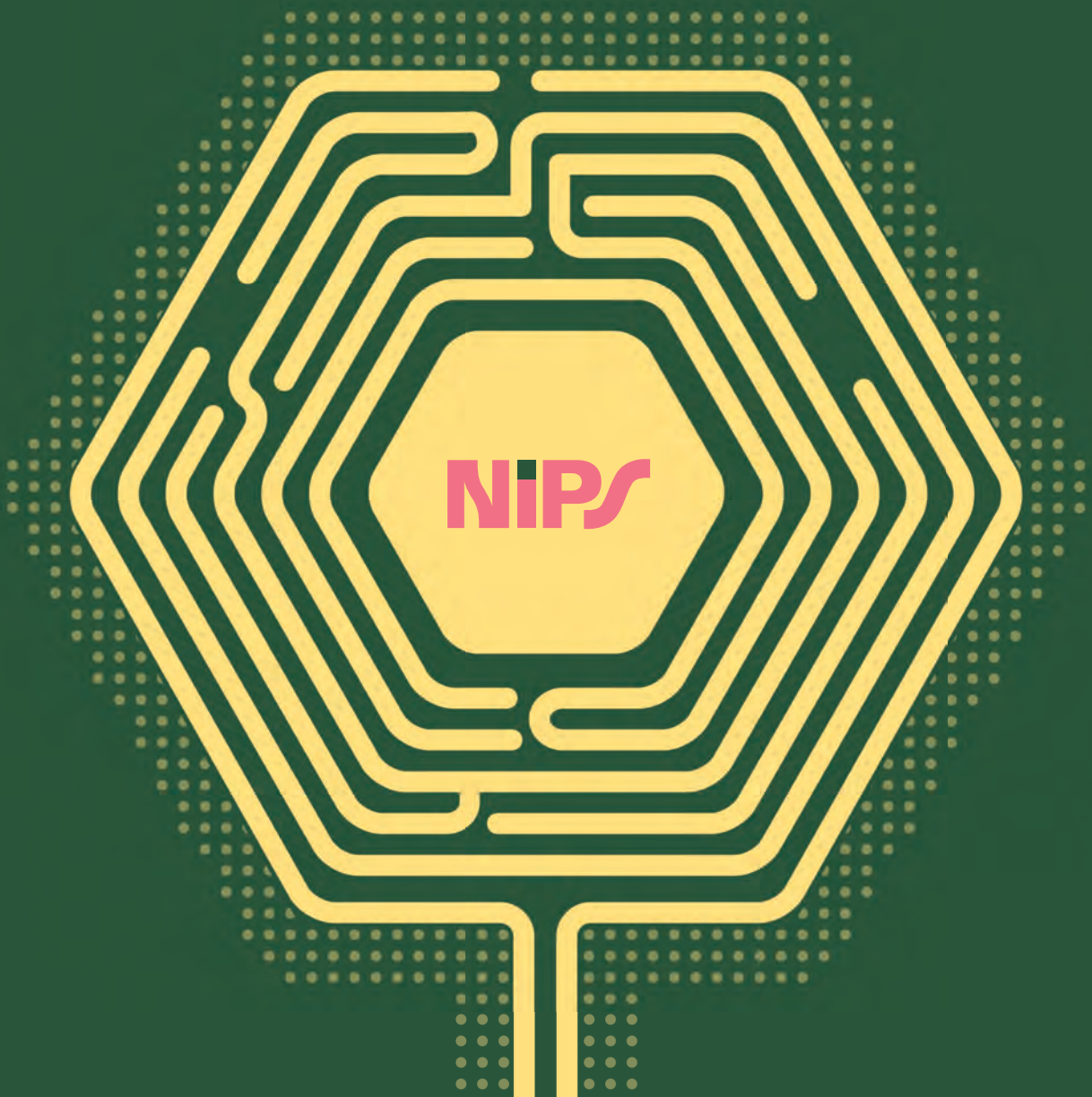
National Institutes of Natural Sciences

National Institute for Physiological Sciences 2018



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 interacts with other organs to control and regulate our body. Research of brain is now starting to 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. In fact, techniques of artificial intelligence has been developed on the basis of brain science. Also, research of brain is expected to provide us clues how to ease and circumvent problems in the coming unprecedented ageing society.

The NIPS advocates the following three major 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, we are trying to conduct a leading role in the physiological sciences and brain science both in Japan and abroad.

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 provides various research resources including viral vectors for gene delivery and gene-modified rodents. The NIPS also holds workshops and international symposia to promote domestic and international research collaboration.

The third mission of NIPS is to educate and nurture young scientists. The NIPS is responsible for directing the 5-year Ph.D. course of study in physiological sciences in SOKENDAI (the Graduate University of Advanced Studies). 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 international research collaboration and to publicize our scientific information. Please visit our website (http://www.nips.ac.jp/) for more information.

"To elucidate comprehensively human body functions by integrating the research results from the different levels" is the goal of the NIPS. We all are trying our best step by step to go forward for achieving this goal. Also, we will make every effort to keep the Institute open and cooperative for researchers. Your understanding, and continued support of our activities is cordially appreciated.

Director General

IMOTO, Keiji

M.D., Ph.D.

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 4 departments, 18 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.

Mar., 2018

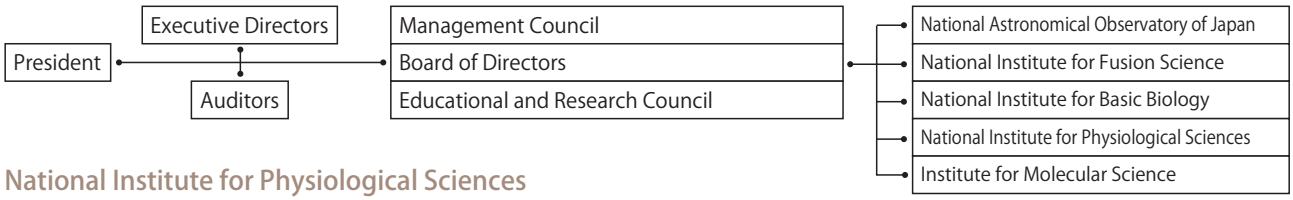
The following were abolished :

Okazaki Institute for Integrative Bioscience

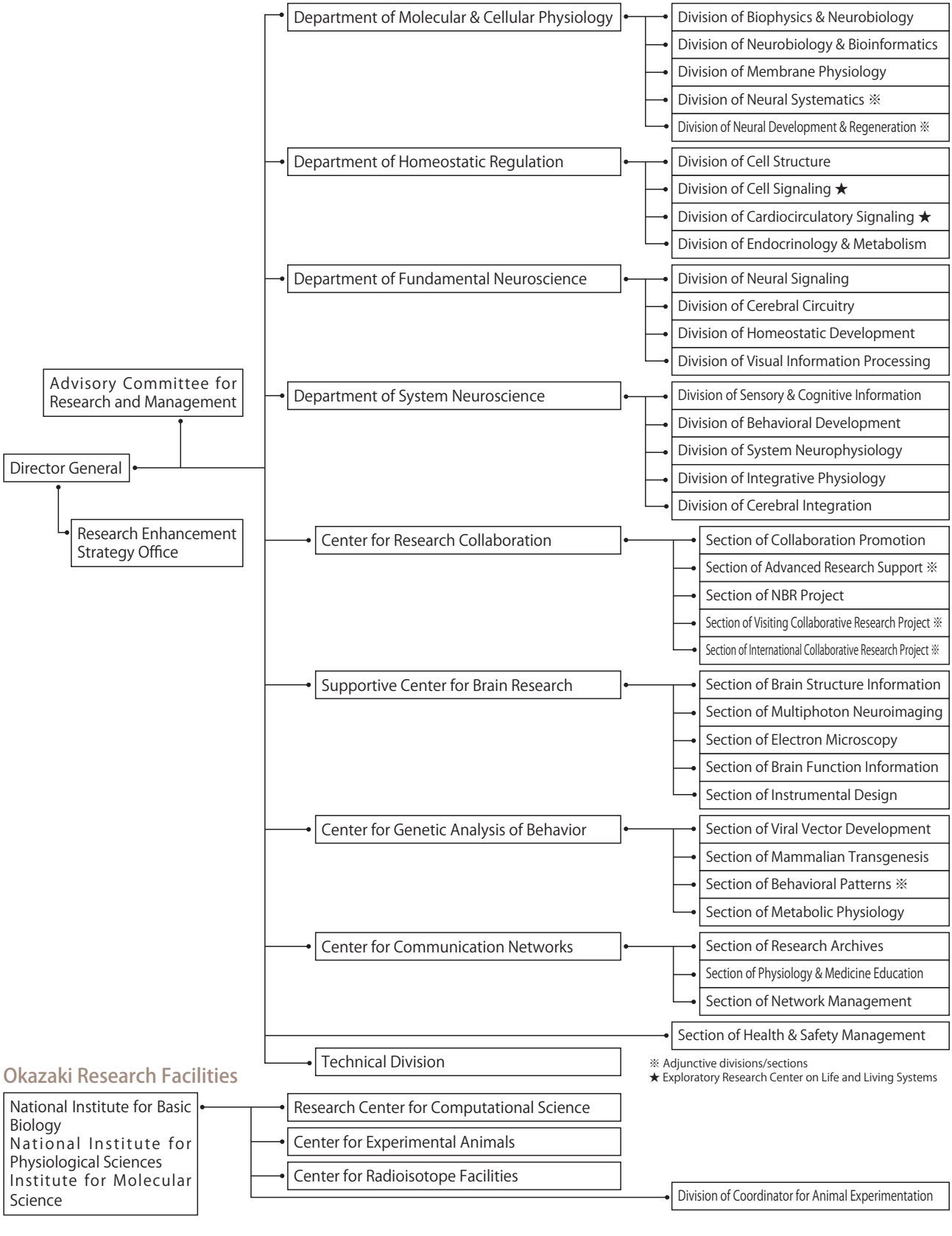
Asterisk (*) denotes adjunct division.

Organization of the Institute

National Institutes of Natural Sciences



National Institute for Physiological Sciences



※ Adjunctive divisions/sections
★ Exploratory Research Center on Life and Living Systems

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）

ASAI, Kiyofumi	Professor, Graduate School of Medical Sciences, Nagoya City University
FUJIYAMA, Fumino	Professor, Systems Neuroscience, Doshisha University Graduate School of Brain Science
○INOUE, Ryuji	Professor, Department of Physiology, Fukuoka University
MIYATA, Takaki	Professor, Department of Anatomy and Cell Biology, Nagoya University Graduate School of Medicine
MUSHIAKE, Hajime	Professor, Graduate School of Medicine, Tohoku University
NAGAMINE, Takashi	Professor, School of Medicine, Sapporo Medical University
TAKADA, Masahiko	Professor, Systems Neuroscience, Primate Research Institute Kyoto University
TAKUWA, Noriko	Professor, Department of Health Medical Sciences, Ishikawa Prefectural Nursing University
UETA, Youichi	Professor, School of Medicine, Department of Physiology, University of Occupational and Environmental Health, Japan
YUZAKI, Michisuke	Professor, School of Medicine, Department of Physiology, Keio University

（Inside）

FUKATA, Masaki	Professor, NIPS
KAKIGI, Ryusuke	Professor, NIPS
KAWAGUCHI, Yasuo	Professor, NIPS
KUBO, Yoshihiro	Professor, NIPS
MINOKOSHI, Yasuhiko	Professor, NIPS
NABEKURA, Junichi	Professor, NIPS
NAMBU, Atsushi	Professor, NIPS
NISHIDA, Motohiko	Professor, NIPS
SADATO,Norihiro	Professor, NIPS
◎TOMINAGA, Makoto	Professor, NIPS
YOSHIMURA,Yumiko	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	KAKIGI, Ryusuke
Chief Researcher / Chairperson for News and Public Affairs	FUKATA, Masaki
Chief Researcher / Chairperson for Educational Problem	FURUSE, Mikio
Chief Researcher / Chairperson for Special Project	YOSHIMURA,Yumiko

Emeritus Professors

OOMURA, Yutaka
HAMA, Kiyoshi
WATANABE, Akira
YAMAGISHI, Shunichi
MORI, Shigemi
OBATA, Kunihiko
KANEKO, Akimichi
MIZUNO, Noboru
NAGAYAMA, Kuniaki
OKADA, Yasunobu
OHMORI, Harunori
IKENAKA, Kazuhiro
KOMATSU, Hidehiko

Deceased Emeritus Professors

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

Emeritus Technical Staff

OHIRA, Hitoo

Division of Biophysics and Neurobiology

KUBO, Yoshihiro
Professor
Biophysics
Neurobiology

TATEYAMA, Michihiro
Associate Professor
Pharmacology
Physiology

SHIMOMURA, Takushi
Assistant Professor
Molecular Physiology
Biophysics

CHEN, I-Shan
Project Assistant Professor
Pharmacology
Physiology

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.

Major target molecules are Two Pore Na^+ channel (TPC), G protein coupled inward rectifier K^+ channel (GIRK), hERG K^+ channel, KCNQ K^+ channel complex, P2X2 ATP receptor channel and various G protein coupled receptors including orphan receptor Prrt3. We also work on TRPA1 channel, Kv1.2 channel, Ca^{2+} activated K^+ channel, Two pore K^+ channel and Melanopsin 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 by the two electrode voltage clamp method. Another is that we perform simultaneous recordings of electro-physiology and opto-physiology 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.

* Chen IS, Tateyama M, Fukata Y, Uesugi M, Kubo Y (2017) J Physiol 595: 5895-5912.
* Tateyama M, Kubo Y (2016) Eur J Pharmacol 788: 122-131.
* Kitazawa M, Kubo Y, Nakajo K (2015) J Biol Chem 290: 22724-22733.
* Nakajo K, Kubo Y (2014) Nature Commun 5: 4100.
* Keceli B, Kubo Y (2014) J Gen Physiol 143: 761-782.

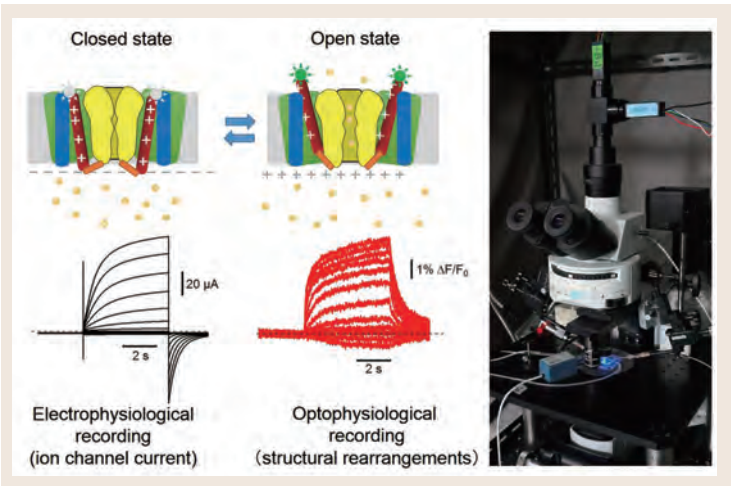
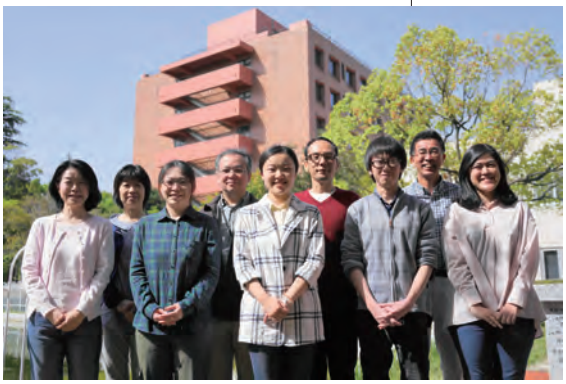


Fig. 1. Analyses of the function and dynamic structural rearrangements the KCNQ1/ KCNE1 K^+ channel complex by simultaneous recordings of electro-physiology and opto-physiology under voltage clamp using Xenopus oocyte expression systems. (Nakajo and Kubo, Nature Commun (2014))



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

HIRATA, Tetsuya
Project Assistant Professor
Biochemistry
Glycobiology
Cell Biology

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 AMPAR regulatory proteins: the DHHC palmitoylating enzymes, ABHD17 depalmitoylating enzymes and the epilepsy-related ligand/receptor, LGI1/ADAM22. So far, we have elucidated the physiological functions of these 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, to quantify the palmitoylation stoichiometry 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）Profiling of protein palmitoylation stoichiometries
4）Observation of synapses with super-resolution microscopy
5）Mouse models of human epilepsy with the LGI1 mutation

