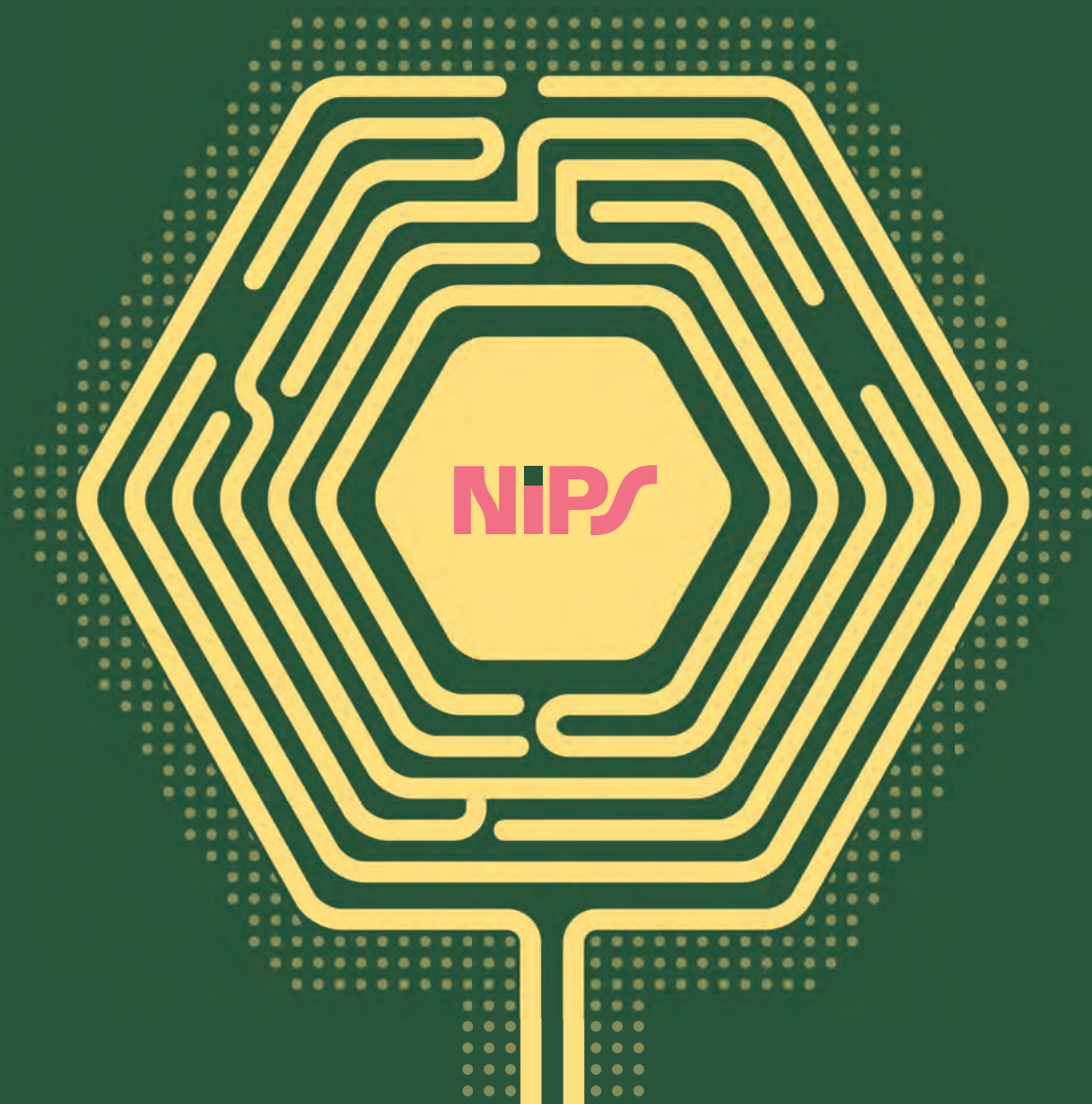


National Institutes of Natural Sciences

# National Institute for Physiological Sciences 2020



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# INTRODUCTION

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The National Institute for Physiological Sciences (NIPS) is an inter-university research institute focused on research and education in human physiology. The NIPS promotes collaborative studies amongst both National and International researchers and organizations to together help understand body functions and their mechanisms. Research at NIPS also provides further understanding of the fundamental mechanisms causing diseases, to enable new and improved treatments for these diseases and their symptoms.

A major focus of current research at NIPS is to understand the brain. Brain, most developed in human among all the creatures, is critical for how we detect, respond and adapt to our environment, through the processes of sensation, motor control and learning and memory. However the brain also directs our individual behaviors and desires, and how we communicate with each other socially through language and emotions. Furthermore, the brain also interacts with our visceral organ systems to regulate body homeostasis, and research at the NIPS also aims to provide a comprehensive understanding of the mechanisms of body homeostasis through our research on the regulation of the cardiovascular system, of the body and cellular metabolism, on temperature control and on how we regulate our biological defenses against damage and pathogens. The NIPS strives to advance our understanding of brain function and body homeostasis, from the molecular, cellular, organ and whole body and society levels, and we provide and develop cutting-edge research technology, including computational and mathematical approaches, to achieve these strategic goals.

The NIPS advocates the following three major missions.

The first mission of NIPS is to conduct cutting-edge research in the physiological sciences across various levels from the molecular and cellular through to organ systems, and to integrate this multi-level information to understand homeostasis in the living body. As research in life sciences has become diversified and “translatable”, NIPS aims to conduct world-leading research focused on the basic medical sciences, especially physiology and brain sciences. To apply and develop rigorous basic research techniques necessary to answer fundamental questions is also part of our mission.

The second mission of NIPS is to play the role of a National and International research hub. The NIPS conducts collaborations with scientists at universities and research institutes to further strengthen and enhance research expertise in Japan at a leading global level. To achieve this goal NIPS also encourage collaborations with foreign researchers, and we provide and develop specialized and cutting-edge research techniques and equipment to facilitate these collaborations. The NIPS provides advanced devices in areas including electron and laser microscopy for subcellular through to human imaging, and in transgenic animals and viral vectors. The NIPS also supports advanced research workshops in various fields to help establish and support research collaborations, discussions and advances and sharing of knowledge. Through these activities the NIPS is a hub for domestic and international research communities to intercommunicate and support each other. At present, NIPS participates in a number of programs as their core organizations, such as Comprehensive Brain Science Network, Advanced Bioimaging Support and Brain/MINS Beyond.

The third mission of NIPS is to provide advanced and thorough education for young scientists. The NIPS is responsible for the 5-year PhD course in physiological sciences of The Graduate University for Advanced Studies, SOKENDAI. The NIPS also provides further education for graduate students and young researchers from other universities and industries in Japan and Internationally, for education through various research training programs that include the annual NIPS Training Course and via NIPS Internships.

To understand human body functions and to apply our extended knowledge to support human life is our ultimate goal. NIPS will make every effort to open our institute to every research community that can work together with us towards this goal. For this purpose, your understanding and support will be appreciated.



Director General  
**NABEKURA, Junichi**  
MD, PhD

1981 MD, Kyushu University, 1987 PhD, Kyushu University, 1987 Postdoc Researcher, Washington University, 1991 Assistant Professor, Tohoku University, 1993 Associate Professor, Akita University, 1995 Associate Professor, Kyushu University, 2003 Professor NIPS, 2013 Vice Director General, NIPS, 2019 Director General, NIPS and Vice President, NINS.  
Specialty: 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, 16 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, SOKENDAI. The University provides 2 courses, 5-year Doctor Course and 3-year Doctor Course (transfer admission after master's course completion). 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

Administrative Council, Education and Research Council and Executive Meeting 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 Center 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 characteristics 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, SOKENDAI 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 Intracellular 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

#### **Oct., 2018**

The following were abolished:

- Department of Molecular and Cellular Physiology
  - Division of Neural Systematics
- Department of Fundamental Neuroscience
  - Division of Cardiocirculatory Signaling

The following was added:

- Department of System Neuroscience
  - Division of Neural Dynamics

#### **Apr., 2019**

Prof. NABEKURA J. was elected the Director-General of the Institute.

The following were abolished:

- Department of Molecular and Cellular Physiology
- Division of Neurobiology and Bioinformatics
- Department of System Neuroscience
- Division of Sensory and Cognitive Information

The following was added:

- Department of Homeostatic Regulation
  - Division of Ultrastructural Research
- Center for Experimental Animals has also been renamed  
Center for Animal Resources and Collaborative Study

#### **Oct., 2019**

The following were abolished:

- Department of System Neuroscience
  - Division of Integrative Physiology

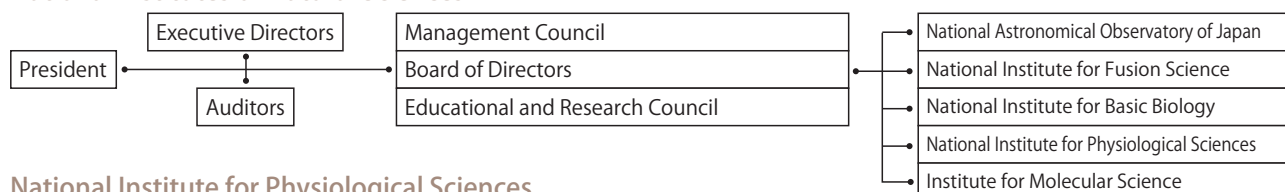
The following was added:

- Department of Fundamental Neuroscience
  - Division of Biophotonics

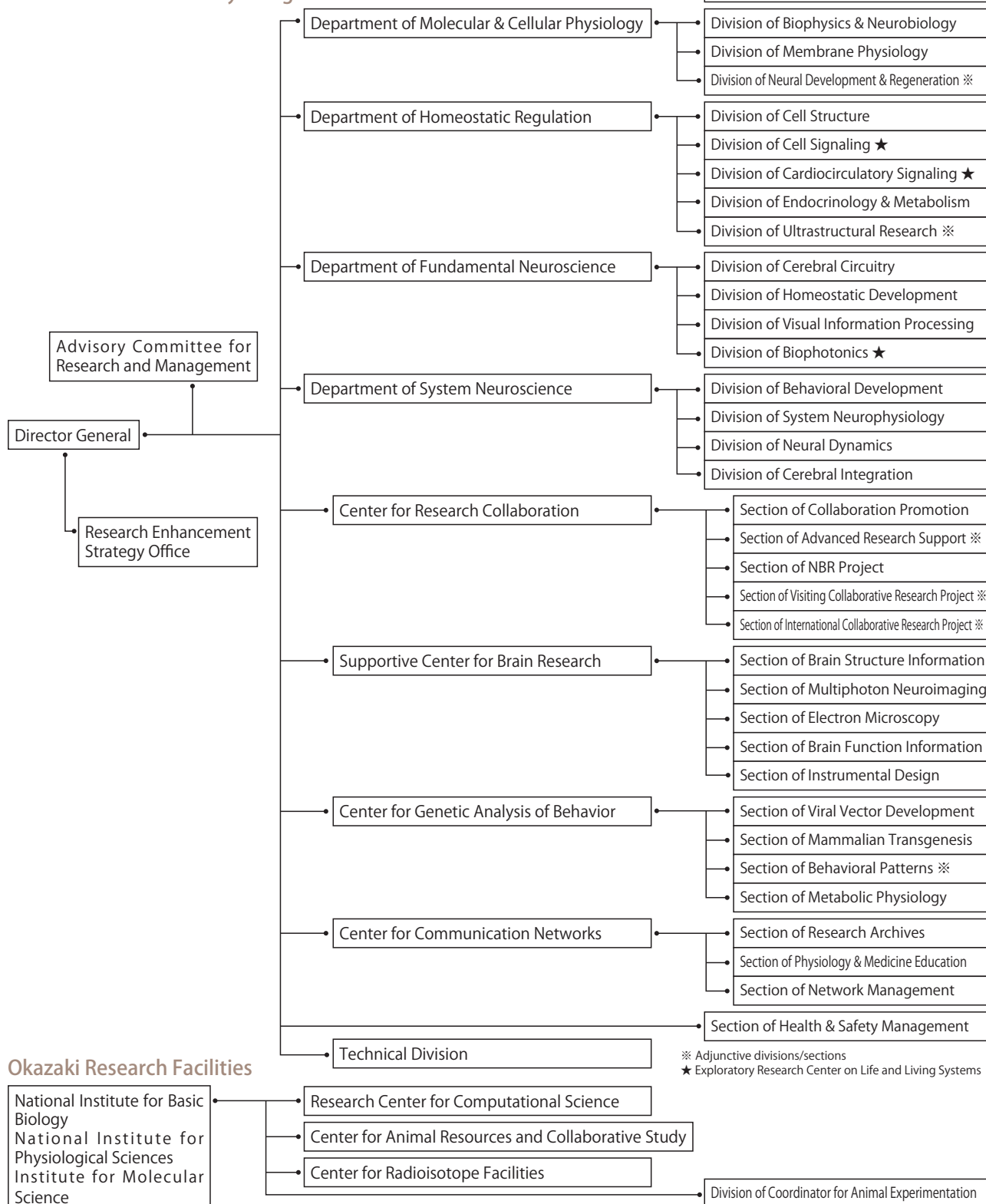
Asterisk (\*) denotes adjunct division.

# Organization of the Institute

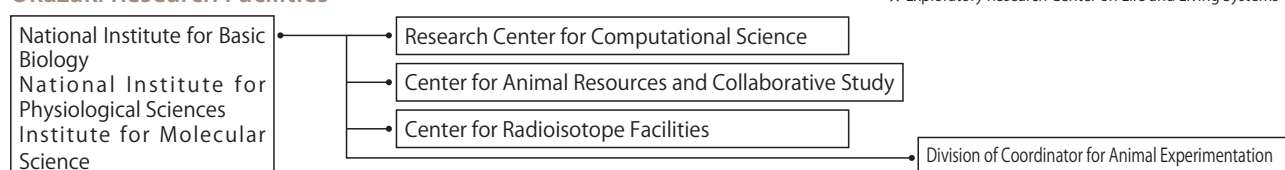
## National Institutes of Natural Sciences



## National Institute for Physiological Sciences



## 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)		UETA, Youichi	Professor, School of Medicine, Department of Physiology, University of Occupational and Environmental Health, Japan
AKAHANE, Satomi	Professor, Graduate School of Medicine, Toho University		
FUJIYAMA, Fumino	Professor, Faculty of Medicine, Hokkaido University		
HIDA, Hideki	Professor, Graduate School of Medical Sciences, Nagoya City University	YUZAKI, Michisuke	Professor, School of Medicine, Department of Physiology, Keio University
○MIYATA, Takaki	Professor, Department of Anatomy and Cell Biology, Nagoya University Graduate School of Medicine	(Inside)	
		◎FUKATA, Masaki	Professor, NIPS
NAKABEPPU, Yusaku	Professor, Medical Institute of Bioregulation, Kyushu University	FURUSE, Mikio	Professor, NIPS
		ISODA, Masaki	Professor, NIPS
NAWA, Hiroyuki	Professor, Brain Research Institute, Niigata University	KAWAGUCHI, Yasuo	Professor, NIPS
		KUBO, Yoshihiro	Professor, NIPS
ONO, Kyoichi	Professor, Graduate School of Medicine and Faculty of Medicine, Akita University	MINOKOSHI, Yasuhiko	Professor, NIPS
		NAMBU, Atsushi	Professor, NIPS
TAKADA, Masahiko	Professor, Systems Neuroscience, Primate Research Institute Kyoto University	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	NABEKURA, Junichi	Chief Researcher /Chairperson for Safety and Research Ethics Problems	TOMINAGA, Makoto
Vice Director General	NAMBU, Atsushi		
Chief Chairperson	KUBO, Yoshihiro	Chief Researcher / Chairperson for News and Public Affairs	FUKATA, Masaki
Chief Researcher / Chairperson for Cooperative Studies	SADATO, Norihiro	Chief Researcher / Chairperson for Educational Problem	FURUSE, Mikio
Chief Researcher / Chairperson for Animal Experiment Problem	MINOKOSHI, Yasuhiko	Chief Researcher / Chairperson for Special Project	YOSHIMURA, Yumiko

## Emeritus Professors

OOMURA, Yutaka	NAGAYAMA, Kuniaki
WATANABE, Akira	OKADA, Yasunobu
YAMAGISHI, Shunichi	OHMORI, Harunori
MORI, Shigemi	KOMATSU, Hidehiko
OBATA, Kunihiko	IMOTO, Keiji
KANEKO, Akimichi	KAKIGI, Ryusuke
MIZUNO, Noboru	KAWAGUCHI, Yasuo

## Deceased Emeritus Professors

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

## 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.

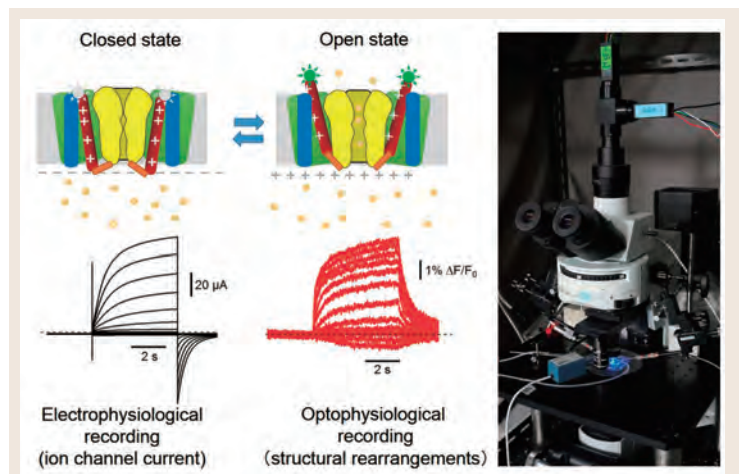
Our experiments start with constructions of mutants, molecular chimeras and fluorescent tagged molecules of ion channels and receptors. We express them in heterologous expression systems such as *Xenopus* oocytes or HEK293 cells. We then analyze the functional features and dynamic structural rearrangements by electrophysiological method such as two electrode voltage clamp and patch clamp. We also use optophysiological methods such as  $\text{Ca}^{2+}$  imaging, FRET analysis under total internal reflection microscope, subunit counting by single molecule imaging, and voltage clamp fluorometry using fluorescent unnatural amino acid.

