hiromi
24
Assistant Professor
*Div. of System Neurophysiology

SATAKE, Shinichiro
17
Assistant Professor
*Div. of Neural Signaling

SATO, Hiroshi
48
Project Professor
*Sec. of Coordinator for Animal Experimentation

SATO, Koji
47
Project Associate Professor (Grant Project)
*Orion Project

SAWAMOTO, Kazunobu
12
Adjunct Professor
*Div. of Neural Development & Regeneration

SETOU, Mitsutoshi
11
Adjunct Professor
*Div. of Neural Systematics

SHIMIZU, Takeshi
9
Assistant Professor
*Div. of Neurobiology & Bioinformatics

SHIMOMURA, Takushi
8
Assistant Professor
*Div. of Biophysics & Neurobiology

SUGAWARA, Taichi
13
Project Assistant Professor
*Div. of Cell Structure

SUZUKI, Yoshiro
14 39
Assistant Professor
*Div. of Cell Signaling
*Sec. of Metabolic Physiology

## T

TAKADA, Masahiko
29
Adjunct Professor
*Sec. of Advanced Research Support

TAKAO, Keizo
38
Professor
*Sec. of Behavioral Patterns

TAKAYAMA, Yasunori
14
Project Assistant Professor (Grant Project)
*Div. of Cell Signaling

TARUSAWA, Etsuko
37
Project Assistant Professor (Grant Project)
*Sec. of Mammalian Transgenesis

TATEYAMA, Michihiro
8
Associate Professor
*Div. of Biophysics & Neurobiology

TOMINAGA, Makoto
14 42
Professor
*Div. of Cell Signaling
*Sec. of Physiology & Medicine Education

## U

UCHIDA, Kunitoshi
14
Assistant Professor
*Div. of Cell Signaling

URANO, Toru
45 48
Project Professor
*Research Enhancement Strategy Office
*Center for Experimental Animals

YOSHIMURA, Takeshi
9
Assistant Professor
*Div. of Neurobiology & Bioinformatics

YOSHIMURA, Yumiko
20 45
Professor
*Div. of Visual Information Processing
*Research Enhancement Strategy Office

## W

WAKE, Hiroaki
19
Professor
*Div. of Homeostatic Development

WANG, Chen-Chi
48
Assistant Professor
*Center for Experimental Animals

## Y

YAMAGATA, Yoko
17
Assistant Professor
*Div. of Neural Signaling

YOKOI, Isao
21
Assistant Professor
*Div. of Sensory & Cognitive Information

YOKOI, Norihiko
10
Assistant Professor
*Div. of Membrane Physiology

YOSHIDA, Masatoshi
23
Assistant Professor
*Div. of Behavioral Development

# National Institute for Physiological Sciences 2016

Published July 2016

National Institutes of Natural Sciences

**National Institute for Physiological Sciences**

Editor: KAKIGI, Ryusuke

Myodaiji, Okazaki 444-8585, Japan

Phone: +81-564-55-7700 Fax: +81-564-52-7913

http://www.nips.ac.jp


National Institute of Natural Sciences

**National Institute for Physiological Sciences**

Myodaiji,Okazaki 444-8585,Japan

Phone:+81-564-55-7700　Fax:+81-564-52-7913

http://www.nips.ac.jp