* Yokoi N, Fukata Y et al., J. Neurosci. **36**, 6431 (2016)
* Yokoi N et al., Nat. Med. **21**, 19 (2015)
* Ohkawa T et al., J. Neurosci. **33**, 18161 (2013)
* Fukata Y et al., J. Cell Biol. **202**, 145 (2013)
* Fukata Y and Fukata M, Nat. Rev. Neurosci. **11**, 161 (2010)

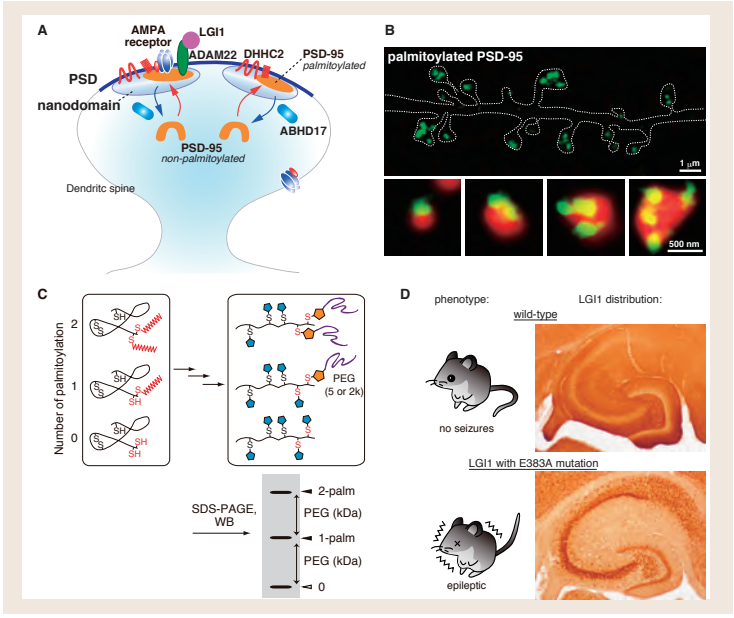
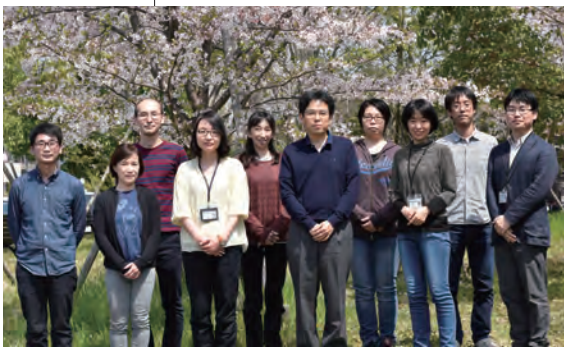


Figure (A) Unique AMPA receptor regulatory proteins: DHHC palmitoylating enzymes, ABHD17 depalmitoylating enzymes and the epilepsy-related ligand/receptor, LGI1 and ADAM22. (B) Discovery of novel postsynaptic nanodomains by palmitoylated PSD-95-specific probe and super-resolution microscopy: a synaptic DHHC protein locally regulates the formation and reorganization of nanodomains. (C) The acyl-PEGyl exchange gel shift (APEGS) method to quantify the palmitoylation stichiometory. (D) Generation and analyses of mouse models of human epilepsy with the LGI1 mutation: Distribution 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 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.

* M. Sawada, et al., PlexinD1 signaling controls morphological changes and migration termination in newborn neurons. EMBO J e97404 (2018)
* H. Jinnou, et al., Radial glial fibers promote neuronal migration and functional recovery after neonatal brain injury. Cell Stem Cell 22: 128-137 (2018)
* T. Fujioka, et al., β 1 integrin signaling promotes neuronal migration along vascular scaffolds in the post-stroke brain EBioMedicine 16: 195-203 (2017)
* N. Kaneko et al., Mechanisms of neuronal migration in the adult brain. J Neurochem 141: 835–847 (2017)
* 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)

Fig.1. Newborn neurons (green) generated by neural stem cells (blue) migrate along radial glial fibers (red) towards the injured brain tissue and differentiate into mature neurons (Jinnou et al., Cell Stem Cell 2018).

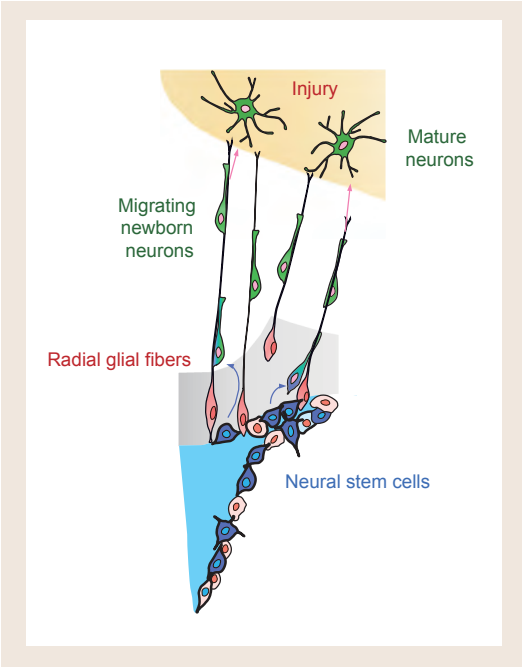
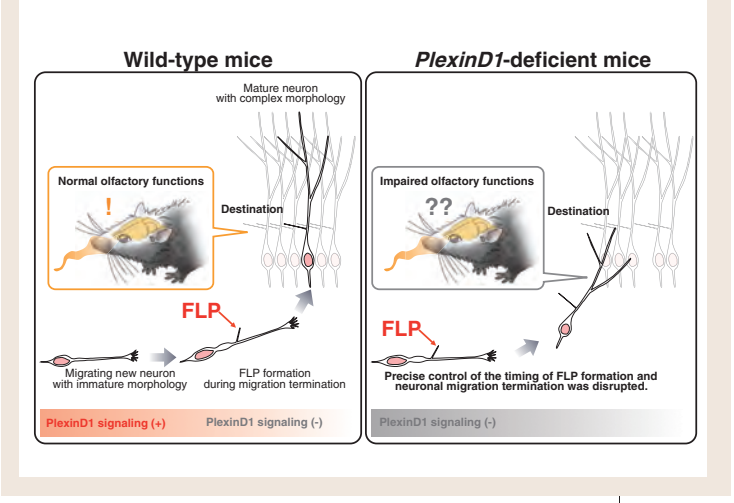


Fig.2. The regulatory mechanism involving Filopodium-like lateral protrusion (FLP) formation links neuronal migration termination and the initiation of differentiation, contributing to the positioning and functions of new neurons in the postnatal olfactory bulbs (Sawada et al., EMBO J 2018).



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

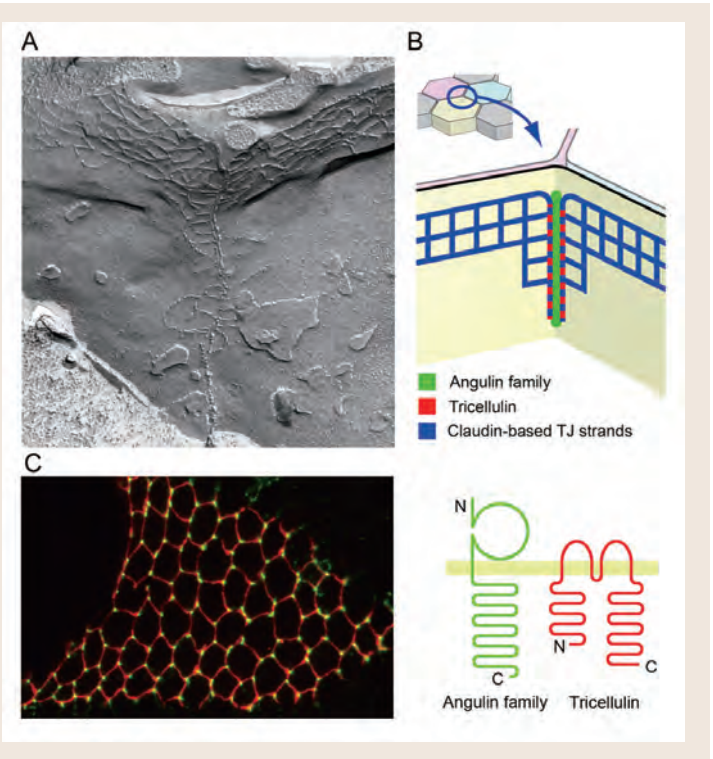
Molecular basis of cell-cell junctions involved in epithelial barrier function

The Epithelium separates body compartments as a barrier and selectively transports various substances, thereby contributing to various 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 the epithelium. 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. Recent development of genome editing techniques have enabled us to perform convincing loss-of-function analyses of the proteins of our interests in cultured epithelial cells. 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. Elucidation of the molecular mechanism behind the polarity formation of epithelial cells.

* T. Higashi et al., J Cell Sci 126, 966 (2013).
* Y. Oda, et al., J Cell Sci 127, 4201 (2014)
* T. Higashi et al., PLoS ONE 10: e0120674 (2015)
* Y. Izumi et al., J Cell Sci 129, 1155 (2016)

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

Thermal Biology Group, Exploratory Research Center on Life and Living Systems

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(Grant Project)
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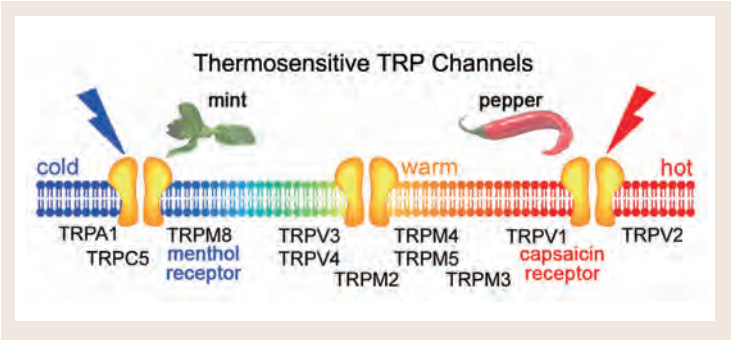
Molecular Mechanisms of thermosensation and nociception

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 eleven thermosensitive TRP channels in mammals (TRPV1, TRPV2, TRPV3, TRPV4, TRPM2, TRPM3, TRPM4, TRPM5, TRPM8, TRPA1, TRPC5) 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. 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. In addition, we are investigating using *Drosophila*.

* TRPV4 heats ups ANO1-dependent exocrine gland fluid secretion. FASEB J. (in press)
* Characterization of TRPA channels in the starfish *Patiria pectinifera*: involvement of thermally activated TRPA1 in thermotaxis in marine planktonic larvae. Sci. Rep. 7: 2173, 2017.
* Lysophosphatidic acid-induced itch is mediated by signaling of LPA5 receptor, phospholipase D and TRPA1/TRPV1. J. Physiol. 595: 2681-2698, 2017.
* Requirement of Extracellular Ca^{2+} Binding to Specific Amino Acids for Heat-evoked Activation of TRPA1. J. Physiol. 595: 2451-2463, 2017.
* Takayama Y, Furue H, Tominaga M. 4-isopropylcyclohexanol has potential analgesic effects through the inhibition of anoctamin 1, TRPV1 and TRPA1 channel activities. Sci. Rep. 7: 43132, 2017.



Eleven thermosensitive TRP channels

Division of Cardiocirculatory Signaling

Cardiocirculatory Dynamism Research Group, Exploratory Research Center on Life and Living Systems

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Cardiovascular Physiology

NUMAGA-TOMITA, Takuro
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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 (mouse), Tail-cuff (mouse and rat), blood pressure telemetry (mouse)
2. Invasive measurements of cardiovascular functions Langendorff perfusion system (mouse and rat), Mouse millar catheter (for P-V loop measurement)
3. Isolation of primary-cultured cells and experiments mechanical stretching machine, Ca^{2+} imaging, FRET imaging, Confocal laser microscopy, Patch-clamp recording, Plate reader (BRET assay, post-translational modification analyses)

* T. Akaike et al., Nature Commun. 8(1):1177 (2017)
* T. Shimauchi et al., JCI insight, 2(15). pii: 93358 (2017)
* S. Oda et al., Sci. Rep. 7(1), 7511 (2017)
* T. Numaga-Tomita et al., Sci. Rep. 6, 39383 (2016)
* N. Kitajima et al., Sci. Rep. 6, 37001 (2016)
* A. Nishimura et al., Sci. Signal. 9, ra7. (2016)

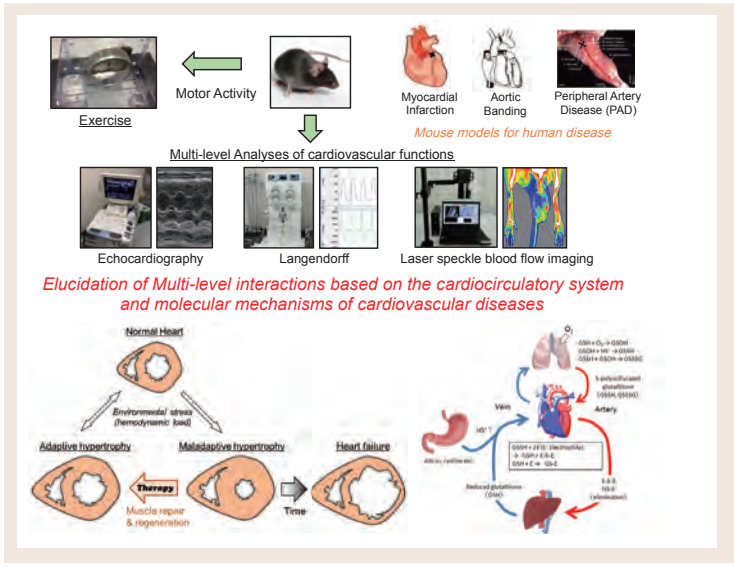

Figure. Measuring systems for cardiovascualr functions and summary of our research using these systems

Division of Endocrinology and Metabolism

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NAKAJIMA, Ken-ichiro
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Molecular Biology
Structural Life Sciences
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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 investigating the role of hypothalamus in body energy balance in mammals. 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, adipokines and myokines.
(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.
* E.A. Coutinho, et al., Diabetes 66, 2372, 2017.
* S. Okamoto, et al., Cell Reports 22, 706, 2018.

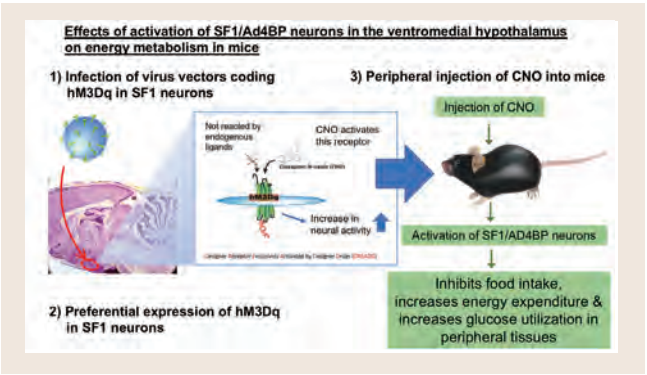

Fig. 1 Effects of activation of SF1/Ad4BP neuron by DREADD technology on energy metabolism in mice. Specific activation of SF1 neurons inhibits food intake and increases energy expenditure. In addition, activation of these neurons increases insulin sensitivity and glucose uptake in some peripheral tissues such as skeletal muscle.

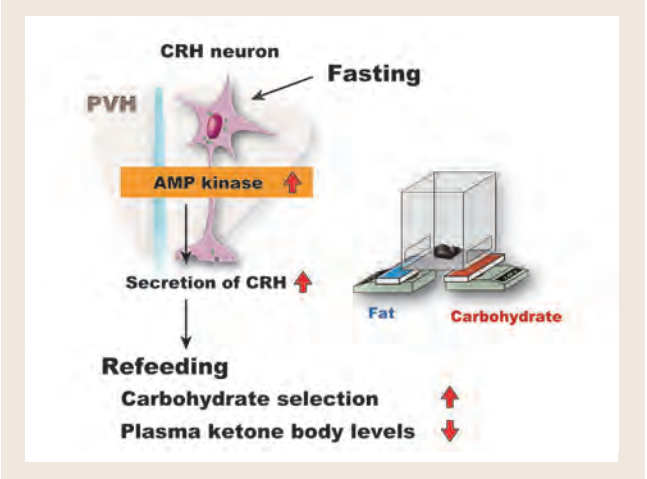

Fig. 2 Discovery of neurons that induce selection of carbohydrate over fat.
AMP kinase-regualted CRH neurons in the PVH is necessary and sufficient to inducse selection of carbohydrate over fat after fasting.