Major target molecules are Two Pore  $\text{Na}^+$  channel (TPC), G protein coupled inward rectifier  $\text{K}^+$  channel (GIRK), hERG  $\text{K}^+$  channel, ATP receptor channel P2X<sub>2</sub>, Sigma-1 receptor and various G protein coupled receptors including an orphan receptor Prt3. We also work, as cooperative research projects, on TRPA1 channels, Kv1.2 channel, Two pore  $\text{K}^+$  channel, voltage-gated  $\text{Ca}^{2+}$  channels and iodide transporter and Opsin, as well as ion channel toxins.

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

- \* Shimomura T, Kubo Y (2019) J Gen Physiol. 151: 986-1006.
- \* Chen IS, Liu C, Tateyama M, Karbat I, Uesugi M, Reuveny E, Kubo Y (2019) Br J Pharmacol 176: 3161-3179.
- \* Kume S, Shimomura T, Tateyama M, Kubo Y (2018) J Physiol 596: 4629-4650.
- \* Tateyama M, Kubo Y (2018) PLoS One 13: e0204447.
- \* Kitazawa M, Kubo Y, Nakajo K (2015) J Biol Chem 290: 22724-22733.

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



# Division of Membrane Physiology

## 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 (AMPA) 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

\* Yamagata A, Miyazaki Y et al., Nat. Commun. 1546 (2018)  
 \* Yokoi N, Fukata Y et al., J. Neurosci. 36, 6431 (2016)  
 \* Yokoi N et al., Nat. Med. 21, 19 (2015)  
 \* Fukata Y et al., J. Cell Biol. 202, 145 (2013)  
 \* Fukata Y and Fukata M, Nat. Rev. Neurosci. 11, 161 (2010)

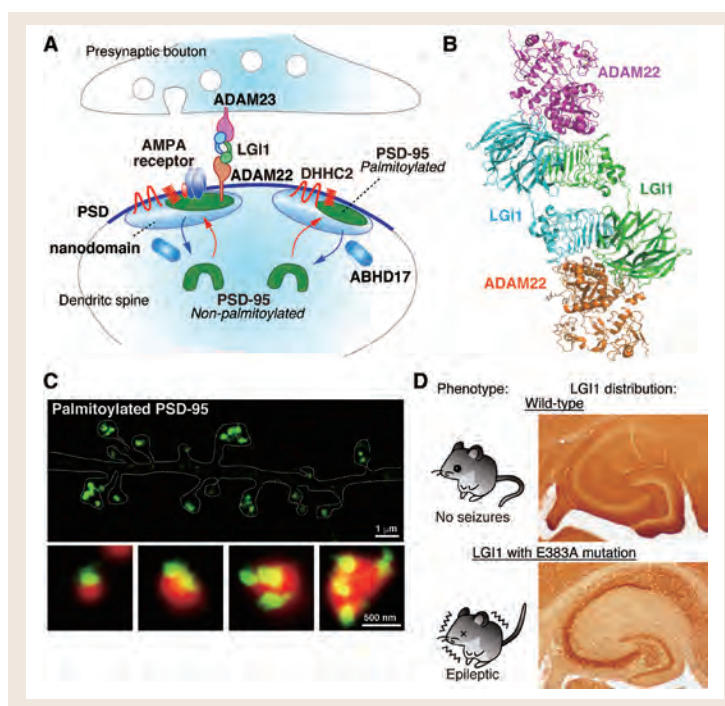


Figure (A) Unique AMPA receptor regulatory proteins: DHHC palmitoylating enzymes, ABHD17 depalmitoylating enzymes and the epilepsy-related ligand/receptor, LGI1 and ADAM22. (B) X-ray crystal structure of the LGI1-ADAM22 dimer-of-dimer complex. (C) Discovery of novel postsynaptic nanodomains by palmitoylated PSD-95-specific probe and super-resolution microscopy: a synaptic DHHC protein locally regulates the formation and reorganization of nanodomains. (D) Generation and analyses of mouse models of human epilepsy with the LGI1 mutation: Distribution of wild-type LGI1 and the E383A mutant protein. This LGI1 mutant protein is misfolded, retained in the ER and does not bind to its receptor, ADAM22.

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

MIYAZAKI, Yuri

Project Assistant Professor  
Neuroscience  
Biochemistry  
Bioinorganic Chemistry  
Structural Biology





# 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.

- \* N. Kaneko, et al., New neurons use Slit-Robo signaling to migrate through the glial meshwork and approach a lesion for functional regeneration. *Sci Adv* 4: eaav0618 (2018)
- \* K. Fujikake, et al., Detachment of chain-forming new neurons by Fyn-mediated control of cell-cell adhesion in the postnatal brain. *J Neurosci* 38: 4598-4609 (2018)
- \* 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)
- \* 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. Neuroblasts(red) migrate toward a lesion through a meshwork of processes from a single astrocyte(blue), as shown by serial block-face scanning electron microscopy (SBF-SEM) (Kaneko et al., *Sci.Adv* 2018).

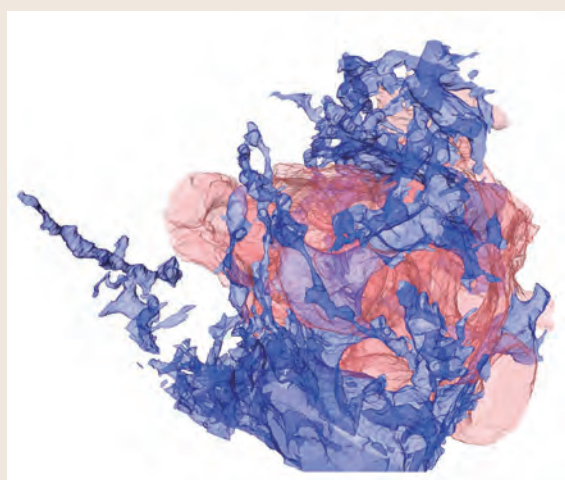
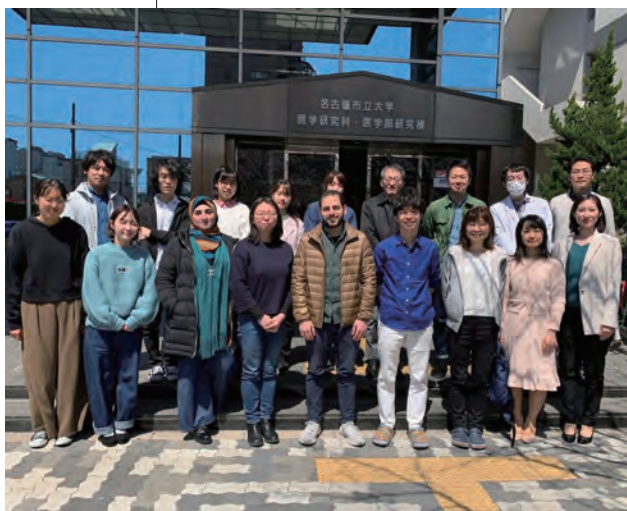
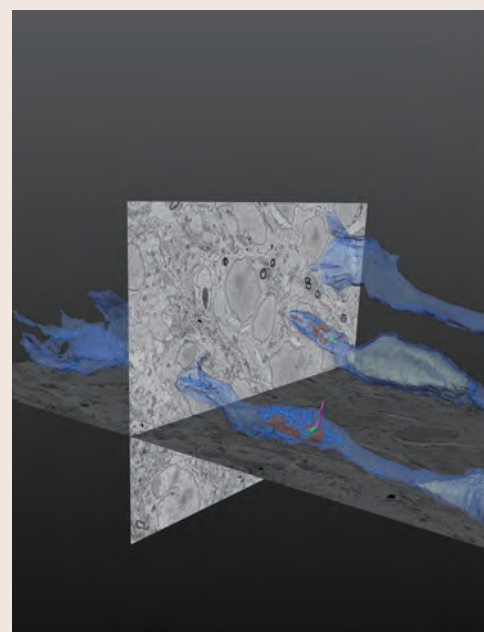


Fig.2. High-resolution three-dimensional images of migratory neuroblasts generated by serial block-face scanning electron microscopy. Each neuroblast possesses either a pair of centrioles (green), or a basal body (green) with a non-extended or extended primary cilium (pink). The localization and orientation of the primary cilium are altered depending on the mitotic state, saltatory migration, and deceleration of neuroblasts. Nucleus, Golgi apparatus, and mitochondria are shown in yellow, orange, and blue, respectively.

(Matsumoto et al., *J Neurosci* 2019).



# Division of Cell Structure

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

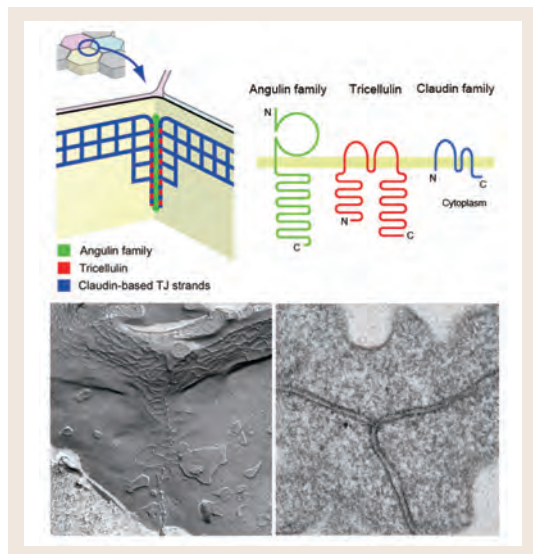
The Epithelium separates body compartments as a barrier and selectively transports various substances, thereby contributing to various functions of organs and homeostasis. Our laboratory aims to clarify the molecular bases of specialized cell structures that are responsible for these basic roles of the 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. The following are ongoing projects: 1) Molecular mechanism behind the diversity of the morphology and function of tight junctions. 2) Molecular dissection of tricellular tight junctions. 3) Physiological function of tight junctions and their related junctional structures in vivo utilizing genetically modified mice. 4) Roles of septate junctions in intestinal barrier function and regulation of stem cell proliferation in fruit fly.

\* Otani et al., J Cell Biol 218, 3372 (2019)  
\* Izumi et al., J Cell Sci 132(18). pii: jcs232108 (2019)  
\* Oda, Sugawara et al., J Biol Chem 295, 4289 (2020)

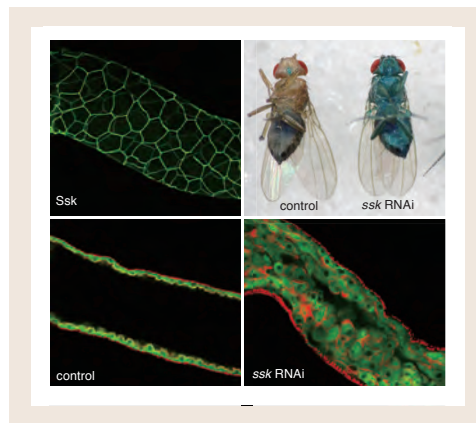
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Molecular architecture and morphology of tricellular tight junctions. Tricellular tight junctions (tTJs) are cell-cell junctions located at tricellular contacts, where the corners of three epithelial cells meet. tTJs contain two types of tTJ-specific membrane proteins, angulin family and tricellulin, and pull claudin-based tight junctions to the center of tricellular contacts.



Roles of smooth septate junctions in the *Drosophila* midgut. When the expression of a smooth septate junction-associated membrane protein Ssk is suppressed in the adult *Drosophila* gut, the intestinal barrier function is impaired, leading to the leakage of blue dye from the intestinal lumen to the body cavity with overproliferation of enterocytes.





# Division of Cell Signaling

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

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Molecular Evolution

**DEROUICHE, Sandra**  
Project Assistant Professor  
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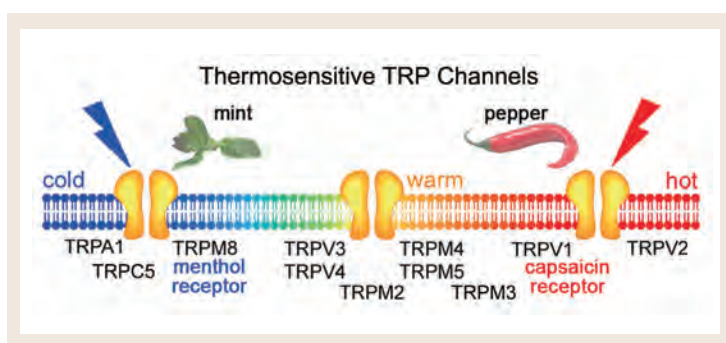
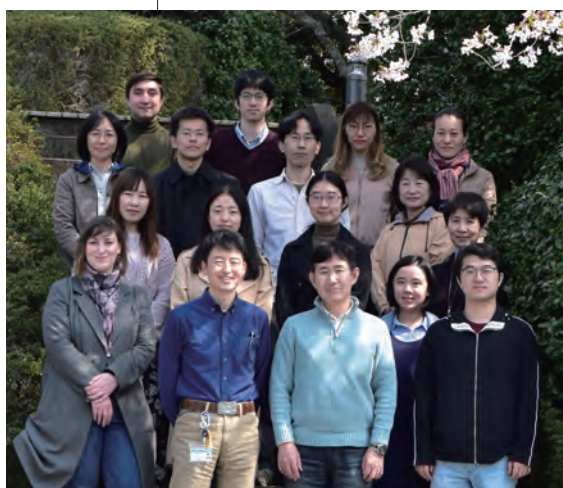
### Molecular Mechanisms of thermosensation and nociception

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 15°C and over 43°C 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. 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.

We are also investigating thermosensation in *Drosophila* (fruit flies) through behavioral analyses utilizing plenty of genetical tools. In addition, since TRP channels are nociceptors, we are developing novel insecticides/repellents that could be used to control insect pests.