Division of Cerebral Circuitry

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MORISHIMA, Mieko
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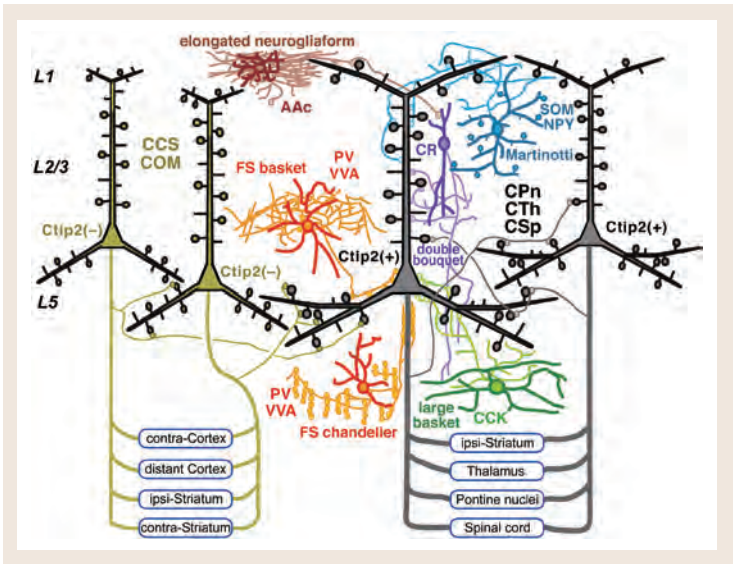
Neuroscience

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, and the relationship between the local and long-distance recurrent subnetworks. Once we establish the organization of pyramidal and GABAergic cells in the neocortex, we would like to identify the mechanisms that drive their 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.

* Pyramidal cell subtypes and their synaptic connections in layer 5 of rat frontal cortex. Kawaguchi Y. (2017) Cereb Cortex 27: 5755–5771.
* Segregated excitatory-inhibitory recurrent subnetworks in layer 5 of the rat frontal cortex. Morishima M. et al. (2017) Cereb Cortex 27: 5846–5857.
* A carbon nanotube tape for serial-section electron microscopy of brain ultrastructure. Kubota Y. et al. (2018) Nature Commun 9: 437



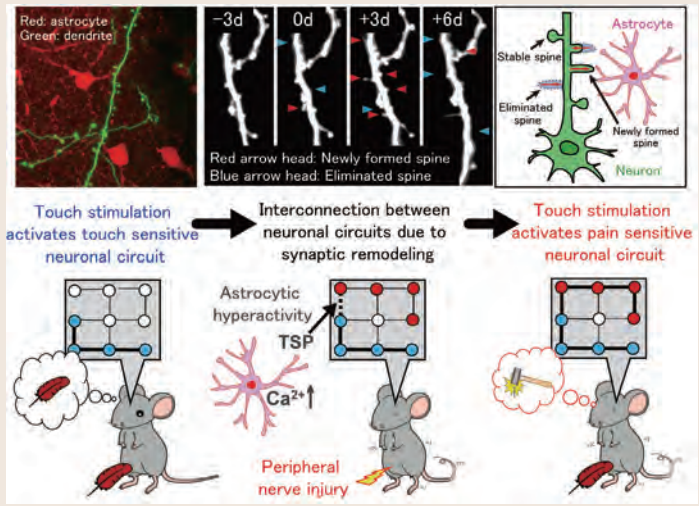
Basic subtypes and connections of GABA cells and layer 5 pyramidal cells in the frontal cortex. Molecules expressed in GABA cells: AAc, alpha-actinin-2; CCK, cholecystokinin; CR, calretinin; NPY neuropeptide Y; PV, parvalbumin; SOM, somatostatin; VVA, binding with *Vicia villosa*. Pyramidal cell groups: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

Division of Homeostatic Development

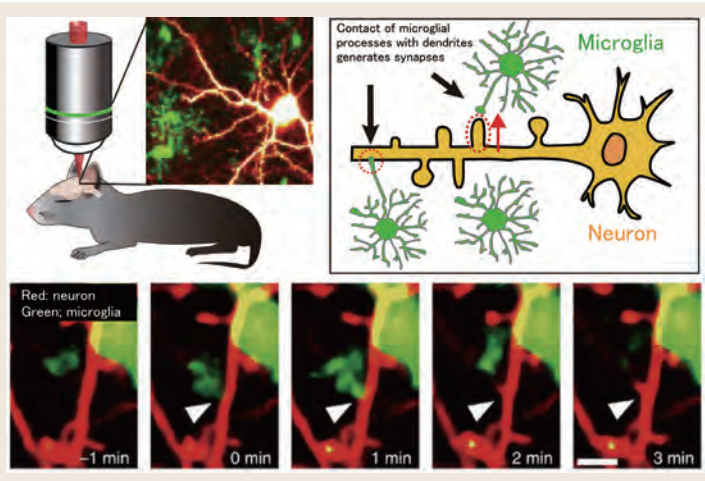
Remodeling of Neuronal Circuits in Development and Recovery, — *In vivo* Imaging and Electrophysiological Study —

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 Glial contribution for the function of neuronal circuits. Glia have 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, controlling activity and analyzing function of neurons and glia in living animals using multi-photon microscopy.

* Cortical astrocytes rewire somatosensory cortical circuits for peripheral neuropathic pain.
Kim SK, Hayashi H, Ishikawa T, Shibata K, Shigetomi E, Shinozaki Y, Inada H, Roh SE, Kim SJ, Lee G, Bae H, Moorhouse AJ, Mikoshiba K, Fukazawa Y, Koizumi S, Nabekura J.
J Clin Invest. 2016 May 2;126(5):1983-97.
* Microglia contact induces synapse formation in developing somatosensory cortex.
Miyamoto A, Wake H, Ishikawa AW, Eto K, Shibata K, Murakoshi H, Koizumi S, Moorhouse AJ, Yoshimura Y, Nabekura J.
Nat Commun. 2016 Aug 25;7:12540.



Transinet acceleration of synaptic plasticity in the primary sensory cortex of a neuropathic pain model mouse



Facilitation of spine formation by micrlglial contact during development

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Division of Visual Information Processing

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Assistant Professor
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Molecular Cell biology

KIMURA, Rie
Project Assistant Professor
Neurophysiology

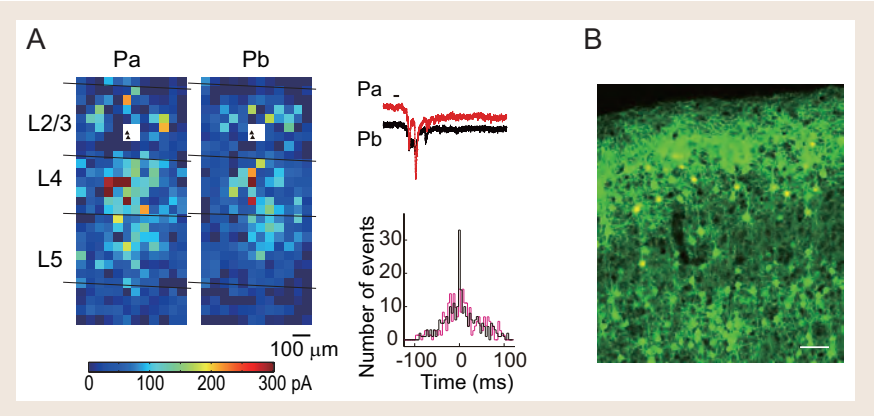
YONEDA, Taisuke
Project Assistant Professor
Neuroscience

Analysis of mechanisms underlying information processing and activity-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
* Tarusawa E. et al., (2016) Establishment of high reciprocal connectivity between clonal cortical neurons is regulated by the Dnmt3b DNA methyltransferase and clustered protocadherins. BMC Biol. 14(1):103



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 pyramidal neurons (yellow) in neocortex.

Division of Behavioral Development

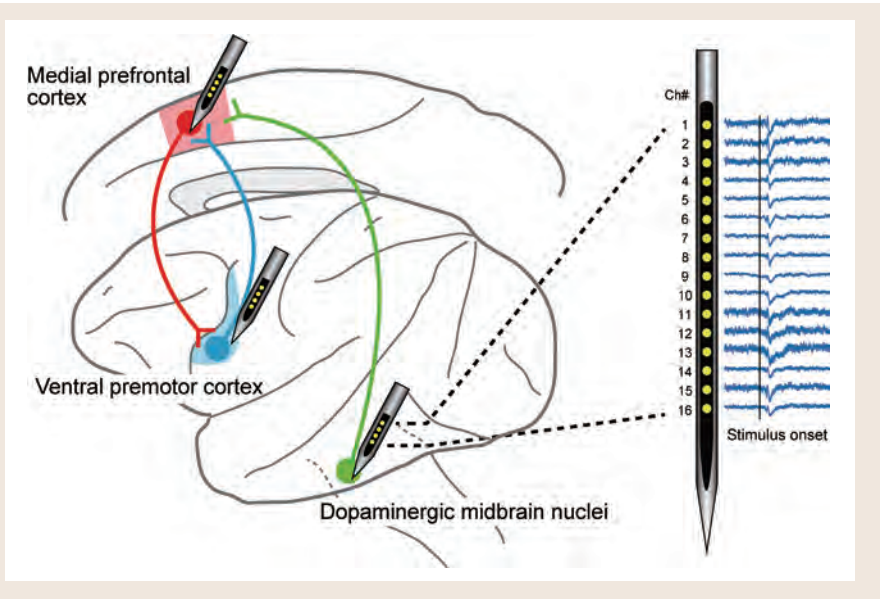
• Physiological understanding of social cognitive functions

• Neural mechanism of blindsight

There has been a rapid progress in the study of social brain functions. This field of research, called social neuroscience, aims to clarify the neural basis of social functioning. In social neuroscience, studies on human subjects are surely indispensable as they can tell us about our social mind most directly. Yet research using other animal species, in particular nonhuman primates, is also crucial for understanding social brain functions at the cellular and network levels. We have developed novel, experimental paradigms using macaque monkeys together with multi-site neuron recording techniques toward the physiological understanding of social cognitive functions.

We also focus on the neural mechanism underlying blindsight, i.e., a phenomenon known as "vision without awareness." Using monkeys with lesions in the primary visual cortex, we have carried out psychophysics, electrophysiological recording, and functional brain imaging to better understand blindsight.

* Yoshida K et al. (2016) Sci Adv, 2: e1600558.
* Yoshida M et al. (2015) Sci Rep, 5:10755.
* Yoshida K et al. (2012) Nat Neurosci, 15: 1307-1312.
* Yoshida M et al. (2012) Curr Biol, 22: 1429-1434.
* Yoshida K et al. (2011) Curr Biol, 21: 249-253.



We record neural activity simultaneously from multiple brain regions to understand social brain functions at the network level.

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Neurogenomics

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Division of System Neurophysiology

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Mechanism of voluntary movements
Pathophysiology of movement disorders

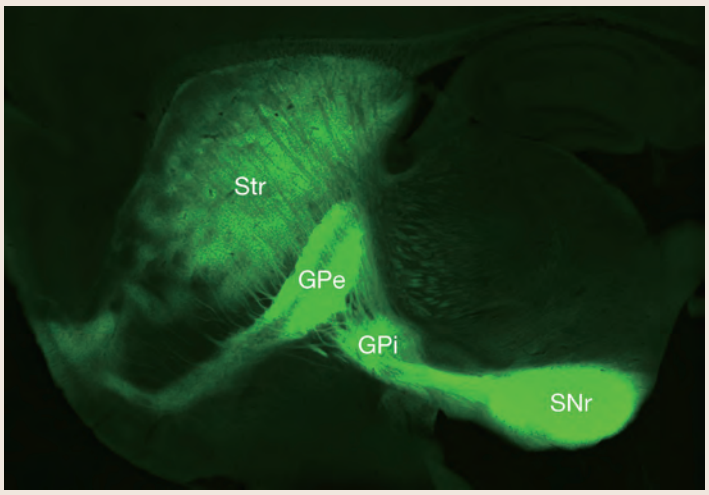
The brain areas, such as the cerebral cortex, basal ganglia and cerebellum, play a major role in controlling voluntary movements. On the other hand, malfunctions of these structures result in movement disorders, such as Parkinson's disease and dystonia. The major goal of our research projects is to elucidate 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 nonhuman primates.

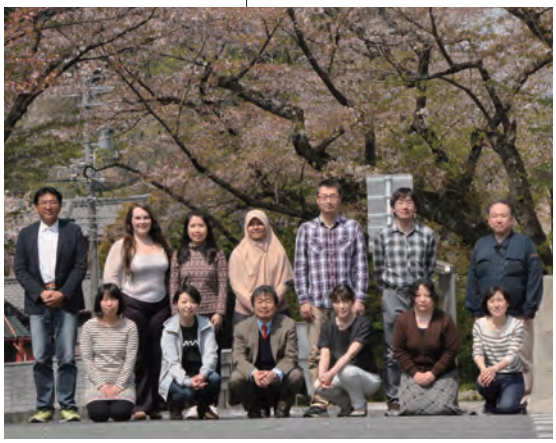
The current topics under study are as follows:

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, optogenetics or chemogenetics.
3) Elucidation of the pathophysiology of movement disorders by applying electrophysiological methods to animal models.

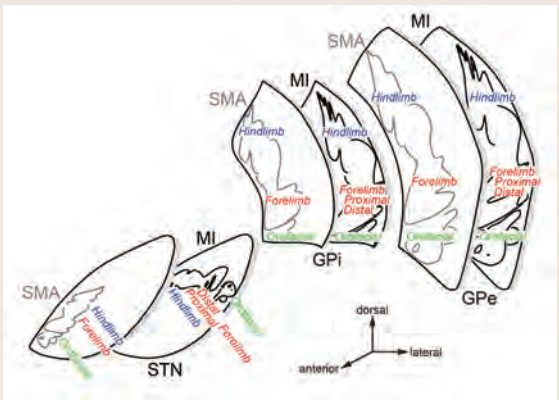
* S. Chiken, A. Nambu, *J Neurosci* **33**: 2268-2280 (2013)
* S. Chiken et al., *Cereb Cortex* **25**: 4885-4897 (2015)
* H. Sano, H. Murata, A. Nambu, *J Neurochemi* **134**: 371-381 (2015)
* H. Iwamuro et al., *Eur J Neurosci* **46**: 2684-2701 (2017)
* M. Ozaki et al., *Cereb Cortex* **27**: 5716-5726 (2017)

A sagittal section of the mouse brain showing the 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).





Cortical stimulation of the face, forelimb and hindlimb areas in the motor cortices of monkeys induced responses in the subthalamic nucleus (STN) and the internal (GPi) and external (GPe) segments of the globus pallidus, and revealed somatotopic maps of these structures. These maps contribute to stereotactic surgery for Parkinson's disease.



Division of Integrative Physiology

KAKIGI, Ryusuke
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INUI, Koji
Associate Professor
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Psychiatry

KIDA, Tetsuo
Project Associate Professor
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.

(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.