- \* Elucidating the functional evolution of heat sensors among *Xenopus* species adapted to different thermal niches by ancestral sequence reconstruction. *Molec. Eco.* 28: 3561-3571, 2019.
- \* Diverse sensitivities of TRPA1 from different mosquito species to thermal and chemical stimuli. *Sci. Rep.* 9(1):20200, 2019.
- \* TRPV4 heats up ANO1-dependent exocrine gland fluid secretion. *FASEB J.* 32 (4): 1841-1854, 2018.
- \* The ATP transporter VNUT mediates induction of Dectin-1-triggered *Candida* nociception. *iScience* 6: 306-318, 2018.
- \* A Switch in Thermal Preference in *Drosophila* Larvae Depends on Multiple Rhodopsins. *Cell Rep.* 17(2), 336-344, 2016.

Eleven thermosensitive TRP channels



# Division of Cardiocirculatory Signaling

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

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

Our cardiocirculatory function is mainly controlled 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,  $\text{Ca}^{2+}$  imaging, FRET imaging, Confocal laser microscopy, Patch-clamp recording, Plate reader (BRET assay, post-translational modification analyses)

\* A. Nishimura et al. Science Signal. 12(587). pii: eaaw1920 (2019)  
 \* K. Nishiyama et al. Br J Pharmacol. 176(18):3723-3738 (2019)  
 \* T. Numaga-Tomita et al. FASEB J. 33(9):9785-9796 (2019)  
 \* A. Nishimura et al., Sci. Signal. 11, eaat5185 (2018)  
 \* T. Akaike et al., Nature Commun. 8(1):1177 (2017)  
 \* T. Shimauchi et al., JCI insight, 2(15). pii: 93358 (2017)

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TANAKA, Tomohiro  
 Project Assistant Professor  
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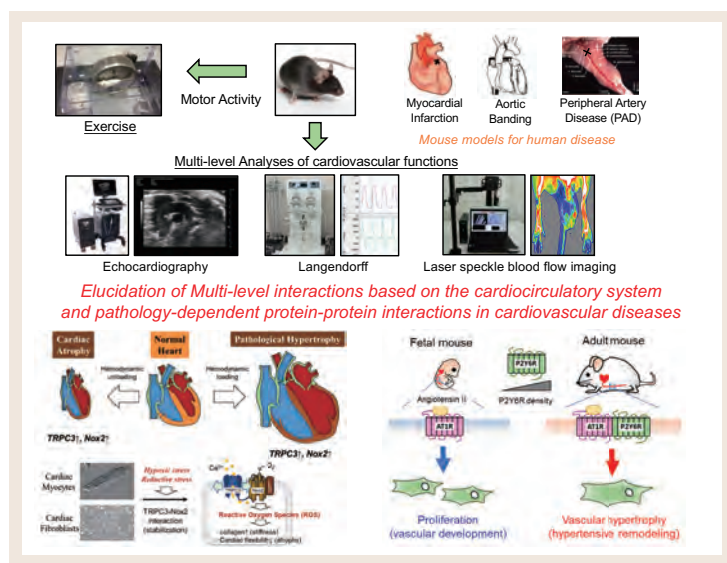


Figure. Measuring systems for cardiovascular functions and summary of our research using these systems



# Division of Endocrinology and Metabolism

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Molecular Biology  
Structural Life Sciences  
Endocrinology and Metabolism

## 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, glucose and lipid metabolism and taste sensations.
- (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.
- (5) Neuronal circuits that regulate hunger-induced taste modification.

\* 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.  
\* S. Okamoto, et al., Cell Reports 22, 706, 2018.  
\* O Fu, et al., Nat Commun 10, 4560, 2019.

Fig. 1 Discovery of neurons that induce selection of carbohydrate over fat.

AMP kinase-regulated CRH neurons in the PVH is necessary and sufficient to induce selection of carbohydrate over fat after fasting.

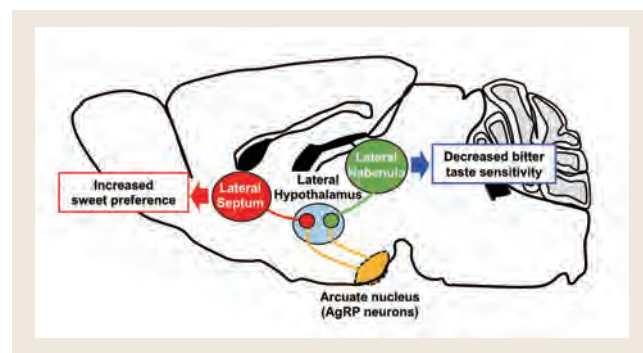
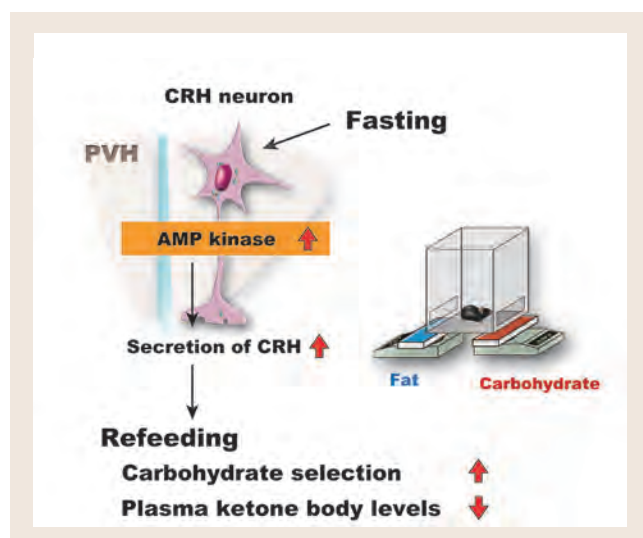
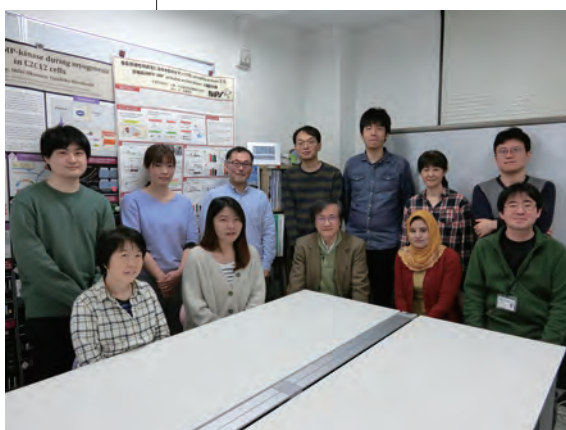


Fig. 2 Neuronal circuits that regulate hunger-induced taste modification. Hypothalamic AgRP neurons regulate appetitive and aversive taste preferences via two distinct neuronal pathways.





# Division of Ultrastructural Research

## Ultrastructural analyses with microscopic approaches including electron microscopic 3D reconstruction

### Regulatory mechanisms and roles of mitochondrial dynamics in myelin diseases

Our goal is to understand structural changes in biological phenomena including development, functional maintenance and pathophysiology of the nervous system, and elucidate their molecular mechanisms and roles. We utilize various imaging approaches including 3D ultrastructural analyses with serial block-face scanning electron microscopy (SBEM) and animal models, and also engage in development of new technologies and many collaborative projects.

We are interested in intercellular associations of the nervous system. Among them, we would like to clarify the structural and functional changes and their molecular background in myelination and myelin diseases. One of our focuses is on mitochondrial dynamics, which are involved in pathophysiology of various diseases. We are trying to clarify the association of mitochondria and myelin diseases, and develop approaches for their regulation.

- \* Life Sci Alliance. 2(4). pii: e201900308 (2019)
- \* Nguyen et al. Front Neural Circuits. 12:108 (2018)
- \* Katoh et al. Sci Rep. 7:4942 (2017)
- \* Morizawa et al. Nat Commun. 2017 8:28 (2017)
- \* Ohno et al. PNAS 111:9953-8 (2014)

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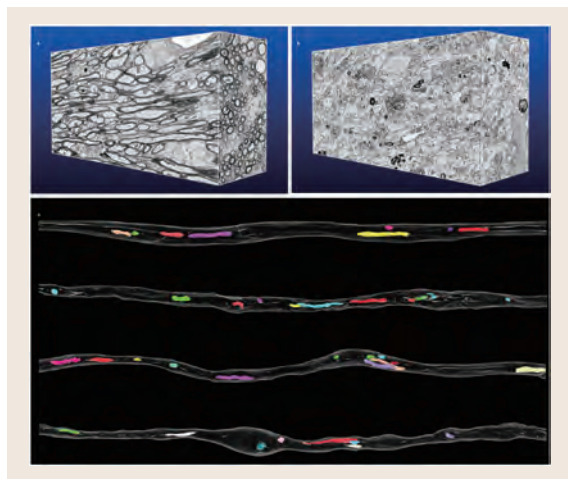


Figure 1. Reconstruction of serial electron microscopic images from corpus callosum of control (a) and demyelination model (b) mice, and 3D reconstruction of axonal mitochondria (c). Modified from Ohno et al. (2014).

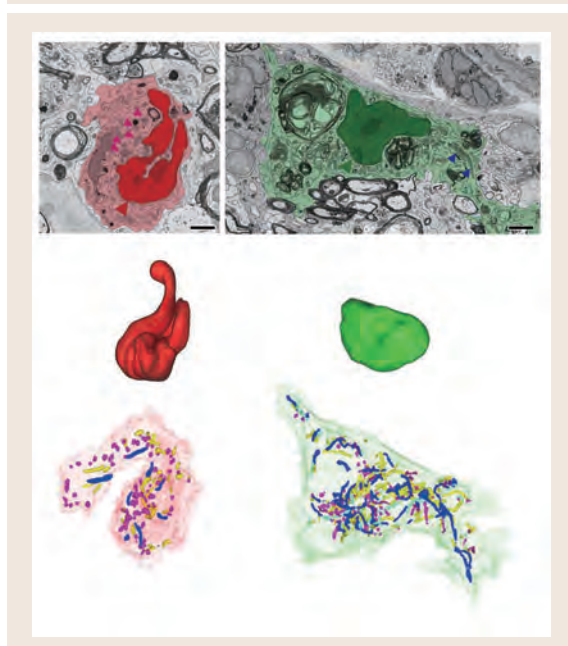


Figure 2. Colored electron microscopic images (upper row) and 3D reconstruction of nuclei (middle row) and mitochondria (lower row) of monocyte- (red) and microglia-derived (green) macrophages in a mouse spinal cord of a demyelination model. Modified from Katoh et al. (2017).



# Division of Homeostatic Development

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

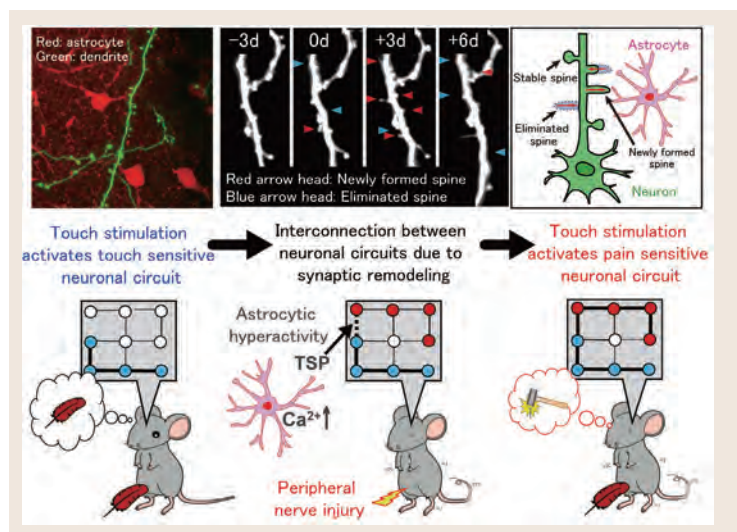
Remodeling of neuronal circuits takes place during development, learning and recovery after brain damage. The main goal of our research is to understand the regulation of neural circuits remodeling. In details, we are focusing on Glial contribution for the function of neuronal circuits. Glia has been known as a key factor to regulate neural circuits through their physiological function. We are trying to determine their contribution onto the neural circuits in development and learning by visualizing fine structure, controlling activity and analyzing function of neuron and glia in living animals using multi-photon microscopy.

### Innovative technology development across fields

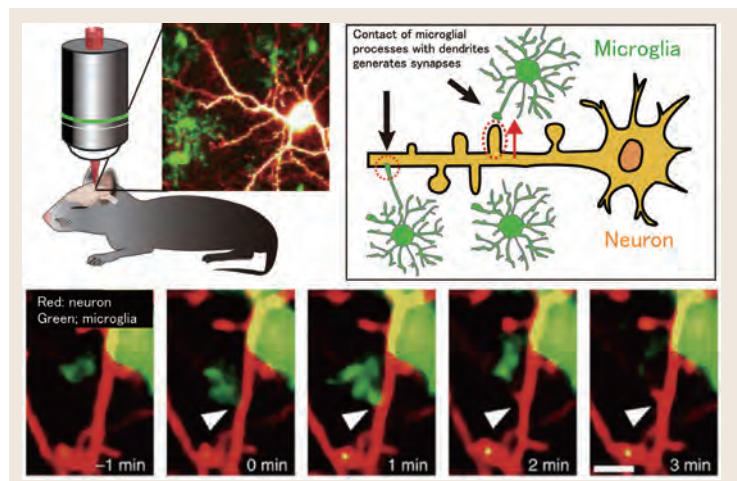
The progress of technology has brought about a breakthrough in life science. We contributed to novel technology development through collaborative research across fields. Recently, we revealed neural activity-dependent pH changes in the living brain with single-cell level resolution using a CMOS image sensor which we had newly developed.

- \* 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.
- \* CMOS-based bio-image sensor spatially resolves neural activity-dependent proton dynamics in the living brain. Horiuchi H, Agetsuma M, Ishida J, Nakamura Y, Cheung DL, Nanasaki S, Kimura Y, Iwata T, Takahashi K, Sawada K, Nabekura J. Nat Commun. 2020 Feb 5;11(1):712.

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



Facilitation of spine formation by microglial contact during development





# Division of Visual Information Processing

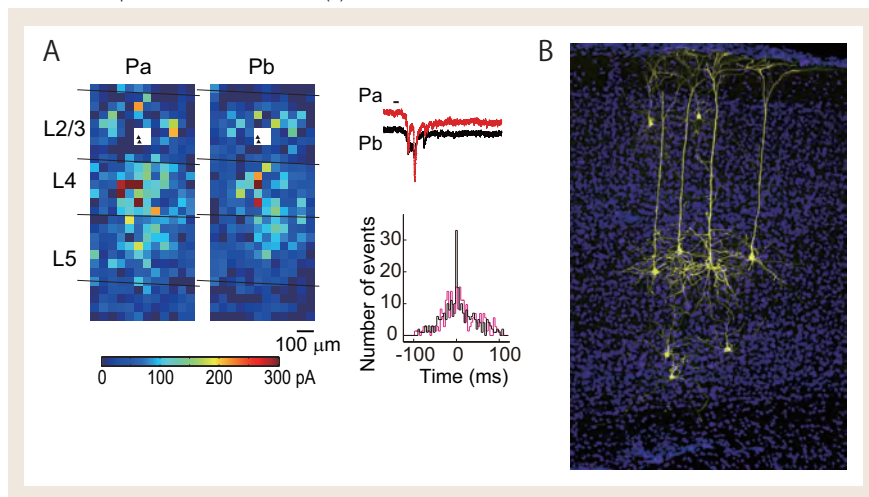
## Analysis of mechanisms underlying information processing and activity-dependent functional developments in neocortex

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 AW, Komatsu Y, Yoshimura Y (2018) Experience-Dependent Development of Feature-Selective Synchronization in the Primary Visual Cortex. *J Neurosci.* 38(36):7852-7869.

\* 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.



Electrophysiological 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.