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

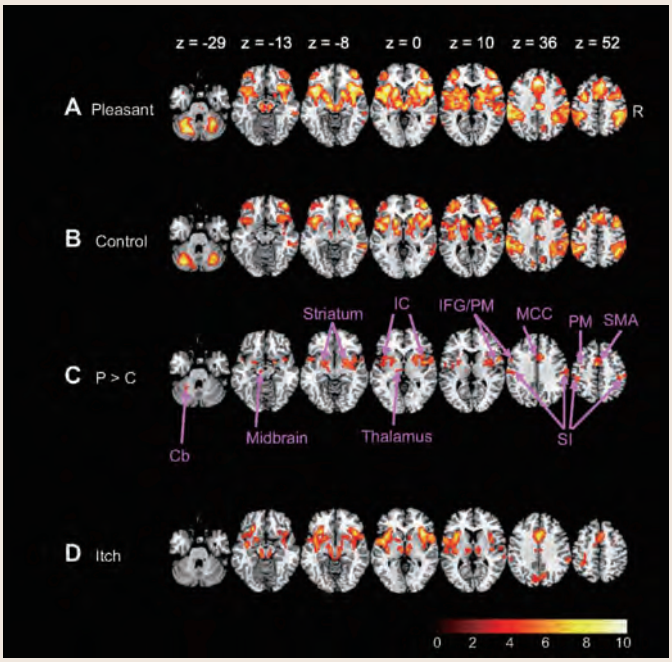

Figure 1. Brain activation during scratching and itch stimuli. *A* and *B*: brain regions significantly activated while scratching stimuli were applied in the pleasant (*A*) and control (*B*) conditions. R, right hemisphere. *C*: brain regions that showed significantly higher activity in the pleasant 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)

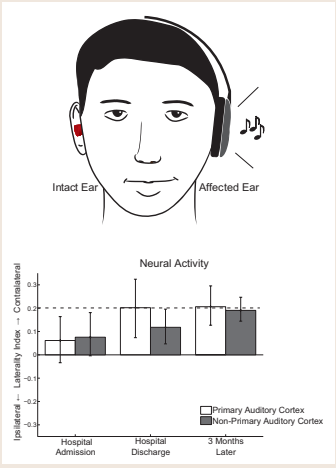

Figure 2. The canal of the intact ear was plugged. Sounds were only presented to the affected ear (upper panel). The auditory responses demonstrated the small laterality indices at entering hospital but became almost normal (= 0.2) at three months after discharge (lower panel).
(Okamoto et al. *Sci Rep*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

Division of Cerebral Integration

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Neuroscience

FUKUNAGA, Masaki
Associate Professor
Magnetic Resonance
Neuroimaging
Neuroscience

KOIKE, Takahiko
Assistant Professor
EEG-fMRI Recording
Neuroimaging
Neuroscience

SUGAWARA, Sho
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Project Assistant Professor
(Grant Project)
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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 focus of our research activities. Hyper-scanning fMRI (3T) has been installed to evaluate two individuals as one neural network during social interaction, combined with 7T MRI data to evaluate the detailed structures of the neural network that represent the social cognition. Multimodal approach including EEG , MEG, TMS, and NIR is considered when appropriate.

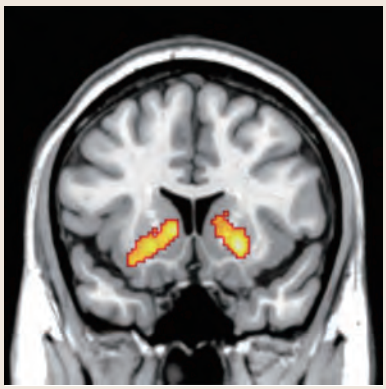


Figure 1. Brain areas commonly activated by social and monetary rewards. Why are we nice to others? One answer provided by social psychologists is because it pays off. A social psychological theory stated that we do something nice to others for a good reputation or social approval just like we work for 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.

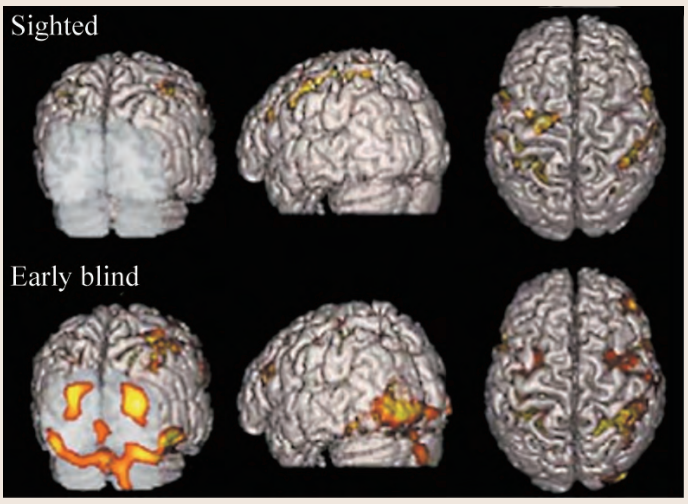


Figure 2. Activation in a sighted (upper row) and blind subject (bottom row) during tactile discrimination tasks similar to reading Braille. The primary and association visual cortices of the blind are activated bilaterally (bottom row) whereas no such activation in the sighted. Only pixels with significant 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.

* T. Koike et al. Neuroimage 125, 401 (2016).
* 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).

Individual Researches

The roles and mechanisms of membrane traffic

OHASHI, Masato
Assistant Professor
Molecular Cell Biology
Biochemistry
Developmental Biology

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).
* M. Ohashi, N. Mizushima, Y. Kabeya, T. Yoshimori, Localization of mammalian NAD(P)H steroid dehydrogenase-like protein on lipid droplets. J. Biol. Chem. 278, 36819-36829 (2003).
* M. Ohashi et al., A role for phosphatidylinositol transfer protein in secretory vesicle formation. Nature 377, 544-547 (1995).

Individual Researches

The mechanism of fertilization, egg activation, and oocyte maturation

MOHRI, Tatsuma
Assistant Professor
Cell Biology
Cell Physiology

Fertilization is a pivotal event when the sperm approaches, attaches to, enters, and activates the egg. Although it is quite important for sexual organisms as the only phenomenon that creates a new generation in nature, the physiological molecular mechanisms are still unsolved. Thus, it is not clear how the sperm approaches, enters, and activates the egg. Furthermore, how oocytes mature and acquire fertilizability remains unclear. I have been studying 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 and other accompanying phenomena such as the intracellular $[Ca^{2+}]_i$, the intracellular pH, changes in the cortical cytoskelton, morphological and electrical changes in mitochondria, and the relationships among them in eggs of sea urchins and starfishes using imaging techniques and the voltage clamp method. Furthermore, I am investigating the mechanism underlying the release of $[Ca^{2+}]_i$ during oocyte maturation using starfish oocytes. If you are interested in egg/oocyte activation in any organism, please communicate with me.

* PI Ivonnet, T Mohri, DH McCulloh, ***Mol Reprod Dev***. doi: 10.1002/mrd.22866 (2017)
* 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).

Center for Research Collaboration

KUBO, Yoshihiro
Professor
Director

Outline

This center named "Center for Collaborative Research" was established in April 2016. It consists of 5 sections of Collaboration Promotion, Advanced Research Support, National Bio-Resource (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 is in charge of facilitation of joint researches utilizing the facilities of NIPS. It responds to inquiries about available research facilities and laboratories suitable to achieve research aims, and also coordinates the joint research. Thus, it serves as a sort of "concierge" of joint research with NIPS. It also call for requests of facilities and experimental techniques which researchers wish to have in NIPS. To advertise the collaborative research activity of NIPS, we organized in 2016 and 2017, NIPS research meetings in universities outside of NIPS. In 2018, we plan to organize two meetings again outside of NIPS.

(2) NIPS, in cooperation with NIBB, started "Supporting Platform for Advanced Bio-Imaging" project supported by JSPS KAKENHI in 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. Another activity of this section is to support "The Next Generation Brain Research" Project. It is to organize a symposium of wide-ranged brain science researchers including the ones belonging to MEXT priority research areas. This activity was succeeded from the former "Comprehensive Brain Science Network" ended in 2016.

(3) NIPS has been in charge of supply of monkeys for brain science experiments, as a part of National Bio-Resource Project. This time the "Primate Model Development" section in the "Supportive Center for Brain Research" was moved to the "Center for Collaborative Research" as a new section named "National Bio-Resource (NBR) Project", clarifying the responsible section for the project. In 2017, the primary responsible role of NBR Project was transferred from NIPS to the Primate Research Center in Kyoto University. NIPS will continue to cooperatively contribute to the activity of NBR Project.

(4) The aim of the "Visiting Collaborative Research Project" section is to facilitate collaborative researches with researchers staying in NIPS using a sabbatical leave. The section was moved from "Center for Multidisciplinary Brain Research" which was closed in 2016. In 2018, NIPS will promote this activity by calling for sabbatical researchers.

(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. From 2017, NIPS invited Professor Denis Le Bihan (Former Director of Neurospin in France) as a new P.I.

In summary, the "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

SAKAMOTO, Kiwako
Assistant Professor
Neurophysiology

National Institute for Physiological Sciences (NIPS) is an inter-university research institute, which organizes some of the latest large experimental equipment and devices that are difficult for other universities or research institutes to purchase, maintain, manage, or operate, such as serial block-face scanning electron (SBF-SEM) , multiphoton excitation microscopes, dual functional magnetic resonance imaging (dual fMRI) , 7-tesla ultra high magnetic field MRI machines, and magneto-encephalography (MEG) systems, with the aim of providing facilities and technical support for researchers on a nationwide basis. NIPS also actively develops, produces, and provides viral vectors for neuroscience research with technical support, as a center for the production of high-quality viral vectors that are difficult for individual research laboratories to create or purify.

Section of Collaboration Promotion has been organized as a consultation window to help researchers belonging to other universities or research institutes throughout Japan smoothly launch joint research projects in NIPS. Its aim is to support researchers who maintain passive attitudes toward such projects for various reasons, including unestablished research networks or lack of knowledge about methods to embody their ideas as studies. In addition to these, NIPS also offers research techniques and devices to corporate researchers who aim to develop new technologies or products.

The primary purpose of us is to promote liaison between researchers in diverse fields and NIPS. It comprehensively performs activities to support joint research and enhance its recognition, such as setting up exhibition booths to introduce joint research in NIPS at meetings of related academic societies and study meetings held outside NIPS.

▶ Section of Advanced Research Support

KANO, Masanobu
Adjunct Professor
Neurophysiology

TAKADA, Masahiko
Adjunct Professor
Neuroanatomy

MARUYAMA, Megumi
Project Associate Professor
Neurophysiology
Environmental Physiology

Advanced Bioimaging Support (ABiS)

Advanced Research Support has operated the administrative office of ABiS (FY2016–2021 Grant-in-Aid for Scientific Research on Innovative Areas — Platforms for Advanced Technologies and Research Resources) since FY2016. ABiS is a framework for supporting cutting-edge imaging techniques (observation of samples and data analysis) using various types of microscopy and MRI, for research conducted by core organizations such as the National Institute for Physiological Sciences (NIPS) and the National Institute for Basic Biology (NIBB). Through the collaborative research that these institutes promote, ABiS is forming a network with domestic partner organizations to provide custom-made support for bioimaging techniques.

JISEDAI-NOU Project

Advanced Research Support has also operated the administrative office of the JISEDAI-NOU Project since FY2016. This project, which is led by members of the brain science–related Grant-in-Aid for Scientific Research on Innovative Areas, promotes efforts that support the brain science community, including planning symposia with a focus on cultivating young researchers, disseminating related information via a mailing list, and operating a website. It will contribute to the promotion of brain research by taking advantage of the established community that developed over the course of the Comprehensive Brain Science Network project (FY2010–2015, Grant-in-Aid for Scientific Research on Innovative Areas).

The promotion of National Bio-Resource Project "Japanese monkey"

The improvement of the monkeys quality, and development of molecular methods for the detection of B virus and Simian retrovirus.

NAMBU, Atsushi
Professor
Neurophysiology

HIGASHINO, Atsunori
Project Assistant Professor
(Grant Project)
Molecular biology
Primatology

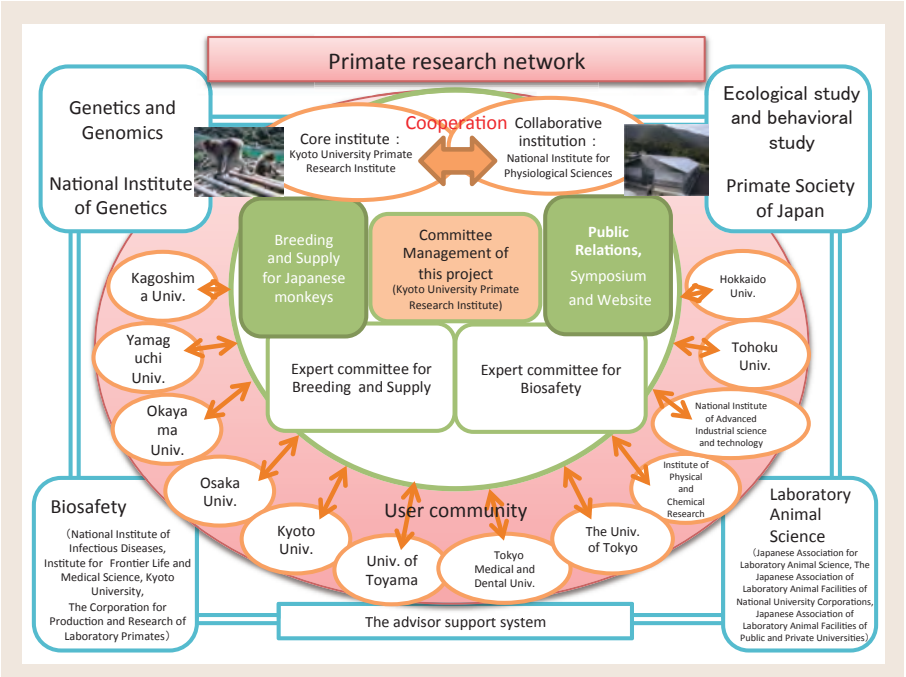
This laboratory has been organized since 2002, for acceleration of National Bio-Resource Project (NBRP) “Japanese monkey”. This project has addressed breeding of, and supply for, Japanese monkeys. The use of wild Japanese macaques for research purposes has been strictly limited since 2001, however, the neuroscientists have got supports from the NBRP of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan, which was initiated in 2002. National Institute for Physiological Sciences (NIPS) became the core institute for this project and Kyoto University Primate Research Institute (KUPRI) joined the program as a collaborative institute. The core and collaborative institutes will switch their roles from 2017. We will promote the integration of breeding facilities for efficient management.

The Japanese macaques have high cognitive abilities, and dexterous hands. This animal is relatively close to human being in the experimental animals. Therefore, these macaques have been used for research of higher brain functions and various diseases.

NBRP “Japanese monkey” has been established as a stable breeding and supply system for Japanese macaques for laboratory use. We have performed the projects with emphasis on the followings: (1) The establishment of the breeding system, (2) The provision of the monkey for researchers in Japan, (3) Data collection of the characteristics of the Japanese macaques, and (4) The integrative administration of NBRP "Japanese monkey".

We have administered this resource project and coordinated with researchers. We have collected the data about Japanese macaques for the improvement of monkey quality. Furthermore, we have developed database with copy number variation and whole genome sequence. One of our aims is the development of the detection system for various pathogens in the Japanese macaques, including B virus and Simian retrovirus, in pursuance of supplying high-grade bio-resource.

* T. Isa et al., Japanese Macaques as laboratory Animals. Exp. Anim. 58 (5), 451-457 (2009)



▶ Section of International Collaborative Research Project

LE BIHAN, Denis
Foreign Adjunct Professor
Magnetic Resonance Neuroscience

In FY2014, the National Institute for Physiological Sciences (NIPS) established the Section of International Collaborative Research Project and welcomed Dr. Ravshan Sabirov, an adjunct professor, to run the section until FY2016. In FY2017, we invited Dr. Denis Le Bihan to join as a new Principal Investigator of the section. He is a leading authority on Magnetic Resonance Imaging (MRI) and is well-known around the world as an inventor of the revolutionary imaging method called diffusion-weighted imaging. In 2007, Dr. Le Bihan founded NeuroSpin, which belongs to the Life Science Bureau, a basic research division of France's *Commissariat à l'énergie atomique et aux énergies alternatives* (CEA). The institute conducts brain research using MRI at a very high level of technological sophistication and is also leading the development of the world's highest-performance MRI instrument, the Human-oriented 11.7 Tesla Device. NIPS has promoted exchanges with Dr. Le Bihan to advance collaborative research that takes advantage of the strengths of both institutes, with the primary goals of introducing the Human-oriented 7 Tesla Device and applying it to neuroscience research. Accordingly, CEA and NIPS signed a memorandum of understanding on academic research cooperation on January 13, 2017. As part of this collaborative research, Dr. Le Bihan readily agreed to become an adjunct professor of NIPS. His mission is to promote international collaborative research using ultra-high field MRI. We will continue collaborative research with researchers inside and outside NIPS in collaboration with the Division of Cerebral Integration, which is also a part of NIPS. These efforts are expected to make a major contribution to the development of MRI imaging technology and brain science in Japan.