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Biophysics

## Quantitative analysis and elucidation of underlying mechanism of physiological functions by innovative bioimaging utilizing cutting-edge technologies of photonics

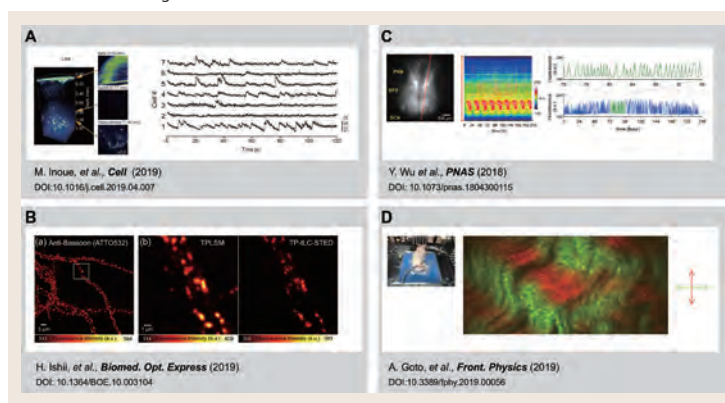
By utilizing such advanced optical technologies as near-infrared ultrashort light pulse lasers, adaptive optics, nanomaterials, we have advanced innovative imaging methods based on nonlinear optical processes. We also have driven applications of these methods to the life- and medical sciences. By facilitating our original world-leading ultra-deep, super-resolution, and ultra-high-speed imaging methods with a combination of genetic engineering and nanoparticles, we aim to realize less-invasive "*in vivo*" observation and manipulation for living organisms and tissues to establish a quantitative visualization analysis method for physiological functions. Through visualization analysis of neural circuits, activities, and exocytosis, we will elucidate the mechanism of the emergence of neural functions, including biological rhythms, and their molecular basis.

Recently, we successfully developed multiphoton microscopy to realize cross-sectional fluorescence imaging at the deepest layer in the world. As a result, we visualized neurons in the dentate gyrus of the hippocampus at 1.6 mm depth from the brain surface under anesthesia. Noticeably, we here observed the activity of hippocampal CA1 neurons at a video rate (Fig. A). On the other hand, in order to enable ultra-micromorphology for molecular dynamics in living cells, we are also pursuing super-resolution microscopy by utilizing new laser technology, including vector beams (Fig. B). Utilizing long-term imaging technology for living cell functions, we are promoting research on the generation and the function of ultradian and circadian rhythms (Fig. C). In local neural circuits, endocrine or exocrine glands, and model animals and plants, high-speed three-dimensional "*in vivo*" imaging is unlocking the principles underlying the emergence of physiological functions and is also exploring the molecular basis of the pathogenic mechanism of diseases such as cancer and diabetes (Fig. D).

In this research department, these methods collaborate widely with various laboratories covering not only life sciences but also applied physics, chemistry, medicine, and pharmaceutical sciences. Now, we are weaving a new tapestry of interdisciplinary areas applicable to medical science by pursuing cell physiology of neural and secretion activities and by advancing imaging methodology, which can visualize physiological phenomena *in vivo* "as they are." We are looking for graduate students or young researchers who can share our passion for pioneering new academic fields. We are looking for graduate students or young researchers who can share our passion for pioneering new academic fields.

- \* M. Inoue *et al.*, *Cell* 177,1346-1360.e24 (2019).
- \* H. Ishii *et al.*, *Biomed. Opt. Express*, 10, 3104-3113 (2019).
- \* Y. Wu *et al.*, *Proc. Natl. Acad. Sci. USA*, 115, E9469-E9478 (2018).
- \* A. Goto *et al.*, *Front. Phys.*, 7, 56-1-56-9 (2019).

Fig. (A) "*in vivo*" video-rate imaging of neural activities of mouse CA1 neurons. (B) Two-photon nanoscopy –breaking the limit of the spatial resolution < 100 nm. (C) Visualizing neuronal circuits controlling circadian and ultradian rhythms. (D) Fast "*in vivo*" imaging of molecular orientation using second harmonic generation.

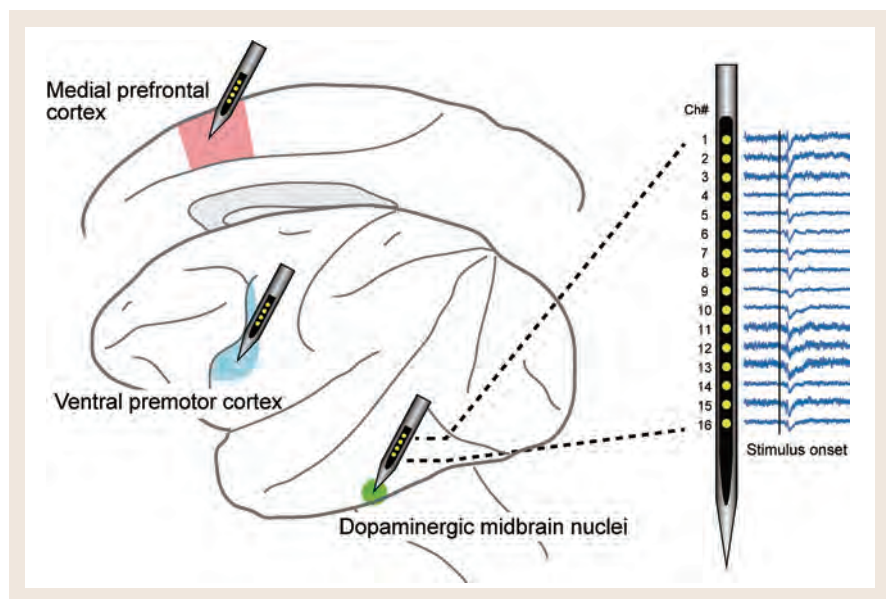


# Division of Behavioral Development

## System-level understanding of social cognitive functions

There is increasing attention to social neuroscience, a discipline dedicated to clarifying the neural basis of social cognitive functions. In social neuroscience, studies on human subjects are surely indispensable, as they can tell us about our social mind most directly. Yet research using nonhuman primates is of equal importance for understanding social brain functions at the cellular and network levels. Nonhuman primates are phylogenetically close to humans, they have brain structure similar to humans, and they offer unique opportunities to directly record or manipulate neural activity. Our laboratory develops novel, behavioral tasks using two monkeys facing each other and carries out electrophysiological recordings of single-neuron activities and local field potentials across networks of brain regions to achieve a system-level understanding of social cognition, such as decision making on the basis of behavioral information regarding the self and others. We also perform pathway-selective blockade of neural activity using viral vectors to establish a causal relationship between a target neural pathway and a particular social cognitive function. Furthermore, we perform cognitive genomics studies in macaques with loss-of-function mutations in genes associated with human psychiatric and neurodevelopmental disorders, thereby clarifying the genetic basis of social cognitive functions.

\* Noritake A et al (in press) Proc Natl Acad Sci USA  
\* Noritake A et al (2018) Nat Neurosci 21: 1452-1462  
\* Yoshida K et al (2016) Sci Adv 2: e1600558  
\* Yoshida K et al (2012) Nat Neurosci 15: 1307-1312  
\* Yoshida K et al (2011) Curr Biol 21: 249-253



Multi-site, multi-electrode neural recordings for clarifying the neural basis of social cognitive functions

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## Mechanism of voluntary movements

## Pathophysiology of movement disorders

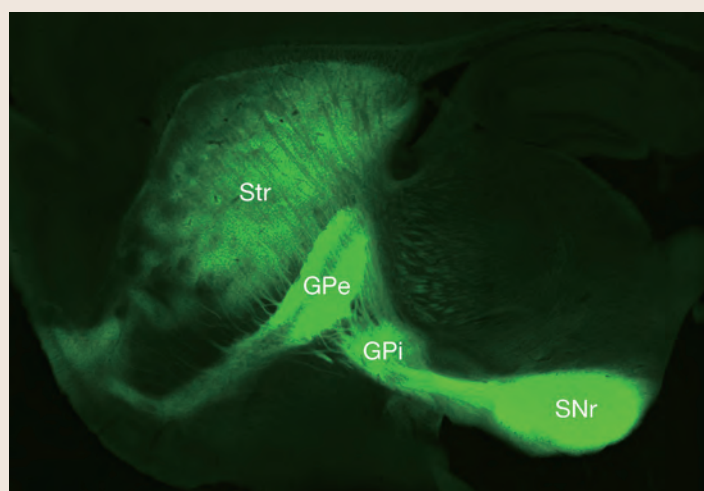
The brain areas, such as the cerebral cortex, basal ganglia and cerebellum, play a major role in controlling voluntary movements. On the other hand, malfunctions of these structures result in movement disorders, such as Parkinson's disease and dystonia. The major goal of our research project is to elucidate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

The current topics under study are as follows:

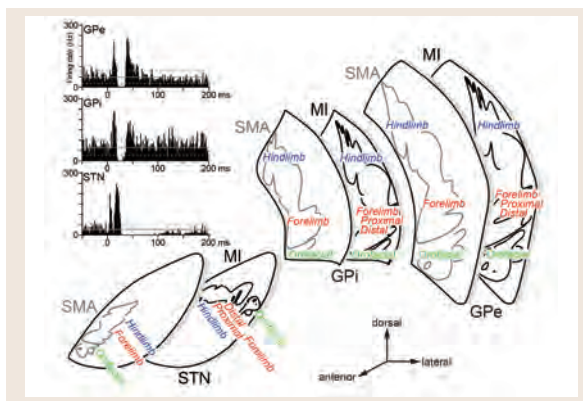
- 1) Elucidation of information flows through the neuronal networks by electrophysiological and anatomical methods.
- 2) Understanding the mechanism how the brain controls voluntary movements and higher brain functions by electrophysiological recordings of neuronal activity from animals performing motor 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 of Parkinson's disease and dystonia. Development of new therapies by suppressing abnormal neuronal activity.

\* S. Chiken et al., *Cereb Cortex* **25**: 4885-4897 (2015)  
\* H. Sano, H. Murata, A. Nambu, *J Neurochem* **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)  
\* H. Sano, A. Nambu, *Neurochem Int* **124**: (2019)

A sagittal section of the mouse brain showing selective expression of channelrhodopsin-2 (C128S) in striatal projection neurons as visualized by enhanced yellow fluorescent protein signals. Strong fluorescence was observed in the striatum (Str) as well as 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, hand and foot 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, such as deep brain stimulation (DBS), for Parkinson's disease.

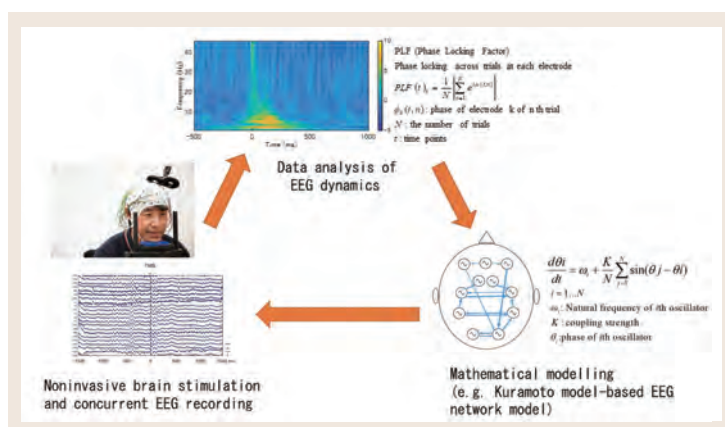


# Division of Neural Dynamics

## Understanding the functional roles of neural dynamics

The brain can be regarded as a dynamical system, which is composed of a number of connected nonlinear elements (e.g., neurons and glial cells) and exhibits a wide variety of nonlinear dynamics in its activity. For instance, depending on the brain state, the human brain exhibits transient oscillations and synchrony at various frequency bands. We investigate functional roles of nonlinear neural dynamics such as oscillation, synchrony, and noise-induced phenomena in perception, cognition, motor, and social functions from a computational neuroscience perspective. We measure and analyze scalp electroencephalographic (EEG) signals in humans while subjects are engaged in cognitive tasks, at rest, or during noninvasive brain stimulation such as transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). We also analyze electrocorticographic (ECoG), magnetoencephalographic (MEG), and functional magnetic resonance imaging (fMRI) data in humans as well as imaging and electrophysiological data in distinct modalities in animals. We promote computational studies by data analysis and mathematical modeling based on nonlinear dynamical systems theory, information theory, signal processing theory, complex network analysis, and statistical machine learning theory. We also analyze clinical data for stroke and epilepsy patients obtained from collaborators and try to understand clinical symptoms in terms of altered neural dynamics and explore brain-machine interface applications. Moreover, we try to investigate the relationships between neural dynamics and modulating factors such as autonomic nervous activity and excitation/inhibition balance in neural circuits to understand the functional roles of neural dynamics from an integrative perspective.

- \* Ueda K, Nishiura Y, Kitajo K (2020) Mathematical mechanism of state-dependent phase resetting properties of alpha rhythm in the human brain. *Neuroscience Research*, 4387, 1-13
- \* Okazaki YO, Mizuno Y, T. Kitajo K (2020) Probing dynamical cortical gating of attention with concurrent TMS-EEG. *Scientific Reports*, 10, 4959, 1-10.
- \* Glim S, Okazaki Y, Nakagawa Y, Mizuno Y, Hanakawa T, Kitajo K (2019) Phase-amplitude coupling of neural oscillations can be effectively probed with concurrent TMS-EEG. *Neural Plasticity*, 6263907, 1-14
- \* Kawano T et al. (2017) Large-scale phase synchrony reflects clinical status after stroke: An EEG study. *Neurorehabilitation & Neural Repair*, 31, 6, 561-570
- \* Kajihara T, Anwar MN, Kawasaki M, Mizuno Y, Nakazawa K, Kitajo K (2015) Neural dynamics in motor preparation: From phase-mediated global computation to amplitude-mediated local computation. *NeuroImage* 118, 445-455.



We measure neural activity in humans by the TMS-EEG concurrent recording paradigm. Then we analyze the EEG data and mathematically model the neural dynamics to understand the functional roles of the neural dynamics



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Professor  
Computational Neuroscience  
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**UEHARA, Kazumasa**  
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Project Assistant Professor  
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# Division of Cerebral Integration

**SADATO, Norihiro**  
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Functional Neuroimaging  
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**FUKUNAGA, Masaki**  
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Neuroimaging  
Neuroscience

**KOIKE, Takahiko**  
Assistant Professor  
Social Neuroscience  
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**GODA, Naokazu**  
Assistant Professor  
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Neuroimaging  
Psychophysics

**NAKAGAWA, Eri**  
Project Assistant Professor  
(Grant Project)  
Foreign Language Education  
Psycholinguistics

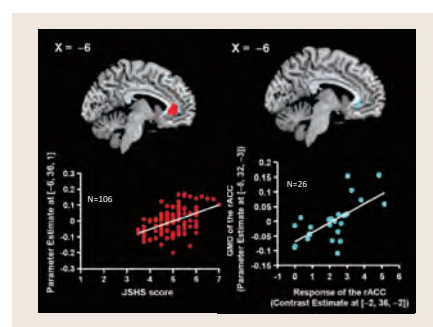
**YAMAMOTO, Tetuya**  
Project Assistant Professor  
(Grant Project)  
Neuroimaging  
Visual Neuroscience  
Visual Psychology

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

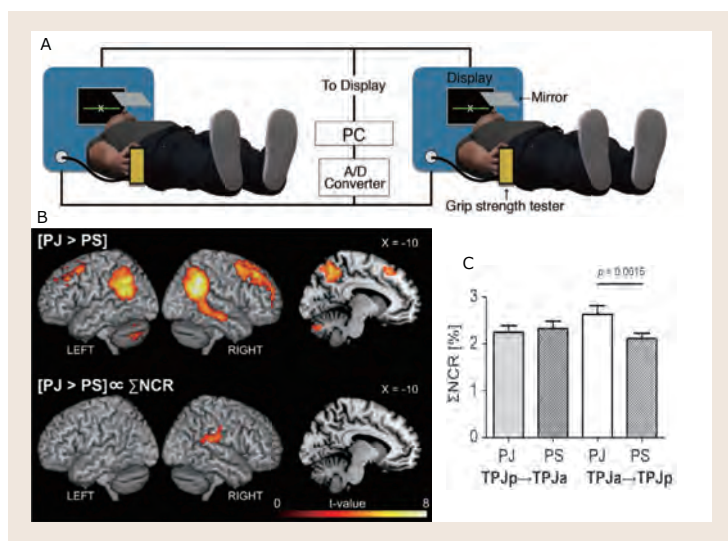
The goal of Division of Cerebral Integration is to understand the physiology of human voluntary movement and other mental processing including language and social interaction using noninvasive functional neuroimaging technique, mainly fMRI. In particular, neural mechanisms of the social interaction is 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.