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 living organisms by high-voltage electron microscopy

High-resolution structural analysis of biomolecules by phase-contrast cryo-electron microscopy

In this laboratory, we will visualize living organisms using electron microscopes in order to clarify the function of life from its structure. By applying advanced image analysis techniques such as single particle analysis and electron tomography, we investigate these at 3D. The main facilities include an energy-filtered phase-contrast cryo-electron microscope (JEM2200FS: 200 kV) equipped with Zernike phase plate and a high-voltage electron microscope for medical and biological researches (H-1250 M: 1 MV) (Fig. 1). Through these electron microscopes, we are conducting three-dimensional morphological observation of microorganisms, cells, etc., and high-resolution 3D structure analysis of biological macromolecules such as large protein complex and viral particles. An example of the research is shown in Figure 2.

* Okamoto et al., Sci Rep 7, 13291 (2017)
* Satoh et al., Sci Rep 7, 12142 (2017)
* Murata & Wolf, Biochim Biophys Acta 1862, 324 (2017)
* Conley et al., J Gen Virol 98, 68 (2017)
* Song et al., Sci Rep 7, 1221 (2017)
* Murata et al., Sci Rep 7, 44176 (2017)

Fig. 1 High-voltage electron microscope for medical and biological researches, H-1250M: 1MV (left) and Phase-contrast cryo-electron microscope with energy filter, JEM2200FS: 200kV (right).

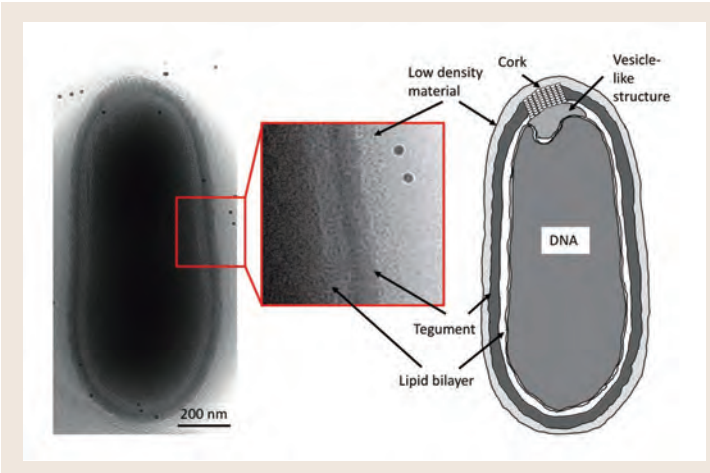


Fig. 2 Intact structure of Pithovirus revealed by cryo-electron microscopes. (Okamoto et al. 2017).

▶ Section of Multiphoton Neuroimaging

NABEKURA, Junichi
Professor
Neuroscience

MURAKOSHI, Hideji
Associate Professor
Biophysics
Neuroscience

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

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 photo-activatable probes, new fluorescent proteins, electrophysiology. These techniques will enable us to reveal the system of neural networks and underlying molecular mechanisms in living mouse neurons.

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

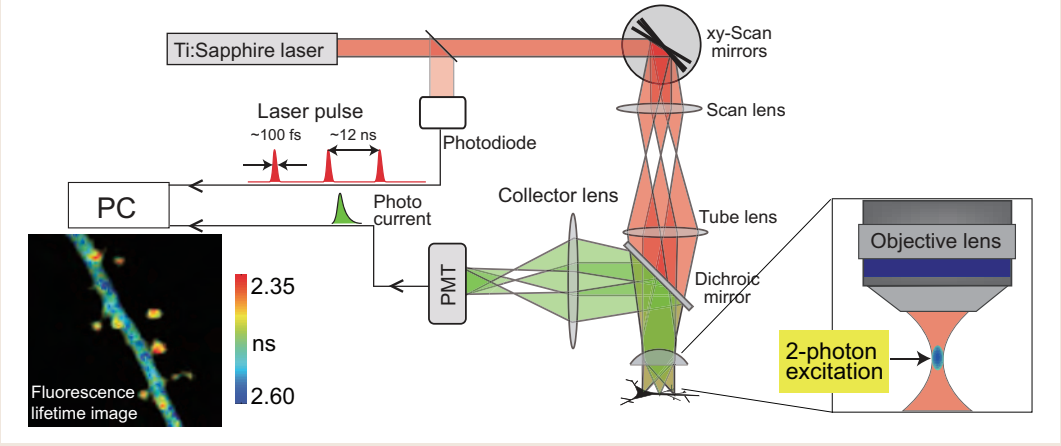


Figure 1. Two-photon excitation is the phenomenon that two photons of half energy than needed for one photon excitation can excite a fluorescent molecule. The advantages of 2-photon excitation are 1) Because infrared light is used for excitation, it minimizes excitation-light scattering in the tissue 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

SONG, Chihong
Project Assistant Professor
Cell Biology
Structural Biology

Support for electron microscopy

Ultrastructures of tissues, cells and macromolecules are observed using transmission or scanning electron microscopes (JEOL JEM1010, Zeiss Σ IGMA). The facility also provides instruments for their specimen preparations, i.e. ultra-microtome (Leica UC7), high-pressure freezing device (BAL-TEC HPM010), and freeze fracture and replica machine (BAL-TEC BAF060), vacuum evaporator (JEOL JEE-400), etc. For digital image analysis, image processing software and volume rendering software (FEI Amira) are available. Serial block-face SEMs (Gatan 3view/ Zeiss Σ IGMA/VP & MARLIN; Fig. 1) and Array tomography SEM system (Zeiss ATLAS5) have opened since 2013 (Fig. 1), which reveal 3D structures of biological thick specimens. The SBF-SEMs, especially, are used for many collaborative projects.

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

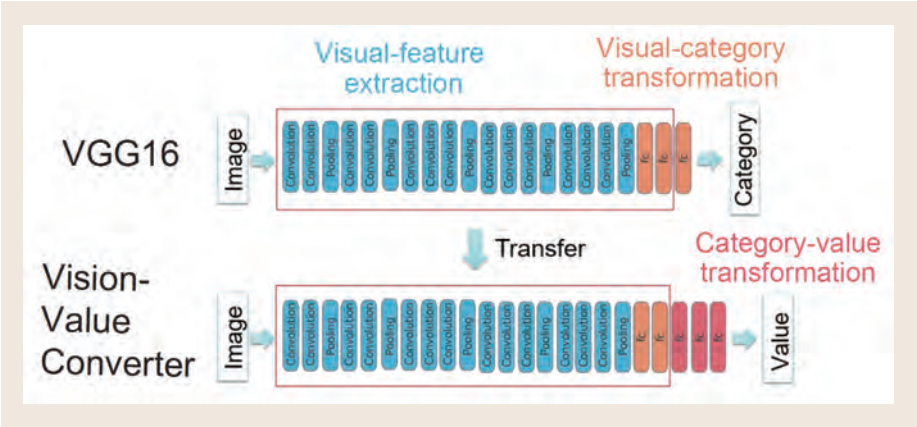
SADATO, Norihiro
Professor
Functional Neuroimaging
Neuroscience

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.

Recently, we focus on the combination of functional MRI and deep learning. Specifically, we built artificial intelligence that could predict the price of art. We further apply individual optimization to the AI, which results in making the AI mimic individual's preferences (Publicly offered research group in "Correspondence and fusion of artificial intelligence and brain science"). In our lab, students can learn how to analyze functional MRI data as well as how to use deep learning.

* J. Chikazoe and S. Konishi, "Functional neuroimaging approaches to human memory" , Memory in Social Context: Brain, Mind, and Society, T. Tsukiura and S. Umeda Ed.. Springer. (2018)



A schematic figure of transfer learning for vision-value converter, based on VGG 16. We used the same structure for vision-to-category transformation as VGG16 and added new layers for category-to-value transformation.

Center for Genetic Analysis of Behavior

YOSHIMURA, Yumiko
Professor
Director

Outline

The center produces gene-modified rat/mouse using TALEN and CRISPER/Cas9, etc. The center also provides virus vectors for cell type-specific gene modification. The center has facilities to monitor behavior, neuronal activity and metabolism in those gene-modified rat/mice, which are open for the collaboratory use from researchers of all over the world.

▶ Section of Viral Vector Development

NAMBU, Atsushi
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., Front. Neuroanat. 11, 65 (2017).
*② K. Kobayashi et al., Neurosci. Lett. 630, 45 (2016).
*③ T. Nagai et al., Neuron. 89, 550 (2016).
*④ K. Kobayashi et al., Methods. Mol. Biol. 1382, 175 (2016).
*⑤ AS. Wahl et al., Science. 344, 1250 (2014).

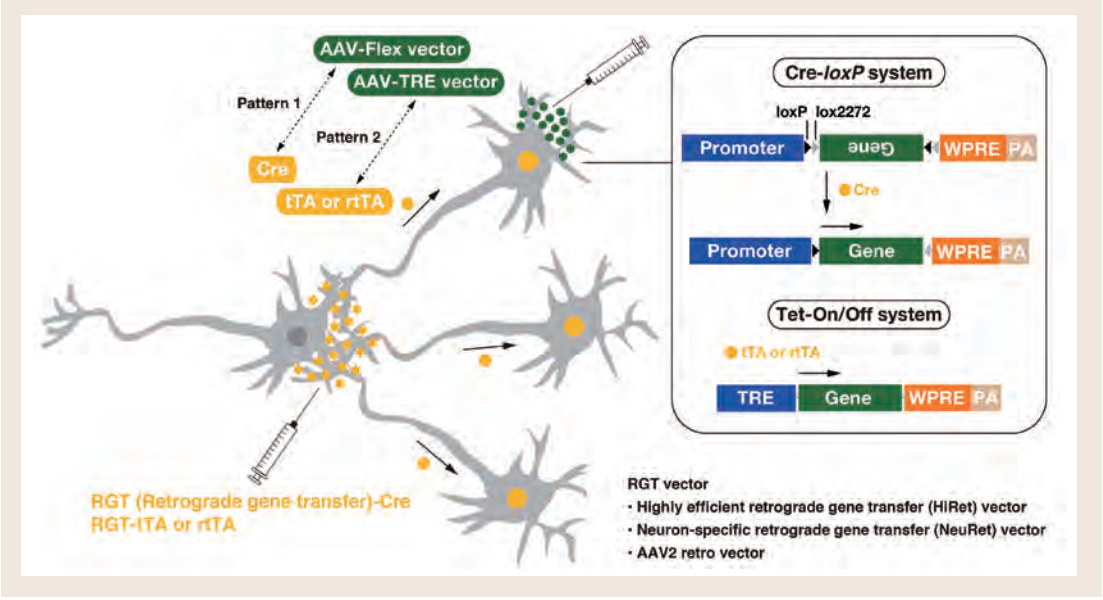


Figure 1. Application of viral vectors to brain research. Conditional gene expression in the specific neural pathway becomes possible by using a dual viral vector system. These useful viral vectors are available to collaborators.

▶ Section of Mammalian Transgenesis

HIRABAYASHI, Masumi
Associate Professor
Laboratory Animal Science

KOBAYASHI, Toshihiro
Assistant Professor
Stem Cell Biology
Developmental Technology

Development of Advanced Reproductive / Transgenic Technologies in Laboratory Animals

Genetically modified animals such as transgenic and knockout animals are essential tools for current life science research. In particular, recent progress on gene editing technologies including CRISPR/Cas9 system has enabled us to generate desired such animals more efficiently and rapidly. Our facility, Section of Mammalian Transgenesis, routinely generates a variety of genetically modified mice and rats according to requests from internal and external laboratories. In addition, we have developed novel reproductive and developmental technologies using early rodent embryos and the stem cells. One of our current projects is an application of our techniques to regenerative medicine. Recently, as a collaborative research, we have established "blastocyst complementation" method which can create a specific organ from pluripotent stem cells in organ-deficient animals. Through developing new technologies and generating model animals in various mammalian species, we aim to understand the underlying mechanisms on stem cell self-renewal/differentiation, early embryo development and organogenesis, which would contribute to future regenerative medicine as well as life science research.

* M. Hirabayashi *et al.*, J Reprod Dev. 63, 611 (2017).
* T. Goto *et al*., Transgenic Res. 25, 533 (2016).
* H. Hara *et al*., Cell Reprogram. 18, 108 (2016).

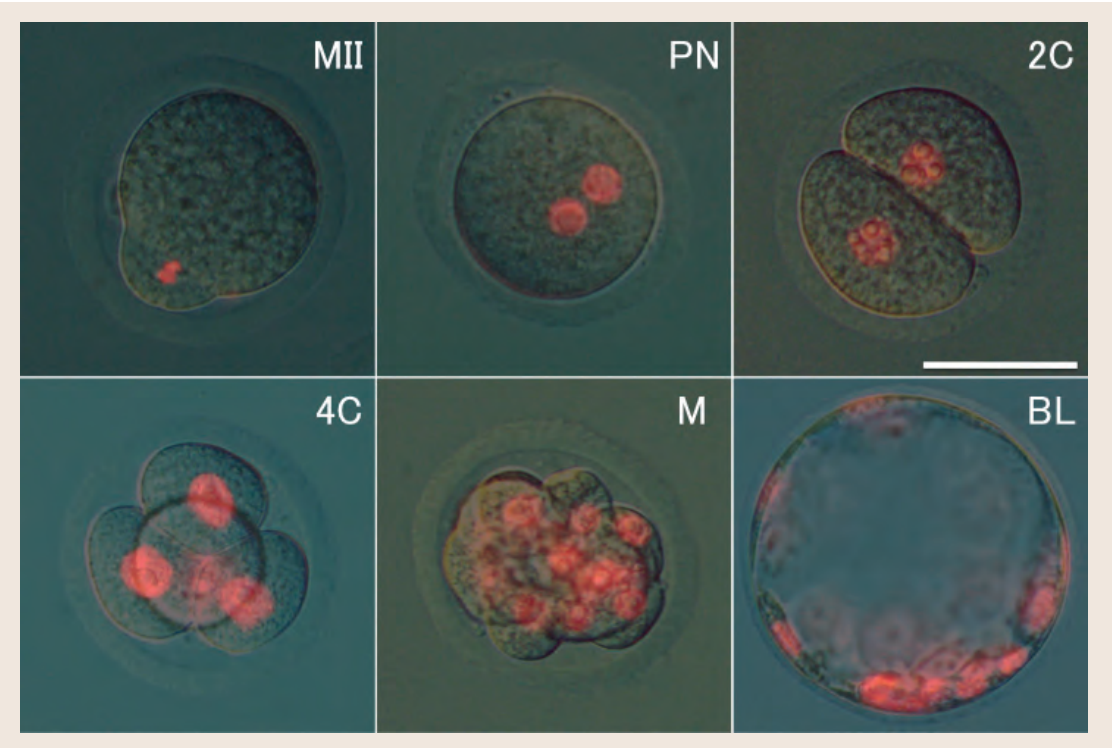


Fig. 1 Images of Rosa26-H2B/tdTomato knock-in rat zygotes, following 560-nm excitation.
MII: Metaphase-II stage oocyte. PN: Pronuclear stage zygote. 2C: 2-cell stage embryo. 4C: 4-cell stage embryo. M: Morula. BL: blastocyst.
Scale bar: 50 μ m.

▶ 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 modified 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 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 anesthetized mice.

Center for Communication Networks

FUKATA, Masaki
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

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.

The section was reorganized to be responsible for collecting and archiving various kinds of documents in 2016.

The collection includes the database of documents related to the foundation of the Institute, which was completed owing to the great contribution of Professor Emeritus Shunichi Yamagishi. It also includes the text version of "Oral History" stated by Professor Yamagishi.

▶ Section of Physiology and Medicine Education

TOMINAGA, Makoto
Professor
Molecular and Cellular Physiology

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' was made 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), and it is now provided as 'step-by-step studies of brain science'. Students take the e-Learning-based exams in the end of each semester. Upon taking both 'step-by-step studies of brain science', 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

KAKIGI, Ryusuke
Professor
Neurophysiology

Outline

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.

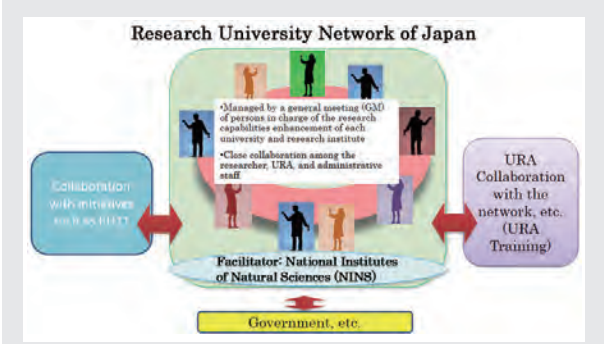
Monthly meetings are held to smoothly conduct the regulatory procedures.