\* Matsunaga M et al. Neuroimage 134:132-141 (2016)  
\* Abe MO et al. Neuroimage 191:150-161(2019)

Happiness has two aspects, a temporary positive emotion and a trait-like long-term sense of being happy, that enforces each other. Voxel-based morphometry showed trait-like subjective happiness was positively correlated with the gray matter density of the rostral anterior cingulate cortex (rACC). Functional MRI demonstrated that experimentally induced temporal happy feelings were positively correlated with subjective happiness level and rACC activity. The rACC response to positive events was also positively correlated with its gray matter density. Thus the rACC is related to happiness. The interaction between structure and function in the rACC may explain the trait-state interaction in happiness.



To evaluate the neural substrates of cooperation, we conducted a hyperscanning functional MRI study with a joint force-production task. We found that the cooperation, the degree of adjustment of individual motor output depending on that of the partner, is mediated by the interconnected subdivisions of the right TPJ. (Collaboration with Associate Professor Masaki O. Abe et al.)



## Individual Researches

### The roles and mechanisms of membrane traffic

Not only does membrane traffic perform intracellular cargo logistics, but it also works as a dynamic integration system of cellular signaling in various physiological aspects including developmental regulation. We currently study the roles and the mechanisms of membrane traffic in developmental morphogenesis, the main theme being the mechanisms of planar cell polarity (PCP) formation. To this end, we are developing new methods. 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).

OHASHI, Masato

Assistant Professor  
Molecular Cell Biology  
Biochemistry  
Developmental Biology

## Individual Researches

### Neuronal information processing in the tripartite synapse

Tripartite (three-part) synapses are defined by physically and functionally interactive structures among pre- and post-synaptic elements, and their surrounding glial processes. Our laboratory focuses on the role of neurotransmitter transporters in the integration of neuronal information in the tripartite synapse. Collaborating with other research groups, we also analyze genetically modified animals to understand the pathophysiology of neurological disorders such as rapid-onset dystonia with Parkinsonism (RDP), alternating hemiplegia of childhood (AHC), and CAPOS syndrome. In addition to classical techniques including electrophysiology, immunohistochemistry, and pharmacology, we recently introduced photo-releasable caged compounds. The following are ongoing projects.

- (1) Molecular mechanisms underlying presynaptic modulation: topographical distance between voltage-gated Ca channels and exocytotic Ca sensors as a key determinant<sup>2,3</sup>
- (2) Intersynaptic neurotransmitter diffusion-mediated crosstalk among adjacent neurons: involvements of glial cells and glutamate transporters in its regulation<sup>1</sup>
- (3) Pathophysiology of neurological disorders originated in haploinsufficiency of the Na pump gene dosage<sup>4</sup>

\*1 S. Satake, S. Konishi, *Eur. J. Neurosci.* in press (2020).

\*2 S. Satake, T. Inoue, K. Imoto, *Cerebellum* 15, 201-207 (2016).

\*3 S. Satake, K. Imoto, *J. Neurosci.* 34, 1462-1474 (2014).

\*4 K. Ikeda, S. Satake et al., *J. Physiol.* 591, 3433-3449 (2013).

SATAKE, Shin'Ichiro

Assistant Professor  
Neurophysiology

# Individual Researches

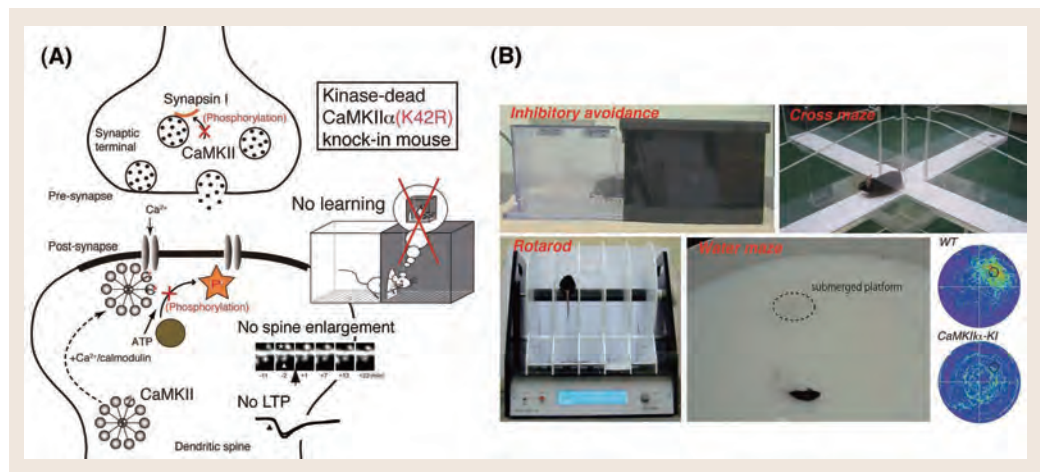
YAMAGATA, Yoko  
Assistant Professor  
Neurochemistry  
Neuroscience

## Brain functions and dysfunctions by protein phosphorylation

Studying molecular mechanisms of learning and memory is important to confront memory-deficient and abnormal memory-associated disorders such as post-traumatic stress disorder (PTSD). An enzyme called  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase II $\alpha$  (CaMKII $\alpha$ ) in the brain has a key role in such mechanisms. To explore its *in vivo* function more in detail and more explicitly, we generated the kinase-dead knock-in mouse of CaMKII $\alpha$ , and have been examining the mouse by using various methods in collaboration with other researchers. We are now exploring the relation between this kinase activity and age-related decline of cognitive functions by behavioral analyses of learning and memory.

- \* Yamagata, Y, et al. (2018) *eNeuro* 5: e0133-18.2018 1-15.
- \* Yamagata, Y, Nairn, AC (2015) *Brain Res.* 1625: 314-323
- \* Yamagata, Y, et al. (2013) *Brain Res.* 1507: 1-10
- \* Yamagata, Y, et al. (2009) *J. Neurosci.* 29: 7607-7618

(A) In the kinase-dead knock-in mouse of CaMKII $\alpha$ , hippocampal synaptic plasticity and hippocampus-dependent learning and memory are severely impaired. (B) We are performing behavioral analyses to explore possible relationship between this kinase activity and age-related decline of cognitive functions.



## Outline

KUBO, Yoshihiro  
Professor  
Director

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, 2017, 2018 and 2019, NIPS research meetings in universities outside of NIPS. In 2020, we plan to organize one international meeting 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. The 2nd 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. The 3rd activity is to support the activity, as an administration office of the core organization, of “Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS)” project, a large scale national project of the Japan Agency for Medical Research and Development (AMED).

(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 2020, 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 to 2019, Professor Denis Le Bihan (Former Director of Neurospin in France) served as a P.I., and he will continue to take the role from 2020.

In summary, the “Center for Collaborative Research” plays critical roles 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.

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## ▶ Section of Collaboration Promotion

NISHIO, Akiko

Project Assistant Professor  
Neurophysiology  
Cognitive Neuroscience

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 microscope (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.

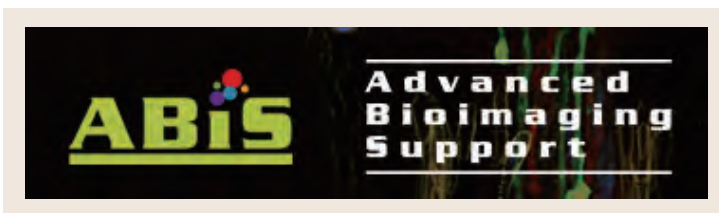
The primary purpose of us is to promote liaison between researchers in diverse fields and NIPS. It comprehensively performs activities to support joint research and enhance its recognition, such as setting up exhibition booths to introduce joint research in NIPS at meetings of related academic societies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



## ▶ Section of Advanced Research Support

### 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).



### Brain/MINDS Beyond

From November 2018, the National Institute for Physiological Sciences (NIPS) has been adopted as the core organization of the newly launched AMED program, the Strategic International Brain Science Research Promotion Program (Brain/MINDS Beyond). This program aims at contributing to the flight of the brain research globally by enhancing collaboration with the domestic projects of other countries across the world. This office, serving as the core organization and operation secretariat, coordinates the domestic efforts for the international promotion of brain science research. It also works in close coordination with two other programs by the AMED, the Strategic Research Program for Brain Sciences (SRPBS) and the Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS).



KANO, Masanobu  
Adjunct Professor  
Neurophysiology

TAKADA, Masahiko  
Adjunct Professor  
Neuroanatomy

MARUYAMA, Megumi  
Project Associate Professor  
Neurophysiology  
Environmental Physiology



## ▶ Section of NBR Project

NAMBU, Atsushi  
Professor  
Neurophysiology

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

#### The improvement of the monkeys quality, and development of the detection system for various pathogens

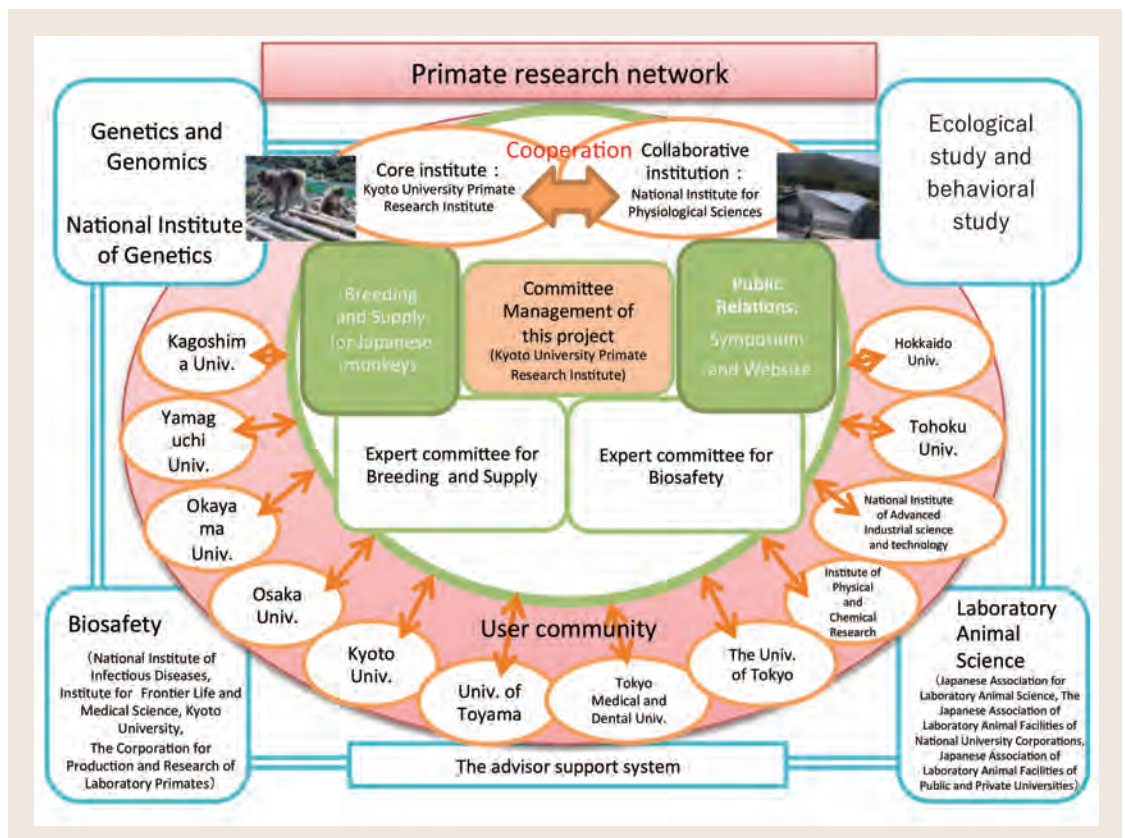
This laboratory has been organized since 2002, for acceleration of National Bio-Resource Project (NBRP) "Japanese monkey". National Institute for Physiological Sciences (NIPS) joined the collaborative institute for this project and Kyoto University Primate Research Institute (KUPRI) became the program as a core institute.

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".

The Japanese macaques have high cognitive abilities, and dexterous hands. Therefore, these macaques have been used for research of higher brain functions and various diseases.

We have administered this resource project and coordinated with researchers. We have collected the data about Japanese macaques for the improvement of monkey quality. 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.

\* 中村克樹, 他., ナショナルバイオリソースプロジェクト「ニホンザル」の現状と課題. 霊長類研究 33 巻 (2017)  
\* T. Isa et al., Japanese Macaques as laboratory Animals. Exp. Anim. 58 (5), 451-457 (2009)



### Introduction of the Section of International Collaborative Research Project

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. Two international projects with Seoul National University (South Korea) and National Health Research Institutes (Taipei) are ongoing together with Division of Cerebral Integration.

LE BIHAN, Denis  
Visiting Professor  
Neuroscience

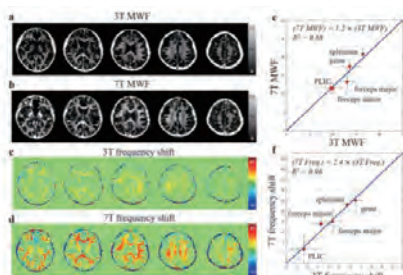
### 7T ultra high field MRI research of molecular brain imaging (Div. Cerebral Integration)



#### Development of 7T Myelin Water Imaging (MWI)

Dept. of Eng., Seoul National University

- Development and optimization of Myelin Water Imaging pulse sequence for 7T MRI
- Estimate and visualize three fractions of water signal in the white matter; axonal-, myelin-, extracellular space-water

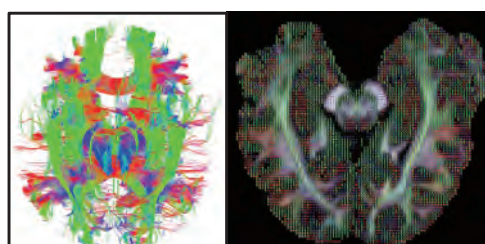


Shin et al. Neuroimage 188:835-844, 2019

#### Development of 7T Diffusion Spectrum Imaging (DSI)

National Health Research Institute, Taiwan

- Development and optimization of Diffusion Spectrum Imaging pulse sequence for 7T MRI
- Model free estimation of water molecular diffusion for structural network/connectivity analysis
- Microstructure analysis of living brain



T: tesla

# Supportive Center for Brain Research

ISODA, Masaki  
Professor  
Director

## Outline

The Center for Brain Experiment was reorganized into the Supportive Center for Brain Research in April 2008 to expand its role of supporting brain science research at the NIPS. The new center was initially comprised of six sections: Sections of Brain Structure Information, Brain Function Information, Multiphoton Neuroimaging, Electron Microscopy, Instrument Design, and Ine Marine Laboratory. In 2010, the Ine Marine Laboratory completed its mission and was closed. In 2012, two sections were newly opened: the Section of Viral Vector Development and the Section of Primate Model Development. The mission of the former was to develop and distribute viral vectors, and the mission of the latter was to breed and supply Japanese macaques, both to researchers for brain research purposes. In April 2016, the Section of Viral Vector Development was relocated to the Center for Genetic Analysis of Behavior. At the same time, the Section of Primate Model Development was changed its name to the NBR Project and relocated to the Center for Research Collaboration.

Brain science is one of the hottest research fields worldwide, of course including Japan, and recent progress in this field is amazing and surprisingly rapid. The NIPS is now widely recognized as an important hub for brain science research in Japan, and most NIPS researchers are engaged in some way in the relevant field. The mission of the Supportive Center for Brain Research is not only to support intramural studies at the NIPS, but also to play a role in promoting fruitful collaborations in the neuroscience community both in Japan and abroad through joint researches.

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### Ultrastructural analysis of cells by high-voltage electron microscopy

### High-resolution structural analysis of biomacromolecules by cryo-electron microscopy

We visualize the fine-structures of biomacromolecules and cells using electron microscopes to elucidate their functions from the structure. By employing advanced image analysis techniques such as single particle analysis and electron tomography, we reconstruct 3D structure from 2D EM images. 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 research (H-1250 M: 1 MV) (Fig. 1). Combined with the latest image processing technologies, these electron microscopes reveal the fine structure of cells and high-resolution structure of biomacromolecules such as large protein complex and viral particles. A recent example of our study is shown in Figure 2.