Research Enhancement Strategy Office

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



NABEKURA, Junichi
Professor
Neuroscience

KUBO, Yoshihiro
Professor
Biophysics
Neurobiology

FUKATA, Masaki
Professor
Neuroscience
Biochemistry
Cell Biology

MINOKOSHI, Yasuhiko
Professor
Endocrinology and Metabolism

YOSHIMURA, Yumiko
Professor
Neurophysiology

URANO, Toru
Project Professor
Loboratory Animal Science
Bacterial Infectious Disease

MARUYAMA, Megumi
Project Associate Professor
Neurophysiology
Environmental Physiology

SAKAMOTO, Kiwako
Assistant Professor
Neurophysiology

Orion Project
(Bioregulatory Signaling)

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

Analysis and reconstruction of 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. We also tackle the development of the biomimetic chemical sensor based on the chemosensory systems.

The genes of olfactory receptors (ORs) encode the large family of seven-transmembrane-domain G protein coupled receptors (GPCRs). Although insect ORs possess the seven transmembrane topology with the intracellular amino terminus, they comprise the odor-gated ion channels (fig. 1). One of the insect gustatory receptor family also comprises the fructose-activated ion channel. 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 (fig. 1).

* 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. (2008) Insect olfactory receptors are heteromeric ligand-gated ion channels. *Nature* 452:1002-6

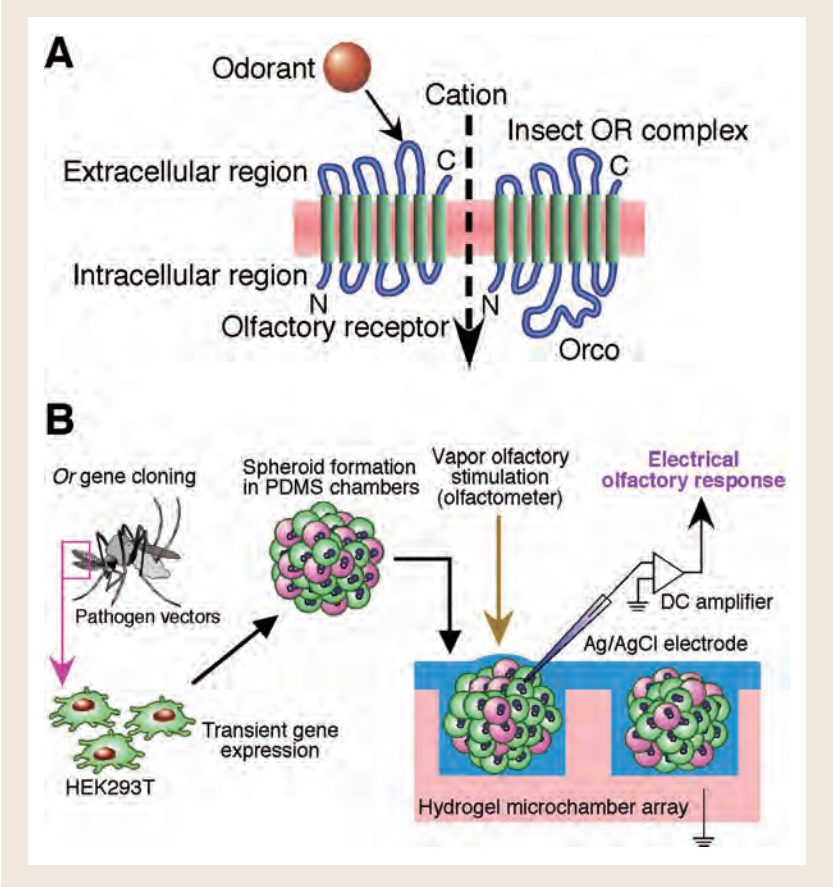


Fig. 1 Ionotoropic function of insect olfactory receptor complex and their application to the olfactory sensor. (A) Schematic model for ligand-gated channel properties of the insect conventional olfactory receptor (OR) + co-receptor (Orco) complex. (B) Vapor chemical detection by using reconstructed insect ORs.

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.

Division of Coordinator for Animal Experimentation

TOMINAGA, Makoto
Professor
Molecular and Cellular Physiology

The Division was established in 2008 under the Institutional Animal Care and Use Committee (IACUC) covered with 3 Institutes at Okazaki (Current with National Institutes of Natural Sciences)

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.

Exploratory Research Center on Life and Living Systems

Okazaki Institute for Integrative Bioscience ended in fiscal 2017.

A new Research Center "Exploratory Research Center in Life and Living Systems (ExCeLLS)" was launched in FY 2018.

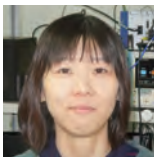
ExCeLLS consists of 18 research groups, and the following 4 research groups also belong to the National Institute for Physiological Sciences.

- Thermal Biology Group　Division of Cell Signaling (See P. 12)
- Cardiocirculatory Dynamism Research Group　Division of Cardiocirculatory Signaling (See P. 13)
- Cognitive Genomics Research Group
- Biofunctional Systems Construction Research Group　Bioregulatory Signaling (See P. 43)

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.

DEROUICHE, Sandra
Division of Cell Signaling
Molecular and Cellular Physiology



UEMATSU, Akiko
Division of Behavioral Development
Neurophysiology

HAMANO, Yuki
Division of Cerebral Integration
Experimental Psychology, Neuroimaging, Neuroscience

TANAKA, Tomohiro
Division of Cardiocirculatory Signaling
Neuropathology

DWI WAHYU, Indriani
Division of System Neurophysiology
Neurophysiology

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.

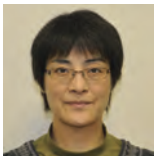
Every year, "Operation Report Meeting" is held to promote the mutual understandings of technical operations and to exchange general information in the division.

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

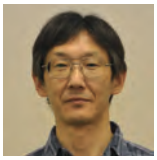
Unit Chief :
SATO, Shigeki
Center for Communication Networks Technical Unit



Assistant Unit Chief :
KUBOTA, Mitsuko
Center for Experimental Animals Technical Unit

Assistant Head :
TOGAWA, Morio
Departments Technical Section

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



Assistant Unit Chief :
MORI, Masahiro
Research Infrastructure Technical Unit

Section Chief :
YOSHIMURA, Nobuaki
Research Centers Technical Section

Unit Chief :
FUKUTA, Naomi
Research Infrastructure Technical Unit

Staff :
KANO, Yuichiro
Molecular & Cellular Physiology Technical Unit

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

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

Staff :
INAHASHI, Hiroki
Molecular & Cellular Physiology Technical Unit

Unit Chief :
NAGATA, Osamu
Homeostatic Regulation Technical Unit

Assistant Unit Chief :
ISHIHARA, Hiromi
Homeostatic Regulation Technical Unit

Staff :
KAMIYA, Emi
Center for Experimental Animals Technical Unit

Unit Chief :
YAMAGUCHI, Noboru
Fundamental Neuroscience Technical Unit

Assistant Unit Chief :
TAKAGI, Masahiro
Fundamental Neuroscience Technical Unit

Staff :
YAMANAKA, Midori
Center for Experimental Animals Technical Unit

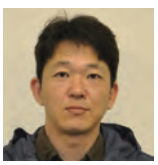
Unit Chief :
TAKESHIMA, Yasuyuki
System Neuroscience Technical Unit

Assistant Unit Chief :
TAKAHASHI, Naoki
System Neuroscience Technical Unit

Unit Chief :
YOSHITOMO, Miki
Center for Research Collaboration Technical Unit

Assistant Unit Chief :
YAMADA, Gen
Supportive Center for Brain Research Technical Unit

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



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

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

Assistant Unit Chief :
MURATA, Yasuhisa
Center for Communication Networks Technical Unit

Large facilities and equipments for cooperative studies

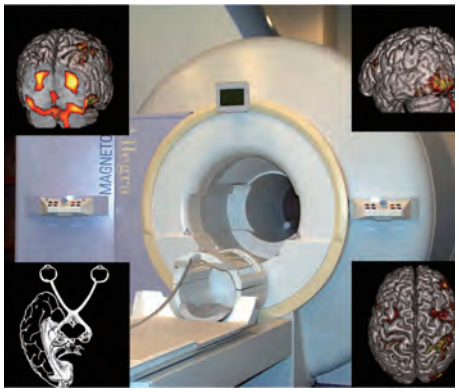
Outline

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 equipment, large-scale equipment, and research facilities, and develops new equipment for morphological and functional 4D imagings of various organs such as the brain.

▶ High Voltage Electron Microscope (HVEM)

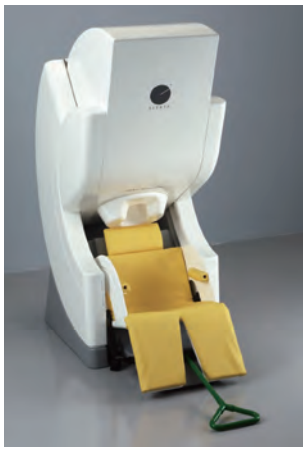
Hitachi H-1250M is the unique high voltage electron microscope specially designed for biological and medical sciences. The microscope usually operates at an accelerating voltage of 1,000 kV. The column pressure is kept at less than 7×10^{-6} Pa near the specimen position. The image acuisition is performed at the magnification ranges from 1k to 1,000 k. Projections of thick biological specimens up to 5 μm 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: 3 tesla, 7 tesla)



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, but MRI also allows exploring 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 a 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. In 2016 and 2017, cooperative study projects using 7T machine were performed for the purpose of technical assessment and development. After confirming stable operation, it will be fully provided for cooperative studies.

▶ 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. Also, background brain activities (brain waves) in various conditions can be analyzed.

▶ Phase Contrast Electron Cryomicroscopy

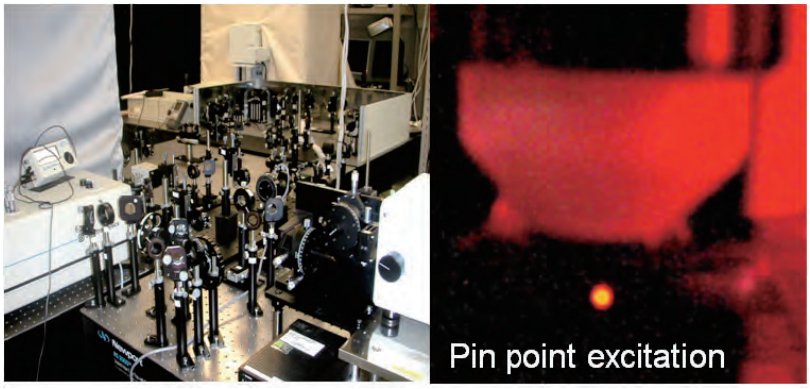
Phase contrast electron cryomicroscopy is an electron microscope developed for observing close-to-life state biological samples with a combination of rapid freezing and ice embedding sample preparation methods. Biological specimens up to 200 nm thicknesses can be observed with high-resolution and high-contrast. 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 equipment. Two different types of SBF-SEM are available; high-resolution and wide-area types. Resin-embedded biological specimens are trimmed by a diamond knife equipped inside the chamber, and the block-face images are acquired by scanning electron microscopy (SEM). 3-D structures of the specimens are finally reconstructed from the acquired serial block-face images. 3-D structures of large biological specimens like a brain tissue can be visualized at the 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 excitation, it had a superior deeper tissue penetration and reduced phototoxicity than those of single-photon excitation. Our 2-photon microscopes have a top level specification for deep tissue imaging and can be applied to the imaging of neurons and glial cells in deep tissues such as mouse brain. Recently, we also developed a 2-photon fluorescence imaging microscope which can be applied to image protein-protein interaction and the protein activity.



▶ 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 recording from motor-related brain regions in the awake state, 2) Regional neural activity detected as intrinsic signals with taking the advantage of light fluorescent dynamics of flavin or hemoglobin, 3) Energy intake and expenditure in free-moving animals, 4) Body temperature, heart rate and blood pressure in free-moving animals, 5) Measurement of cardiac functions using Langendorff-perfused hearts and non-invasive measurement of cardiac functions and peripheral blood flow using anesthetized 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. 31

▶ Instrument Design Room

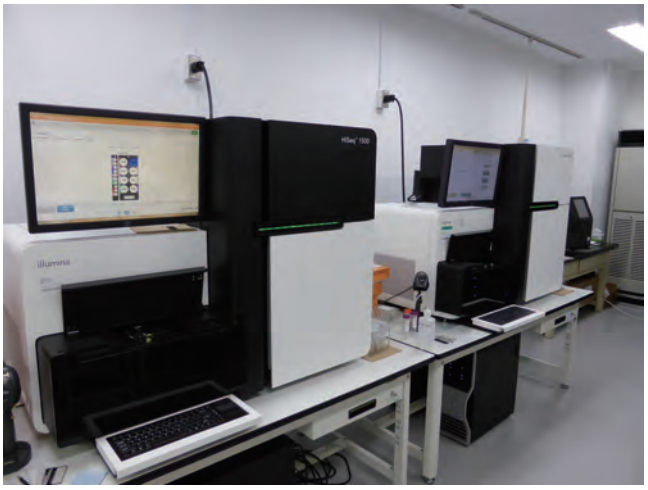
Custom-designed equipments, which are not commercially available, can be constructed in this room. The machine shop is equipped with various types of machines such as milling machines and drill presses. Two 3D-printers also work, and laboratory equipment can be manufactured. The electronic shop is equipped 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.

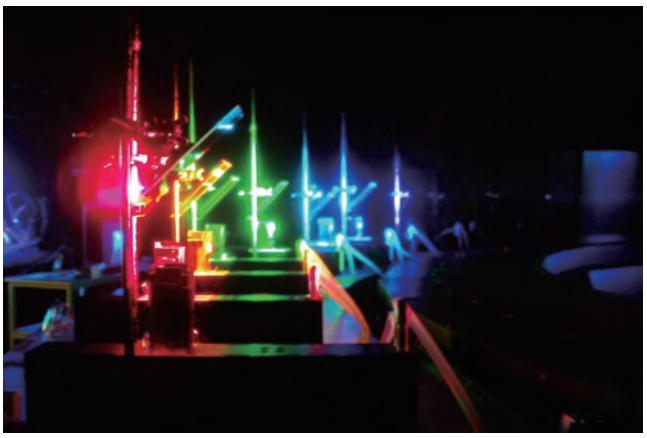
Next generation DNA sequencers (Functional Genomics Facility)



▶ 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 2018, 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. Twenty four meetings were held last year, and 23 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 2017, no International Workshops was conducted.

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 2017, 98 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. Also, "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, and "Analyses of dynamic aspects of the function and structure of membrane proteins" in 2017. 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.

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.

"Behavioral analysis of mouse and rat" was closed due to the shutdown of the Section for Behavior Patterns. In 2016, NIPS performed only the collaborative experiments carried over from last year.

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"

Since genetically modified model animals are extremely effective for gene function analysis at individual level, they are widely used in the field of life sciences. The recent engineering required to create

such model animals has taken huge leaps forward; e.g., a new genome-editing tool (CRISPR/Cas9 system) can relatively easily cut arbitrary sequences on the genome. Section of Mammalian Transgenesis at the Center for Genetic Analysis of Behavior in NIPS has established the latest technology such as the CRISPR/Cas9 system capable of providing endogenous genetic modification to mice and rats. Our staffs familiar to not only physiology and brain science but also reproductive biotechnology, have greatly contributed to researchers all across the country by providing technology to create genetically modified model animals. We can support cooperative studies by providing the technologies to develop adoptive models such as transgenic or knock-out mice and rats. In the calendar year of 2017, we have created a total of 19 transgenic or knock-out mouse and rat lines under 9 collaborative research projects. We will continue to work on the requested creation of genetically modified model animals by applying the new genome-editing tools.

"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) Circuit behavior imaging of flavin and hemoglobin intrinsic signals in the brain using voltage-sensitive dyes.
3) Measuring food intake and energy consumption during free movement.
4) Measuring body temperature, pulse rate, and blood pressure
5) Measuring the cardiac function and blood flow volume of mice *in vivo* or *in vitro.*

Seven collaborative research projects with researchers outside NIPS were conducted in 2017, and five projects are now scheduled in 2018.

"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 the plastic resin are sliced by a diamond-knife and imaged by SEM continuously. Finally, the three-dimensional ultrastructure of the specimens is rebuilt at dozens of nanometer resolution. The program support studies by using these state of the art electron microscopes. In 2017, 24 projects were carried out, and 18 are now scheduled in 2018.

"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 allow us to observe the structure in depth of one millimeter with a spatial resolution of a micrometer. Since the maintenance of two-photon microscope is complicated, NIPS is the only institute which can provide the opportunity for collaborative research with the high-quality experience. Furthermore, we recently build the two-photon fluorescence lifetime microscope system which enables us to observe the intermolecular interactions and the activity of signaling protein in a living cell in the deep tissue. We are also working on single-molecule imaging using quantum dot in a combination of a 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 2017, four planned collaborative projects were carried out, and five were scheduled in 2018. We also discussed 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 only for primates but also for other animals. Thus, a planned collaborative project "Gene transfer into the

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 two 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. 1) Virus vectors helped to identify system circuits that compensated motor functions after spinal cord injury in macaque monkeys. 2) Virus vectors revealed the property of subnetwork composed of excitatory and inhibitory neurons in layer 5 of the rat frontal cortex. 3) Virus vectors identified a specific subset of neurons commanding the dietary preference for carbohydrate over fat in mice.

In 2017, 9 research were performed, and 13 are now scheduled in 2018.

"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 precisely. Therefore, there are gradually increasing needs for the support to perform purification of protein complexes from tissues 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. In 2017, two research were performed , and one is now scheduled in 2018.

"Analyses of dynamic aspects of the function and structure of membrane proteins"

Functional membrane proteins such as ion channels and receptors are strictly designed molecules. They, at the same time, show dynamic changes of the structure and function depending on the situation. To analyze the dynamics aspects by electro- physiological and opto-physiological experiments using in vitro expression systems, we perform this planned collaborative project. In 2018, we plan to conduct 6 research projects.

3. NIPS research meeting

In 2017, more than 1000 researchers took part in a total of 24 meetings, and the numbers keep growing each year. In 2018, 23 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. Also, 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.

In 2016, one NIPS research meeting was held at Kyushu University. Traditionally, NIPS research meetings had been held in Okazaki area. We aimed to contribute to the physiological research communities located in the Kyushu area, and to the functional enhancement of the universities there. As this trial-run meeting won popularity, we conducted one in Tohoku and another in Tokyo area in 2017, both of which obrained popularity. We now schedule one in Nagoya area and another in Tokyo area in 2018. More recently, there have been some 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 were TRPs and SOCs --Unconventional Ca^{2+} Physiology--". In 2016, two NIPS international workshops were conducted, "Towards elucidation of memory engram," and "The 4th International Symposium on Salivary Glands in Honor of Niels Stensen". In 2017, no International Workshops was conducted.

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 at a deep area of the cell at a 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. A digital camera was installed in 2012, which accelerates three-dimensional structural analysis by high-voltage electron tomography. In 2017, ten projects were carried out, and five are now scheduled in 2018.

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. In 2017, 31 projects were carried out, and 34 are now scheduled in 2018.

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." The institute installed a 3 Tesla machine in 2000, which had been ulilized up until 2018. It 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 activaton. 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 3 Tesla 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 a human was introduced in 2014, and the operation was started in 2015. In 2017, two cooperative study projects using 7T machine were performed for the purpose of technical assessment and development, and five are now scheduled in 2018. 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 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 shortly 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).

The 48th NIPS International Symposium

The 48th NIPS International Symposium
"*Neural circuitry and plasticity underlying brain function*"

The 48th NIPS International Symposium "*Neural circuitry and plasticity underlying brain function*" was held at Okazaki Conference Center from October 31th to November 2nd, 2017. Ninety five attendees including 28 attendees from NIPS came to the symposium. Six invited speakers from abroad (USA 4, South Korea 1, Switzerland 1) and 10 domestic invited speakers talked on their outstanding research on novel experimental approaches. Speakers for the special lectures were Professor Edward M Callaway (Salk Institute, USA) and Professor Haruo Kasai (the University of Tokyo, Japan). In addition, 7 short talks presented by young researchers and 26 poster presentations were provided. All speakers presented their recent research focusing on (1) activity- and experience dependent developmental mechanisms, (2) multimodal integration and plasticity, (3) molecular mechanisms for formation and elimination of neural circuits, (4) learning and memory and (5) subcellular mechanisms for information processing. Attendees intensively discussed to share recent results, network with colleagues and shape the scientific direction of this research field.

Program

October 31 (Tue) 2017

Opening remarks

Keiji Imoto (Director General, NIPS, Japan)

Session 1: Activity- and experience dependent developmental mechanisms

Chair: Yoshio Hata (Tottori University, Japan)

13:45 –14:20

Yumiko Yoshimura (NIPS, Japan)

"The roles of visual experience in the maturation of neural responses in the primary visual cortex"

14:20 –14:55

Kenichi Ohki (the University of Tokyo, Japan)

"Gap junctions in postnatal excitatory neurons regulate spine density and response reliability"

Chair: Takuji Iwasato (National Institute of Genetics, Japan)

15:10 – 15:45

Madoka Narushima (NIPS, Japan)

"The metabotropic glutamate receptor subtype 1 mediates experience-dependent maintenance of mature synaptic connectivity in the dorsal lateral geniculate nucleus"

15:45 –16:20

Nobuhiko Yamamoto (Osaka University, Japan)

"Activity-dependent mechanisms for thalamocortical circuit formation"

Session 2: Multimodal integration and plasticity

Chair: Mariko Miyata (Tokyo Women's Medical University, Japan)

16:35 –17:10

Patrick Kanold (University of Maryland, USA)

"Crossmodal induced refinement of auditory cortex circuits"

17:10 –17:45

Seung-Hee Lee (KAIST, Korea)

"Neural circuits for sensory integration"

Short Talk 1:

Chair: Rie Kimura (NIPS, Japan)

17:45 –18:00

Tzu-Huei Kao (the University of Tokyo, Japan)

"Roles of synaptic activity in climbing fiber to Purkinje cell synapse elimination in the developing cerebellum"

18:00 –18:15

Mieko Morishima (NIPS, Japan)

"Pyramidal cell subtype-dependent inhibitory-excitatory circuits in layer 5 of the rat frontal cortex"

18:15 –18:30

Eriko Kuramoto (Kagoshima University, Japan)

"Local connections of excitatory neurons to parvalbumin-containing interneurons in motor-associated cortical areas of mice"

November 1 (Wed) 2017

Special Lecture 1

Chair: Yumiko Yoshimura (NIPS, Japan)

9:00 – 10:00

Edward M. Callaway (Salk Institute, USA)

"Imaging the mouse visual system: parallel pathways and visual cortical areas"

Session 3: Molecular mechanisms for formation and elimination of neural circuits

Chair: Takeshi Yagi (Osaka University, Japan)

10:15 – 10:50

Denis Jabaudon (University of Geneva, Switzerland)

"Dynamic control of neuronal diversity in the developing neocortex"

10:50 – 11:25

Kazuo Emoto (the University of Tokyo, Japan)

"Molecular and cellular basis for neurite remodeling in Drosophila"

11:25 – 12:00

Tomomi Shimogori (RIKEN, Japan)

"Activity dependent Btbd3 protein dynamics for selective dendrite morphogenesis in developing neurons"

Special Lecture 2

Chair: Yumiko Yoshimura (NIPS, Japan)

13:30 – 14:30

Haruo Kasai (the University of Tokyo, Japan)

"Dopamine actions on the dendritic spines and conditioning behaviors"

Short Talk 2:

Chair: Kenji Hayashi (NIPS, Japan)

14:45 – 15:00

Shin-ichi Higashijima (NIBB, Japan)

"Axially-confined in vivo single-cell labeling by primed conversion using blue and red lasers with conventional confocal microscopes"

15:00 – 15:15

Ichiro Aoki (Nagoya University, Japan)

"BK potassium channels resist premature memory overwriting in *C. elegans*"

15:15 – 15:30

Shuntaro Izawa (Nagoya University, Japan)

"MCH neurons in the hypothalamus impairs memory during sleep"

15:30 – 15:45

Eisuke Koya (University of Sussex, United Kingdom)

"Changes in appetitive associative strength and reward value modulate the Intrinsic excitability of nucleus accumbens neuronal ensembles"

15:45 – 18:00

Flash talk, Poster Session

November 2 (Thu) 2017

Session 4: Learning and memory

Chair: Junichi Nabekura (NIPS, Japan)

9:00 –9:35

Wenbiao Gan (New York University School of Medicine, USA)

"Dendritic branches are independent units for memory storage and generalization"

9:35 –10:10

Masanori Murayama (RIKEN, Japan)

"Top-down cortical circuit for perception and memory consolidation in mice"

10:10 –10:45

Takaki Komiyama (UCSD, USA)

"Imaging neural ensembles during learning"

Session 5: Subcellular mechanisms for information processing

Chair: Hiromu Yawo (Tohoku University, Japan)

11:00 –11:35

Hiroshi Kuba (Nagoya University, Japan)

"Tonotopic differentiation of dendritic computation in sound localization circuit"

11:35 –12:10

Yoshiyuki Kubota (NIPS, Japan)

"The Diversity of Cortical Inhibitory Synapses"

Closing remarks

Yumiko Yoshimura (NIPS, Japan)

The Graduate University for Advanced Studies School of Life Science

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)).

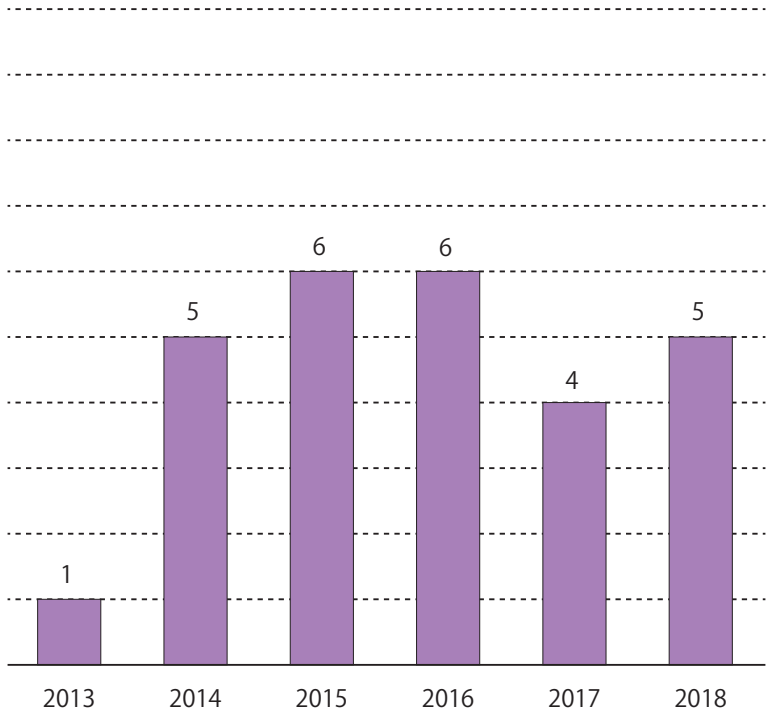
The outline of Department of Physiological Sciences.

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 2018



International Exchanges

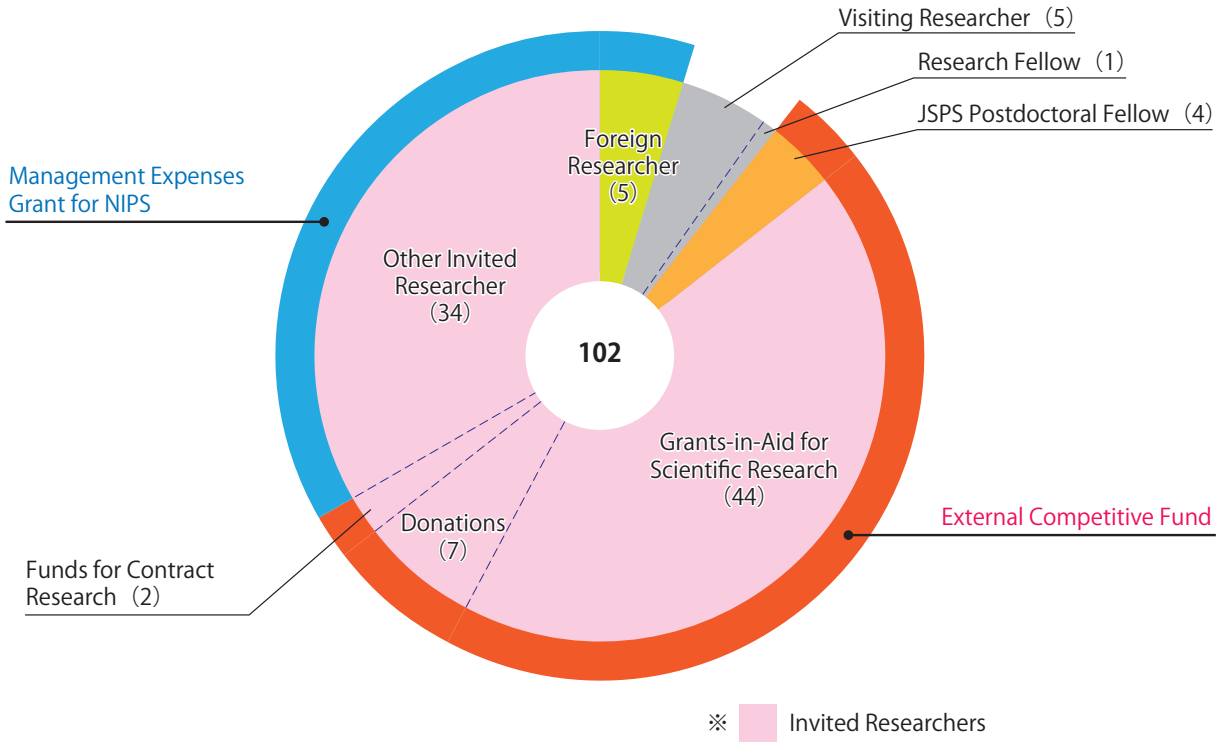
NIPS is an internationally recognized research institution and active international exchanges are performed. NIPS has the positions of foreign research staff (approximately 3 visiting professors and 3 visiting researchers), and world top-class researchers have engaged in research collaboration so far using this framework. Besides the research collaboration, visiting professors contribute to education of young researchers. In FY2014, NIPS started the Section of International Collaborative Research Project, which is run for 3 years by an adjunctive foreign professor as a Principal Investigator (P.I.). In FY2017, Professor Denis Le Bihan (a former Director of Neurospin, France) is running a lab as a P.I. In addition, using the frameworks such as JSPS postdoctoral fellowship, foreign researchers and graduate students conduct research at NIPS. Also many foreign students enter Department of Physiological Sciences of SOKENDAI as a graduate school and engage in research actively.

One of the main international exchange activities at NIPS is the annual international symposium. A NIPS professor serves as an organizer, and usually approximately 10 top researchers from abroad and a similar number of top domestic researchers are invited. The total number of participants is around 100-150. In FY2017, the 48th NIPS International Symposium entitled "Neural circuitry and plasticity underlying brain function" was organized by Professor Yumiko Yoshimura. There were 95 participants including 7 oversea speakers (total 20 speakers). In FY2018, the 49th NIPS International Symposium entitled "Ion channels (tentative)" will be held on Dec 6-8 (Organizers: Professor Keiji Imoto and Professor Yasuo Mori (Kyoto University)). In addition, the international workshop, which is an international version of NIPS research meetings, was launched in FY2008 and NIPS aims to hold it every year.

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); University of New South Wales, Faculty of Medicine (Australia); Neurospin (France); and McGill University (Canada). In FY2017, NIPS organized a joint symposium with Yonsei Univsesity and Korea Univeristy in Seoul, sending 23 researchers, and that with Tübingen University focusing on higher brain function in NIPS inviting 8 researchers. Also a joint symposium with McGill University was held in Montreal, sending 8 NIPS professors. In FY2018, NIPS plans to organize another joint symposium with McGill University in NIPS and also welcomes 5weeks' stay of PhD students in McGill University to facilitate collaboration.