- \* Sheng et al., Nature Plant 5, 1320 (2019)
- \* Burton-Smith et al., JBC 294, 15003 (2019)
- \* Sekiguchi et al., Int J Mol Sci 20, 2308 (2019)
- \* Hirose et al., Mol Plant 12, 715 (2019)
- \* Yoshikawa et al., J. Virol 93, e02130 (2019)
- \* Kubota-Kawai et al., JBC 294, 4304 (2019)

MURATA, Kazuyoshi  
Associate Professor  
Electron Microscopy



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

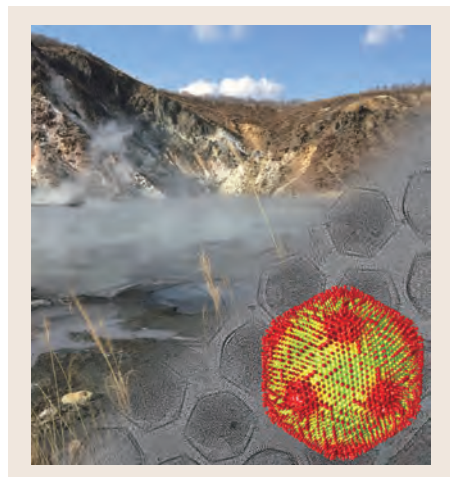


Fig. 2 Medusavirus visualized by cryo-electron microscopy. Medusavirus discovered at a hot spring in Japan (background picture) is evolutionary the closest virus to eukaryotes. (Yoshikawa et al. 2019).



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

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

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

\* Murakoshi et al. Scientific Reports 2019  
\* Saneyoshi et al. Neuron 2019  
\* Chen Xi et al. eLife 2018  
\* Murakoshi et al. Neuron 2017  
\* Hedrick et al. Nature 2016

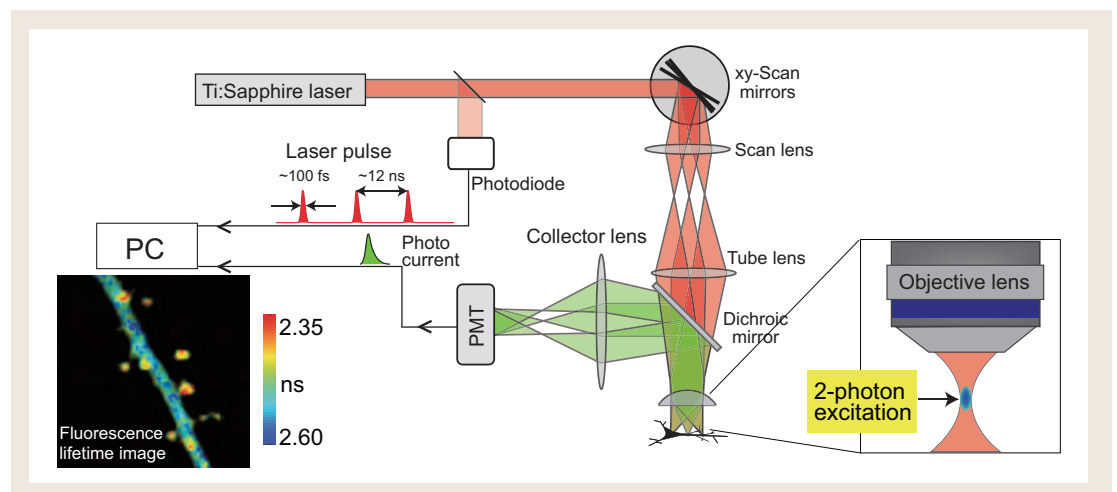


Figure 1. Two-photon excitation is the phenomenon that two photons of half energy than needed for one photon excitation can excite a fluorescent molecule. The advantages of 2-photon excitation are 1) Because infrared light is used for excitation, it minimizes excitation-light scattering in the tissue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

### Support for electron microscopy

Ultrastructures of tissues, cells and macromolecules are observed using transmission or scanning electron microscopes (JEOL JEM1010, Zeiss  $\Sigma$  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  $\Sigma$  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.

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



Fig. 1 Serial block-face SEM (SBF-SEM) Gatan 3view - Zeiss  $\Sigma$  IGMA/VP



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

## ► Section of Brain Function Information

SADATO, Norihiro  
Professor  
Functional Neuroimaging  
Neuroscience

CHIKAZOE, Junichi  
Associate Professor  
Neuroscience

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

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.

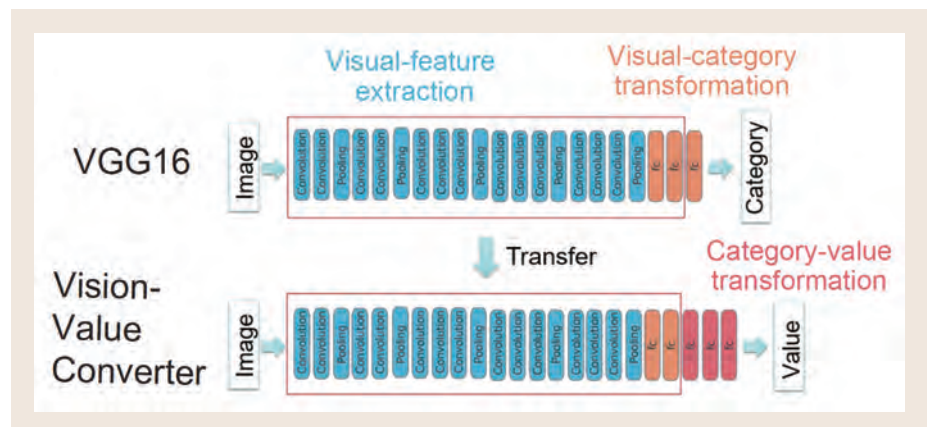
\* J. Chikazoe and S. Konishi, "Functional neuroimaging approaches to human memory",

\* Memory in Social Context: Brain, Mind, and Society, T. Tsukiura and S. Umeda Ed., Springer. (2018)

\* JA Brooks, J Chikazoe, N Sadato, JB Freeman, "The neural representation of facial-emotion categories reflects conceptual structure", Proceedings of the National Academy of Sciences 116 (32), 15861-15870 (2019)

\* J Chikazoe, DH Lee, N Kriegeskorte, AK Anderson, "Distinct representations of basic taste qualities in human gustatory cortex", Nature communications 10 (1), 1-8 (2019)

\* RM Todd, V Miskovic, J Chikazoe, AK Anderson, "Emotional Objectivity: Neural Representations of Emotions and Their Interaction with Cognition", Annual review of psychology 71, 25-48 (2020)



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

## Outline

TOMINAGA, Makoto  
Professor  
Director

Center for Genetic Analysis of Behavior 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/mouse, which are open for the collaborative use from researchers of all over the world.

- ▶ Section of Viral Vector Development 37
- ▶ Section of Mammalian Transgenesis 38
- ▶ Section of Metabolic Physiology 39



## ► Section of Viral Vector Development

NAMBU, Atsushi  
Professor  
Neurophysiology

KOBAYASHI, Kenta  
Associate Professor  
Molecular Neurobiology

Collaboration by providing viral vectors

Functional analysis of specific neural pathways by using viral vectors

Development of the viral vector system useful for analysis of brain functions

A viral vector, which is available to various animal models, is an excellent genetic tool, and at present, it becomes one of most important experimental technologies to analyze brain functions. We set up a system to produce a large amount of high quality viral vectors, AAV and lentiviral vectors. In response to requests, we provide these viral vectors and promote the collaboration.

Brain functions are controlled by complex neural circuits. To understand brain functions, it is necessary to clarify the function of specific neural pathways forming complex circuits. We have succeeded in developing the novel gene transfer system, a dual viral vector system using highly efficient retrograde gene transfer viral vectors, enabling the functional analysis of specific neural pathways (Fig. 1). By using this system, we analyze the function of specific neural pathways forming the cortico-basal ganglia loop. In addition, we work on the development of more efficient retrograde gene transfer viral vector system.

\* K. Kobayashi et al., J. Neural. Transm. (Vienna). 125, 67 (2018)

\* K. Kobayashi et al., Front. Neuroanat. 11, 65 (2017)

\* K. Kobayashi et al., Neurosci. Lett. 630, 45 (2016)

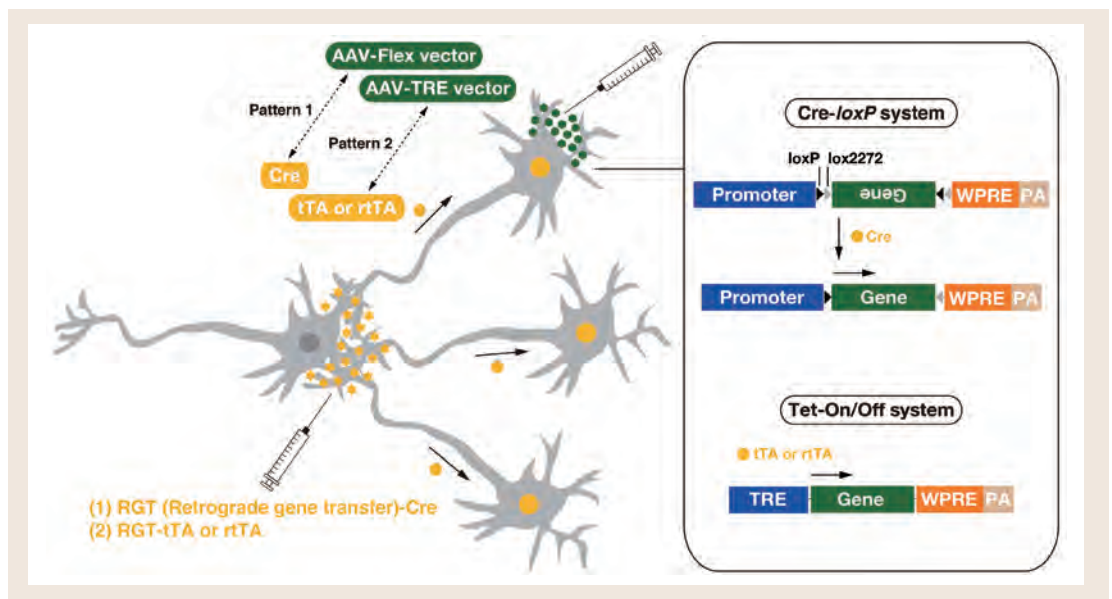


Figure 1. Gene transfer into specific neural pathways using viral vectors. Conditional gene expression in specific neural pathways becomes possible by using a dual viral vector system combining retrograde gene transfer (RGT) viral vectors and AAV vectors. These useful viral vectors are available to collaborators.

## ► Section of Mammalian Transgenesis

### 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.

- \* T. Kobayashi *et al.*, Development. 147, e183798 (2020).
- \* T. Goto *et al.*, Nat Commun. 10, 451 (2019).
- \* M. Hirabayashi and S. Hochi, Methods Mol Biol. 1874, 313 (2019).
- \* T. Yamaguchi *et al.*, Sci Rep. 8, 15289 (2018).
- \* M. Hirabayashi *et al.*, J Reprod Dev. 63, 611 (2017).

HIRABAYASHI, Masumi  
Associate Professor  
Laboratory Animal Science

KOBAYASHI, Toshihiro  
Assistant Professor  
Stem Cell Biology  
Developmental Technology

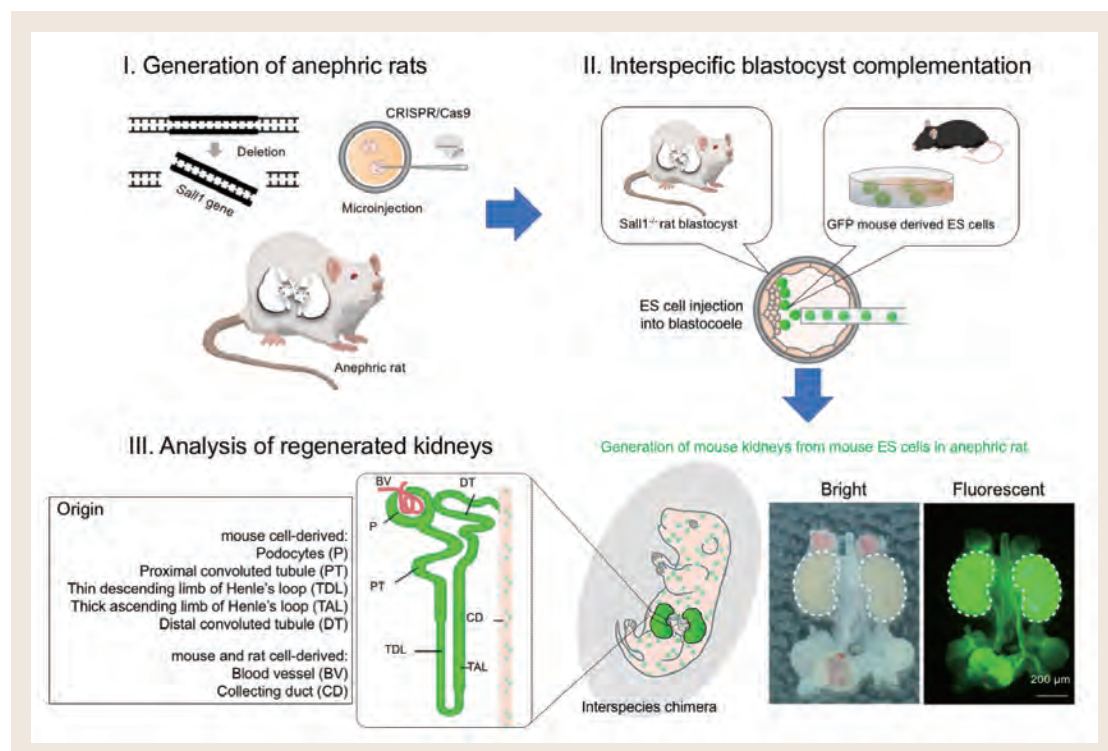


Fig. 1. Kidney regeneration model by interspecific blastocyst complementation. I . Genome editing tool (CRISPR/Cas9) is applied to prepare anephric rats. II . When GFP mouse-derived ES cells are injected into the rat blastocysts that have a fate to be anephric, 3D kidneys are regenerated in developmental niche of the interspecific chimeras. III . Histological analysis of the regenerated kidneys revealed that the most of nephron tissues consisted from GFP-positive mouse cells.

### 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:

- 1) Single unit recording from motor related brain regions in 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) Non-invasive echo-graphic imaging of tissue structure-function relationships (liver, kidney and blood vessels), 4-dimensional changes in cardiac functions, and capillary blood flow (brain and umbilical cord) using anesthetized mice.
- 6) Mouse temperature preference assay with thermal gradient ring.

# Center for Communication Networks

## Outline

FUKATA, Masaki  
Professor  
Director

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 41
- ▶ Section of Physiology and Medicine Education 42
- ▶ Section of Network Management 43



## ▶ Section of Research Archives

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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.

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

The material is presented in very small steps, approximately 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'

'step-by-step studies of brain science', another e-Learning subject, was developed for the Brain Science Course Group of The Graduate University for Advanced Studies, SOKENDAI with Dr. Yoshihisa Kudo (a professor emeritus of Tokyo University of Pharmacy and Life Science). And the part about neuroscience of the above 'step-by-step studies of human life sciences' was provided to the students who take 'step-by-step studies of brain science' as a supplement teaching aid. Students take the e-Learning-based exams in the end of each semester. Upon taking 'step-by-step studies of brain science', students are supposed to learn basic brain science completely.

TOMINAGA, Makoto

Professor  
Molecular and Cellular Physiology

## ► Section of Network Management

Computer services and network supports are now indispensable for research activity. In this section, we manage the “Computer System for Data Analysis in Physiology”, which is a software sharing system for Numeric Computation, data analysis, visualization, mathematics, statistics and electronic design. Three 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)

Ensuring information security is also an important part of our work. We have revised our information security policy in line with our research and are making efforts to maintain the security level by raising awareness among users. In addition, we also cooperate with CSIRT to prevent security incidents, take countermeasures, monitor them, and respond to them when and after they occur.

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



## Outline

TOMINAGA, Makoto

Professor  
Molecular and Cellular Physiology

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

**NAMBU, Atsushi**  
Professor  
Neurophysiology

**KUBO, Yoshihiro**  
Professor  
Biophysics  
Neurobiology

**FUKATA, Masaki**  
Professor  
Neuroscience  
Biochemistry  
Cell Biology

**MINOKOSHI, Yasuhiko**  
Professor  
Endocrinology and Metabolism

**YOSHIMURA, Yumiko**  
Professor  
Neurophysiology

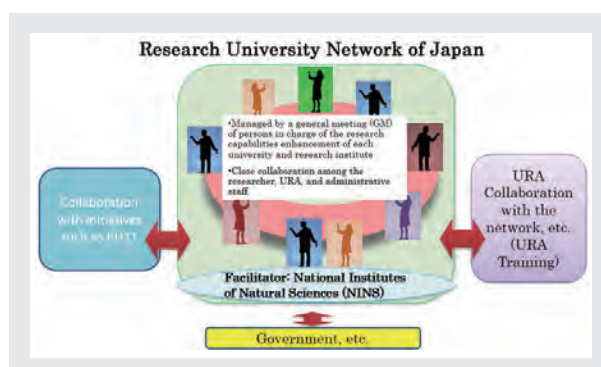
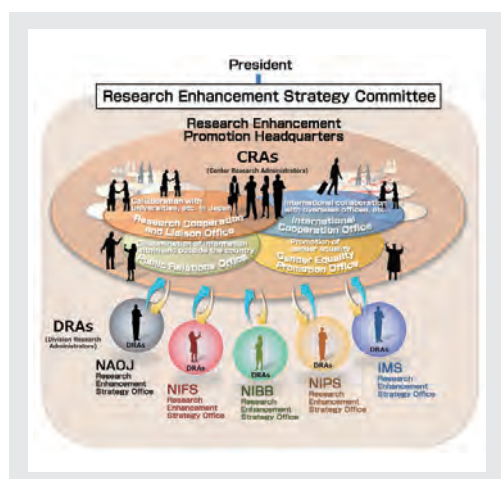
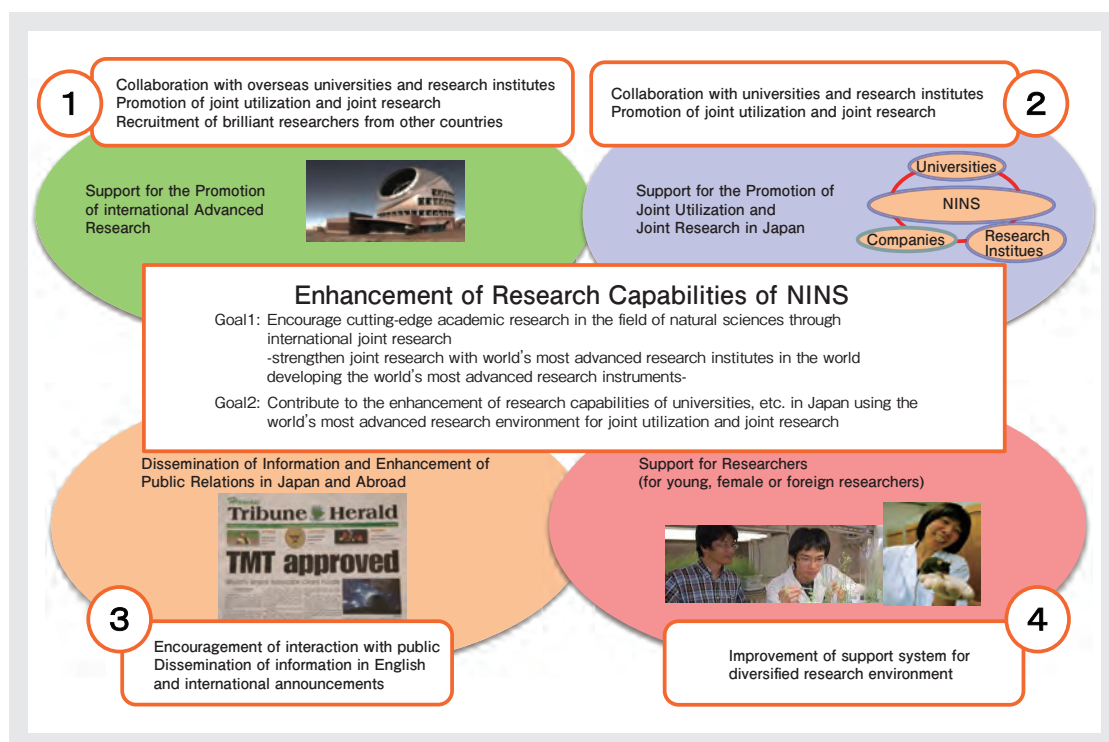
**URANO, Toru**  
Specially Appointed Professor  
Laboratory Animal Science  
Bacterial Infectious Disease

**MARUYAMA, Megumi**  
Project Associate Professor  
Neurophysiology  
Environmental Physiology

**NISHIO, Akiko**  
Project Assistant Professor  
Neurophysiology  
Cognitive Neuroscience

## 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. Research Enhancement Promotion Headquarters and Research Enhancement Strategy Office of this program have been settled at NINS and each of 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 Outreach Activity, 5) International Cooperation, and 6) Promotion of Gender Equality. Specially Appointed Professor, Project Associate and Assistant Professors were assigned to 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.



# Center for Animal Resources and Collaborative Study

The Center for Animal Resources and Collaborative Study is one of the top-class experimental animal centers in Japan. The center was reorganized from the Center for Experimental Animals in FY2019 to further enhance collaborative study based on animal research as a common facility of the interuniversity institutes. In the terrestrial and aquatic animal sections, multiple species including mouse, rat, marmoset, Japanese macaque, fish, and amphibians are maintained and supplied for experimentation.

To enhance and support collaborative animal researches involving domestic and foreign researchers, the principal responsibilities of the center include (1) the appropriate breeding of rodents and other experimental animals, (2) embryo transfer and cryopreservation for genetically modified mouse lines, (3) development and refinement of diagnostic testing methods, microbial containment, and disease prevention strategies, (4) provision of information related to the techniques of animal experimentation as well as promotion of education and awareness with regard to ethical considerations and regulations related to the study of experimental animals. The new building in "Myodaiji" area, which is equipped with the state-of-the-art system including individually ventilated cages rack and experimental rooms for collaboration studies, will be operational in October, 2020. We are capable of supplying high quality animal care and resources to researchers to reach the best research achievements in the world.

## Division of Coordinator for Animal Experimentation

The Division was established in 2008 under the Institutional Animal Care and Use Committee (IACUC) covered with 3 Institutes in 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. On the other hand, it is needed to clarify the social transparency, ethics and animal welfare in the animal experiments based on several rules including 'Law for the humane treatment and management of animals', 'Standard relating to the Care and Management of laboratory animals and relief of pain', 'Fundamental guideline for proper conduct of animal experiment and related activities in academic research institutions under the jurisdiction of MECSST' and domestic Standard. Accordingly, this Division is responsible for the following activities.

1. Education and training of the researchers
2. Review and approval of the animal experiment plans
3. Self-evaluation and self-assessment of animal experiments
4. Information disclosure regarding animal-based research

MINOKOSHI, Yasuhiko  
Professor (Director)

URANO, Toru  
Specially Appointed Professor  
Laboratory Animal Science  
Bacterial Infectious Disease

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

TOMINAGA, Makoto  
Professor  
Molecular and Cellular Physiology

Okazaki Institute for Integrative Bioscience ended in FY 2017.

A new research center “Exploratory Research Center on 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. 13)
- Cardiocirculatory Dynamism Research Group Division of Cardiocirculatory Signaling (See P. 14)
- Biophotonics Research Group Division of Biophotonics (See P. 19)
- Cognitive Genomics Research Group

## 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.



UEMATSU, Akiko  
Division of Behavioral  
Development  
**Neurophysiology**



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



DWI WAHYU, Indriani  
Division of System  
Neurophysiology  
**Neuroscience**



FU, Ou  
Division of Endocrinology and Metabolism  
**Neuroscience,  
Food Science**



SUI TO, Takuto  
Division of Cell Signaling  
**Molecular Biology  
Lipid Biochemistry**



YAMAMOTO, Mariko  
Division of Visual  
Information Processing  
**Neuroscience**



ANDRIANI, Rizki Tsari  
Division of Biophysics &  
Neurobiology  
**Pharmaceutical Science and  
Technology  
Biophysics**





# Technical Division

## Outline

The Technical Division is an organization of technical staffs to support research activities in National Institute 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 :  
MORI, Masahiro  
Research Infrastructure  
Technical Unit



Staff :  
HIRAYAMA, Yuya  
Homeostatic Regulation  
Technical Unit



Assistant Head :  
TOGAWA, Morio  
Departments Technical  
Section



Assistant Unit Chief :  
ISHIHARA, Hiromi  
Homeostatic Regulation  
Technical Unit



Staff :  
WATAKABE, Yuki  
Fundamental  
Neuroscience Technical  
Unit



Section Chief :  
YOSHIMURA, Nobuaki  
Research Centers  
Technical Section



Assistant Unit Chief :  
TAKAHASHI, Naoki  
System Neuroscience  
Technical Unit



Staff :  
INAGAKI, Mariko  
Center for  
Communication Networks  
Technical Unit



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



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



Staff :  
YAMANAKA, Midori  
Center for Experimental  
Animals Technical Unit



Unit Chief :  
FUKUTA, Naomi  
Homeostatic Regulation  
Technical Unit



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



Staff :  
TAKAHASHI, Nobuaki  
Center for Experimental  
Animals Technical Unit



Unit Chief :  
TAKAGI, Masahiro  
Fundamental  
Neuroscience Technical  
Unit



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



Unit Chief :  
SATO, Shigeki  
System Neuroscience  
Technical Unit



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



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



Assistant Unit Chief :  
KAMIYA, Emi  
Center for Experimental  
Animals Technical Unit



Unit Chief :  
YAMAGUCHI, Noboru  
Supportive Center for Brain  
Research Technical Unit



Staff :  
INAHASHI, Hiroki  
Molecular & Cellular  
Physiology Technical Unit



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



Staff :  
KANO, Yuichiro  
Homeostatic Regulation  
Technical Unit

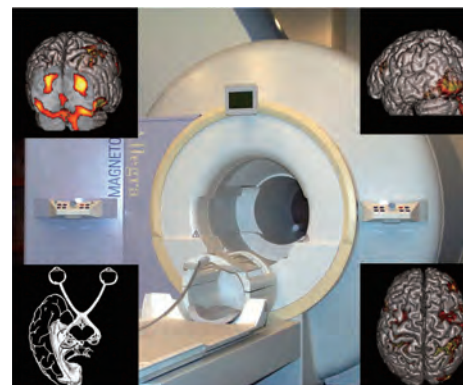
# Large facilities and equipments for cooperative studies

## 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.

## ► 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 (The first 3T machine installed in 2000 was shutdown in 2018). 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. As we have confirmed stable operation in 2018, 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.



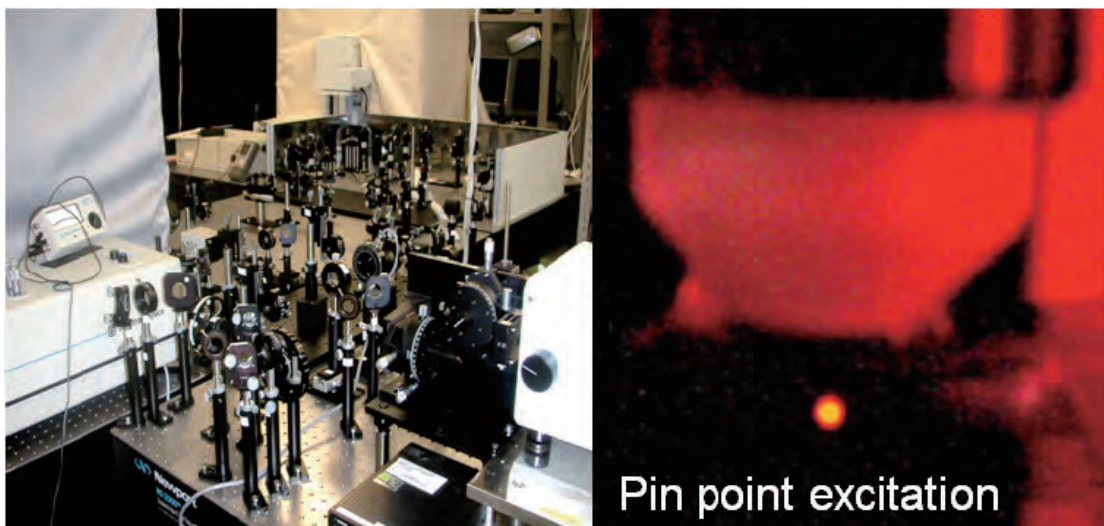


## ► Serial Block-Face Scanning Electron Microscope (SBF-SEM)

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 sliced 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 resolution of several nanometers.



## ► 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 has a superior deeper tissue penetration and reduced phototoxicity compared with single-photon excitation. Our 2-photon microscopes have the 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) Non-invasive echo-graphic imaging of tissue structure-function relationships (liver, kidney and blood vessels), 4-dimensional changes in cardiac functions, and capillary blood flow (brain and umbilical cord) using anesthetized mice, 6) Mouse temperature preference assay with thermal gradient ring.



# 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. 34

### ► 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. 3D-printer and a small laser cutting machine 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 70 different kinds of instruments. Our current focus is supporting functional genomics works that utilize mass spectrometers and DNA sequencers.

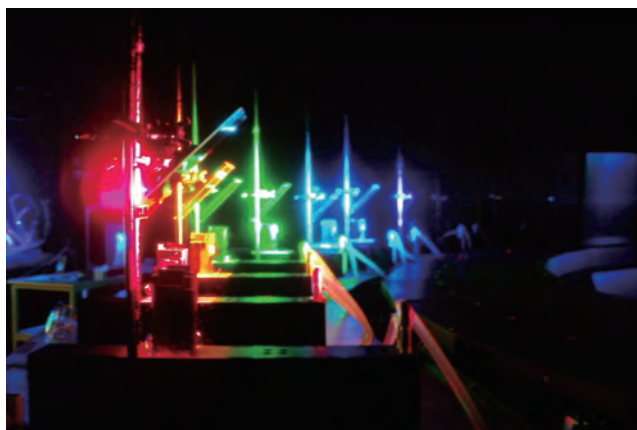
Next generation DNA sequencers (Functional Genomics Facility)



## ► 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 2020, the institute plans to carry out 118 cooperative research projects, and 38 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 meetings were held last year, and 20 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 are inviting overseas researchers, who present their work in English, have shown positive potential for the future of science. In 2019, two International Workshops was conducted, but one is now scheduled in 2020.

## 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 2019, 112 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 2019, we have created a total of 18 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) Non-invasive echo-graphic imaging of tissue structure-function relationships (liver, kidney and blood vessels), 4-dimensional changes in cardiac functions, and capillary blood flow (brain and umbilical cord) using anesthetized mice.
- 6) Mouse temperature preference assay with thermal gradient ring (only for mice).

Seven collaborative research projects with researchers outside NIPS were conducted in 2019, and eleven projects are now scheduled in 2020.

#### **"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 2019, 20 projects were carried out, and 20 are now scheduled in 2020.

#### **"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  $\text{Ca}^{2+}$  imaging, and long-term imaging of neurons in living mice.

In 2019, four planned collaborative projects were carried out, and two were scheduled in 2020. 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.” 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 2019, 16 research were performed, and 18 are now scheduled in 2020.

#### “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 2018 and 2019, one research in each was performed, and one is now scheduled in 2020.

#### “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 2019, we conducted 6 research projects, and 3 are now scheduled in 2020.

### 3. NIPS research meeting

In 2018, more than 1000 researchers took part in a total of 23 meetings. In 2019, 20 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, and in Nagoya and Tokyo in 2018, and one in Osaka in 2019. We now schedule NIPS International Workshop in Kyushu in 2020 (see 4. NIPS International Workshop).