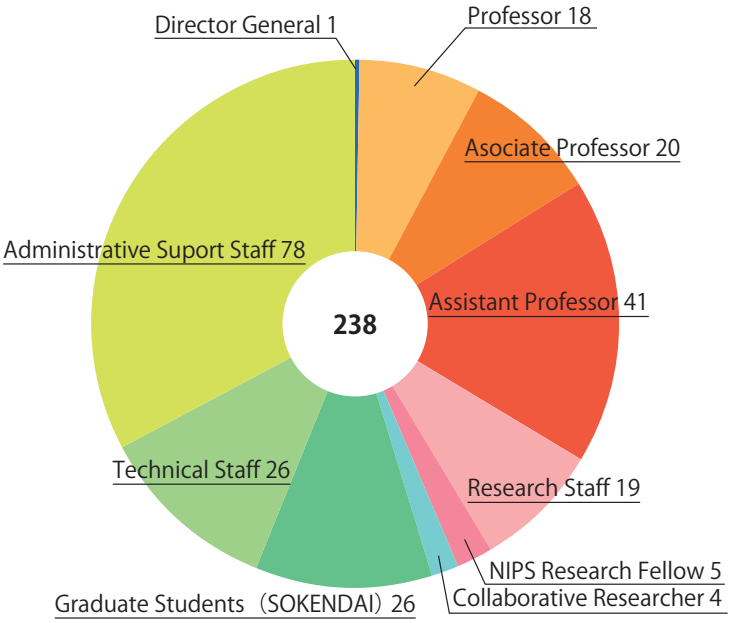
Besides these, many international research collaborations of high quality are performed at the individual researchers' level, supported by the budget of NIPS and also research grants from outside.

Number of Foreign Researchers



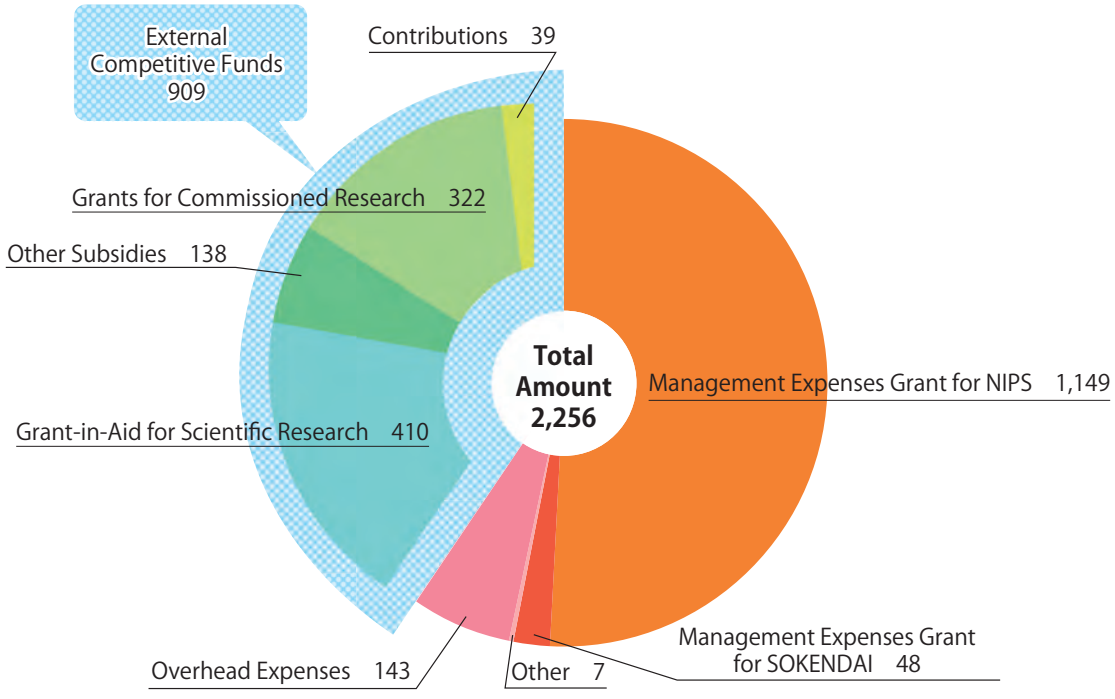
Current State

Staffs



Budget

numbers are in million yen/As of May, 2017



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 The IDENTIFICATION 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 112）
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	14	—	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.

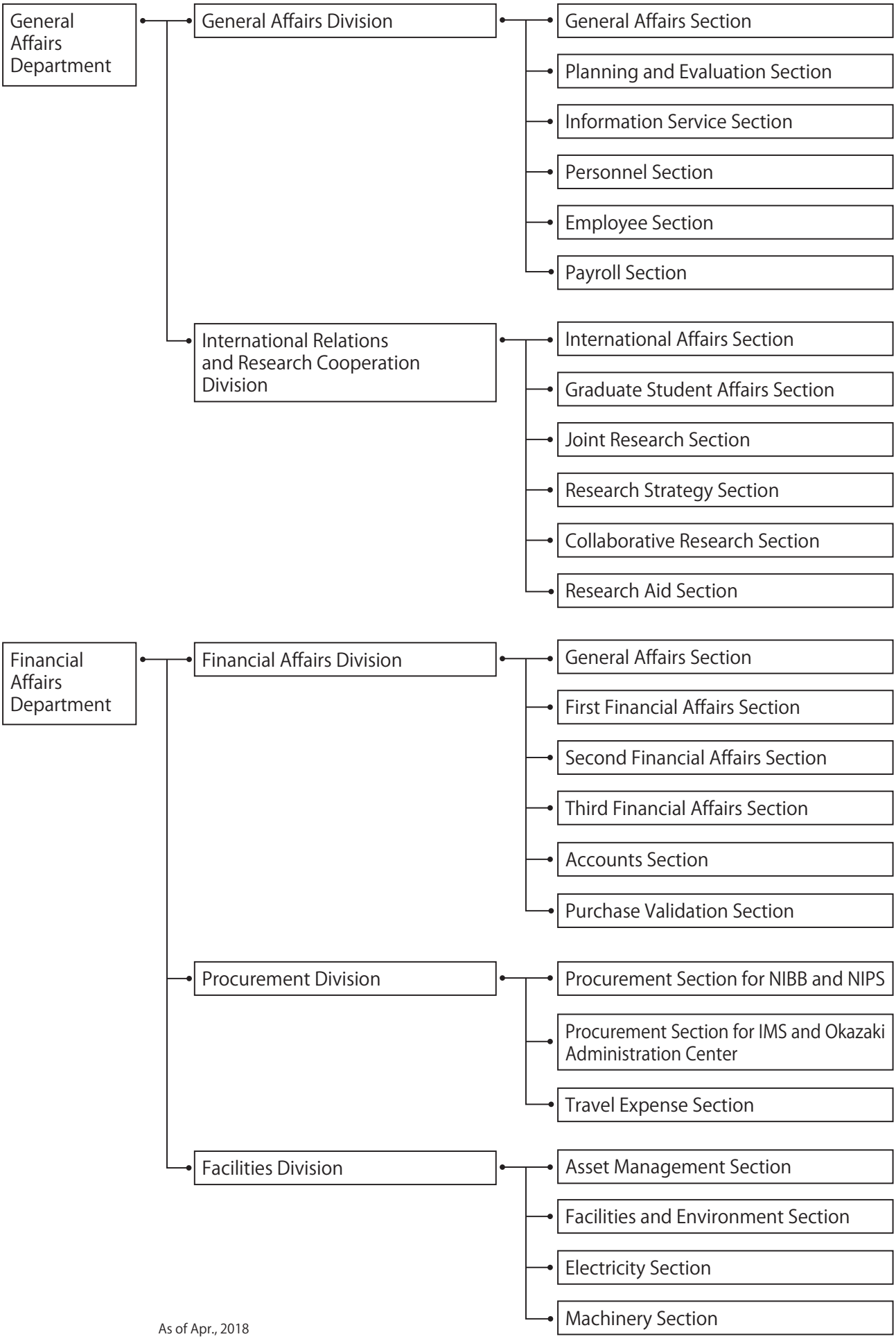
Age: From the 57th day of after the birth to 3 years old

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

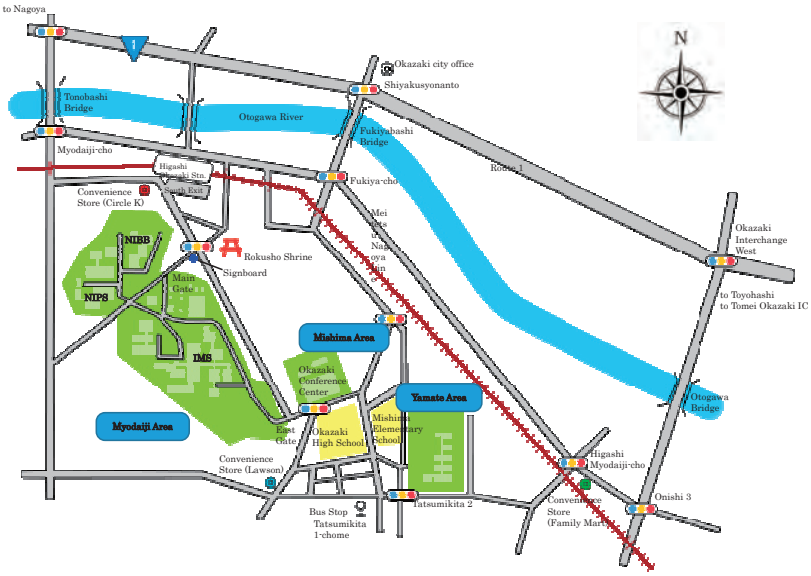
Okazaki Administration Center

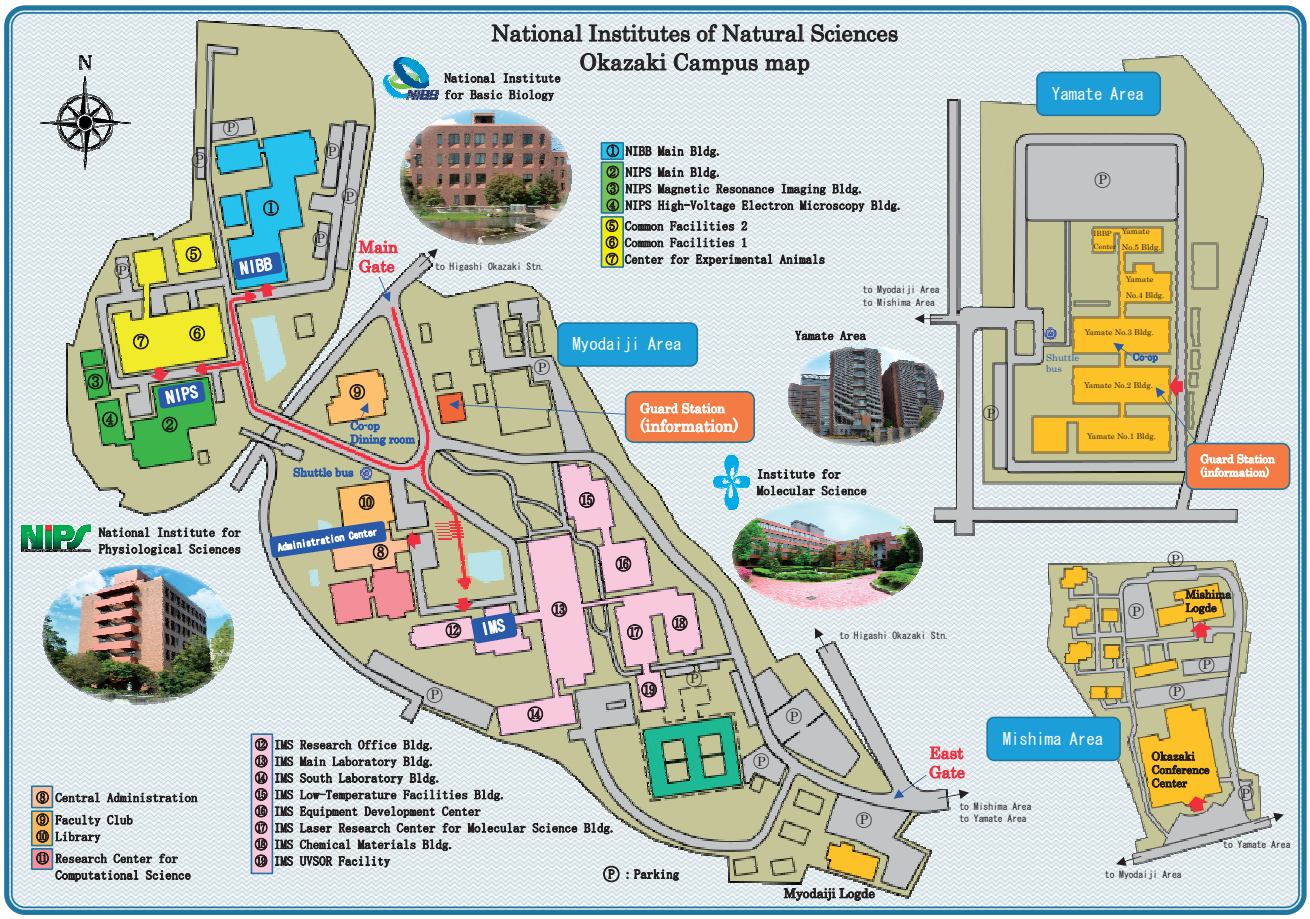


As of Apr., 2018

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	Exploratory Research Center on Life and Living Systems, and others





Location

From Central Japan International Airport

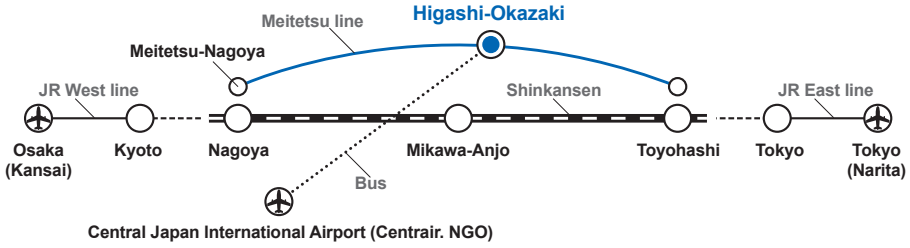
A) By bus
Get on the Meitetsu Airport Bus bound for Okazaki Station and get off at Higashi Okazaki Station

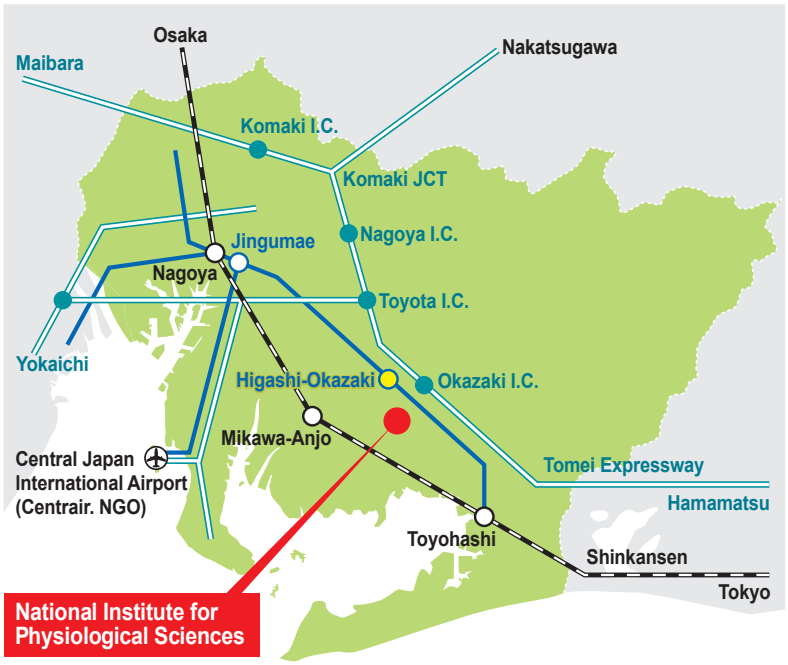
B) By train
Take the Meitetsu train from Central Japan International Airport to Higashi Okazaki Station. NIPS is a 7-minute walk up the hill on the south side of the station.

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.





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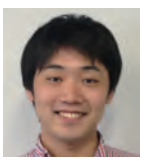

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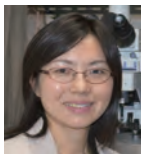

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