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 SOC<sub>s</sub> --Unconventional Ca<sup>2+</sup> 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 and 2018, no International Workshops was conducted. In 2019, two workshops were held. In 2020, one workshop is scheduled in Kyushu as mentioned (see 3. NIPS research meeting).

#### 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 2018, five projects were carried out, and seven in 2019. In January 15, 2019, the manufacturer (Hitachi) terminated the maintenance service of this 38-year-old equipment installed in 1981. For this reason, it was determined to terminate the cooperative study by high voltage electron microscopy in FY2020.

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

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 2019, 36 projects were carried out, and 38 are now scheduled in 2020.

Magnetic resonance imaging involves two research

themes, "non-destructive three-dimensional observation of living organisms" and "structure and energy state observation of organic activity, including brain activators." Currently, the institute has a 3 Tesla machine in 2000, which is twice as powerful as the standard 1.5 Tesla machine, and has a considerable advantage when measuring cerebral blood flow in brain activator tests. Another characteristic is that it is capable of running primate brain activation tests. On top of this, it systematically processes all experimental designs, image data, and statistical image analysis, making it more than just a high-resolution image machine, but something that produces high-quality data that researchers need. In 2010, the two machines were interlocked, becoming a dual system capable of analyzing brain function related to social communication. A new 7 Tesla magnetic resonance imaging machine for 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 were conducted in 2018. As we have confirmed stable operation, it is now 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 50<sup>th</sup> NIPS International Symposium

## The 50<sup>th</sup> NIPS International Symposium “MIRACLES in Cardiovascular Physiology”

The 50<sup>th</sup> NIPS International Symposium “MIRACLES in Cardiovascular Physiology” was held at Okazaki Conference Center from December 5th to 7th, 2019. Professor Motohiro Nishida organized the symposium and also served as Secretary-General. Eight oversea and 18 domestic speakers gave presentations, and there were also 40 poster presentations. The number of participants were as many as 100.

This symposium values the concept of ‘developing new ideas by studying the past’, and both established and rising-sun investigators promoting cutting-edge researches in Metabolism, Interaction, Regulation, Application, Chemical biology, Longevity, Exercise, and Signaling got together to share the respective central questions and actively discuss how to develop an organic Miracle collaboration to solve them.

All lectures highly attracted the attention of audience. Professor Rui Ping Xiao, a top runner of cardiovascular research in China, presented her recent finding on the isoform-specific role of CaMKII in cardiac apoptosis. Professor David Carling presented their new finding on the role of AMPK in vivo revealed by the analyses using AMPK isoform-specific deficient mice. Dr. Ippei Shimizu presented the new finding that Senometabolite promotes pathologies in cardiovascular disorders. Dr Wataru Kimura (Riken) presented the relationship between oxidative metabolism and cardiomyocyte cell cycle regulation. Active discussion and fruitful exchange of research information were done both in oral sessions (both main and local symposiums) and in poster sessions.



## Program

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**December 5, 2019**

Local Symposium (*Chairs: Motohiro Nishida and Hyoungh Kyu Kim*)

**1. Tomohiro Tanaka** *Cardiocirculatory Signaling, NIPS*

Pathology-dependent protein-protein interactions (PPIs) as a new therapeutic target of heart failure

**2. Kazuhiro Nishiyama** *Kyushu University, Grad. Sch. Pharmaceu. Sci.*

Atypical GPCR signaling regulated by cysteine-based post-translational modification and its physiological significance

**3. Sandra Derouiche** *Cell Signaling, NIPS*

Involvement of thermosensitive TRP channels in temperature-dependent microglia movement

**4. Kenichiro Nakajima** *Endocrinology and Metabolism, NIPS*

Hypothalamic regulation of feeding-related behaviors

**5. I-Shan Chen** *Biophysics and Neurobiology, NIPS*

Regulatory mechanisms of GIRK channels by small molecules

**6. Cheung, Dennis Lawrence** *Homeostatic Development, NIPS*

Holographic light patterning for fine scale interrogation of cellular networks

**7. Hideji Murakoshi** *Biophysics Neuroscience, NIPS*

Spatiotemporal manipulation and imaging of signaling molecules in neurons

### Main Symposium

Opening Remark by Prof. **Junichi Nabekura** *Director General of NIPS*

**Session 1** (*Discussion Leaders: Motohiko Sato and Takeda*)

**1. Rui Ping-Xiao** *Institute of Molecular Medicine, Peking University*

Ca<sup>2+</sup>/calmodulin-dependent Kinase II and Cardiac Cell Death

**2. Jin Han** *College of Medicine, Cardiovasc. Metab. Disease Center, Inje University*

Molecular mechanism of exercise-induced cellular adaption

**3. Mitsuhiro Yamada** *Shinshu University School of Medicine*

A $\beta$  arrestin-bias AT1 receptor agonist improves the survival of neonatal knock-in mice bearing a human dilated cardiomyopathy mutation

**4. Satomi Adachi-Akahane** *Grad. Sch. of Med. and Facul. of Med., Toho University*

Ventricular diastolic dysfunction in the early stage of diabetic cardiomyopathy: involvement of insulin-mediated regulation of Ca<sup>2+</sup> signaling

**Session 2** (Discussion Leaders: Jin Han and Kazuho Sakamoto)

**5. David Carling** *MRC London Inst. of Med. Sci., Imperial College London*

Investigating the role of AMPK activation *in vivo*

**6. Yasuhiko Minokoshi** *Endocrinology and Metabolism, NIPS*

AMPK is the metabolic sensor that induces dietary preference for carbohydrate over fat

**7. Ippei Shimizu** *Niigata University Grad. Sch. of Med. and Dent. Sci.*

Senometabolite promotes pathologies in cardiovascular disorders

**8. Wataru Kimura** *RIKEN Center for Biosystems Dynamics Research*

Oxidative Metabolism and Cardiomyocyte Cell Cycle Regulation

**9. Ken Suzuki** *William Harvey Research Institute / Queen Mary University of London*

Myocardial repair, cardiac macrophages and mesenchymal stromal cell-based therapy

**December 6, 2019**

**Session 3** (Discussion Leaders: Woong Sun and Takuro Numaga-Tomita)

**1. Junko Kurokawa** *University of Shizuoka, Sch. of Pharmaceu. Sci.*

Multidisciplinary approaches for functional evaluation of human iPS-derived cardiomyocytes

**2. Yasunari Kanda** *National Institute of Health Sciences (NIHS)*

Development of *in vitro* cardiotoxicity assessment using human iPS cell technology

**3. Satoshi Matsuoka** *Faculty of Medical Sciences, University of Fukui*

Property and roles of mitochondrial  $\text{Na}^+\text{-Ca}^{2+}$  exchange in heart

**Session 4** (Discussion Leaders: Satomi Adachi-Akahane and Akiyuki Nishimura)

**4. Yoshihiro Ishikawa** *Yokohama City University School of Medicine*

Mechanical Stress and Vascular Regeneration

**5. Sang Geon Kim** *Seoul National University, College of Pharmacy*

$\text{G}_{12}/\text{G}_{13}$  regulation of systemic energy metabolism

**6. Hitoshi Kurose** *Graduate School of Pharmaceutical Sciences, Kyushu University*

$\text{G}_{12}$  family G protein-mediated signaling

**Session 5** (Discussion Leaders: Ippei Shimizu and Taichiro Tomida)

**7. Soojka Kim Chung** *Macao University of Science and Technology*

Global Proteomics of Skeletal Muscle and Validation Lead to Identification of PGC-1  $\alpha$  and Fatty Acid Metabolism Downstream to Exchange Protein Directly Activated by cAMP (Epac) for Forced Treadmill Exercise Capacity

**8. Utako Yokoyama** *Tokyo Medical University*

Prostaglandin E receptor EP4-mediated regulation of vascular elasticity

**9. Hisao Yamamura** *Grad. Sch. of Pharmaceu. Sci., Nagoya City University*

Pathophysiological significance of TRPC6 channels in pulmonary arterial hypertension

**Session 6** (*Discussion Leaders: David Carling and Kazuhiro Nishiyama*)

**10. Keiji Kuba** *Akita University Graduate School of Medicine*

mRNA deadenylation-mediated control of cardiac homeostasis

**11. Mariko Omatsu-Kanbe** *Shiga University of Medical Science*

Identification of ANP-marked cardiac progenitor cells in mouse heart that develop into beating cells

**12. Shigeki Kiyonaka** *Graduate School of Engineering, Nagoya University*

Coordination chemogenetics, a new technique for allosteric regulation of membrane receptors

Flash talk by poster presenters

**December 7, 2019**

**Session 7** (*Discussion Leader: Nobuhiko Ohno*)

**1: Akiyuki Nishimura** *Grad. Sch. of Pharmaceu. Sci., Kyushu University*

Pathology-dependent aberrant interaction between mitochondria and actin cytoskeleton causes cardiac fragility

**2: Woong Sun** *Korea University College of Medicine*

Mitochondrial quality surveillance by Drp1-dependent regulation of mitochondrial structure and function

**Session 8** (*Discussion Leaders: Yasunari Kanda and Nobuhiko Ohno*)

**3: Seiryō Sugiura** *UT-Heart Inc*

A Heart simulator coupling the molecular dynamics with the finite element model – Cross-scale integration of our knowledge on heart

**4: Hyoung Kyu Kim** *Cardiovascular and Metabolic Disease Center, Inje University*

Tetrahydrobiopterin rescues late-stage diabetic heart failure via restoring mitochondria function through CaMKK2/CREB/PGC1- $\alpha$  signaling

**5: Junken Aoki** *Graduate School of Pharmaceutical Sciences, Tohoku University*

Lysophospholipid Signaling Protects the Heart from Ischemic Damage by regulating the Vagal Nerve

**Closing Remark (by Motohiro Nishida)**



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)).

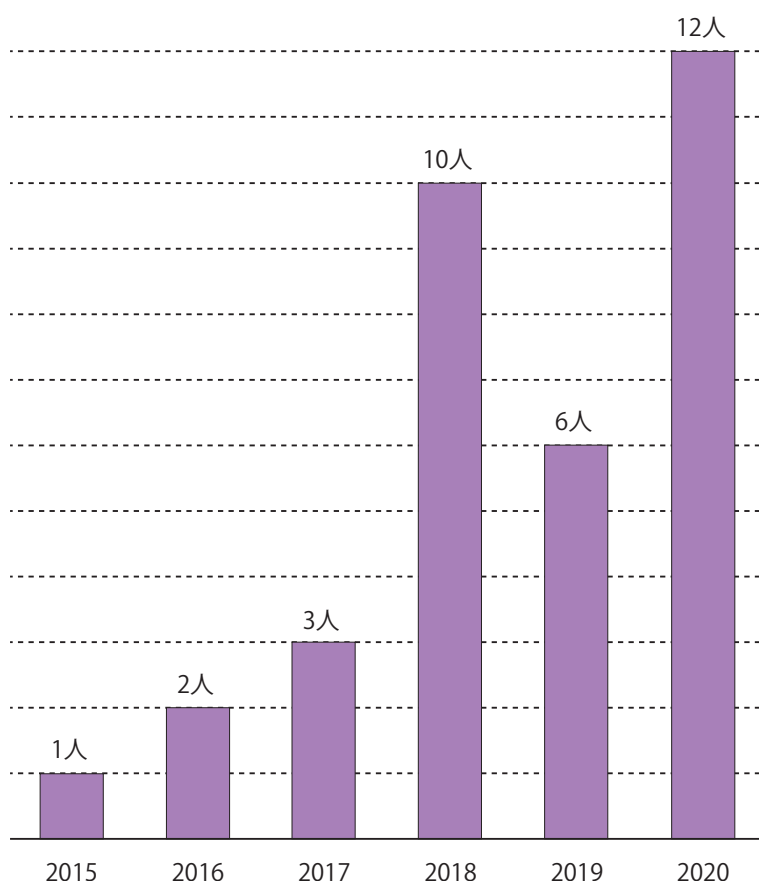
The outline of Department of Physiological Sciences.

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 2020



## International Exchanges

NIPS is an internationally recognized research institution and active international exchanges are performed. NIPS has the positions of foreign research staff, 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 FY2020, Professor Denis Le Bihan (a former Director of Neurospin, France) continues to run 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.

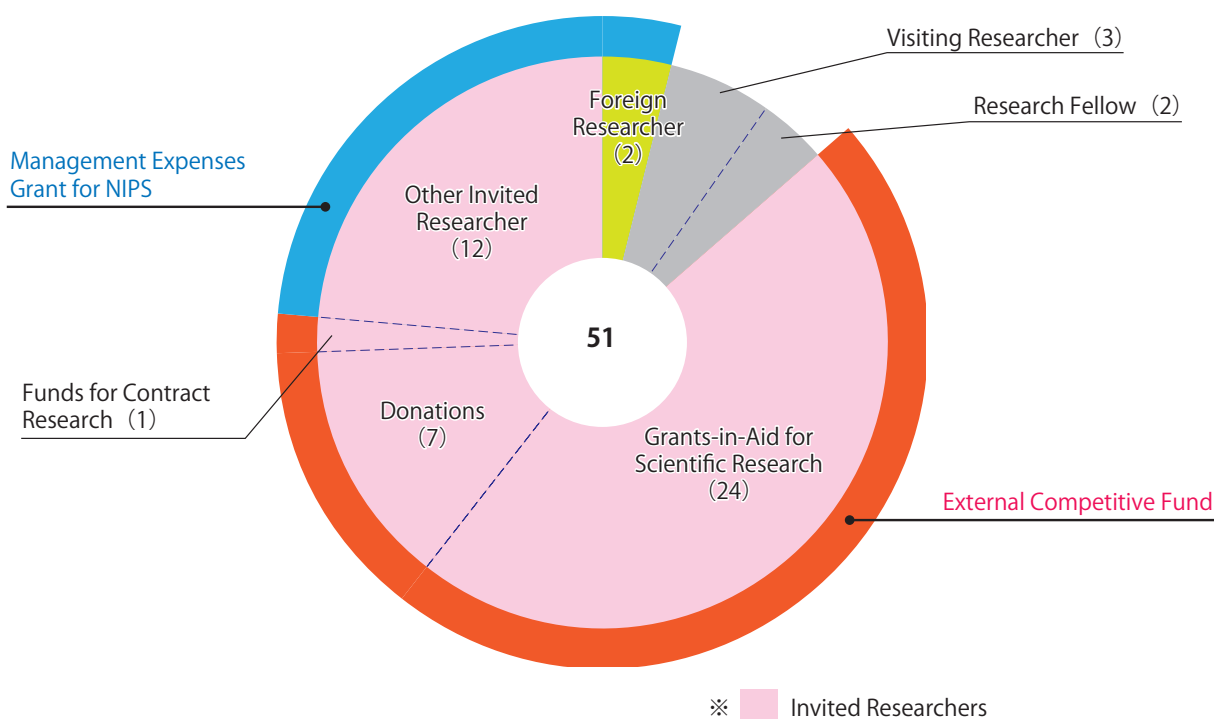
One of the main international exchange activities at NIPS is the annual international symposium. A NIPS professor serves as an organizer, and usually approximately 10 top researchers from abroad and a similar number of top domestic researchers are invited. The total number of participants ranges 100-150. In FY2019, the 50th NIPS International Symposium entitled "MIRACLES in Cardiovascular Physiology" was organized by Professor Motohiro Nishida. There were approximately 100 participants including 8 overseas speakers (total 26 speakers) and 40 poster presenters. In FY2020, the 51st NIPS International Symposium entitled "Intercellular Tight Junction (tentative)" will be held on Dec 9-11 (Organizer: Professor Mikio Furuse). In addition, the international workshop, which is an international version of NIPS research meetings, was

launched in FY2008 and a meeting outside of NIPS is scheduled in FY2020.

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 FY2019, a joint symposium with McGill University was held in McGill University, dispatching 8 NIPS researchers, and two students in McGill University stayed in NIPS for 5 weeks for collaborative research. A joint symposium with Korea University and Yonsei University was held in Korea University, dispatching 24 researchers including 8 graduate students. That with Chulalongkorn University was held in Chulalongkorn University, dispatching 8 NIPS researchers. A joint symposium with Tübingen University and Peking University was organized in NIPS, inviting 13 overseas speakers. In FY2020, a joint symposium with McGill University is planned to be held in NIPS, and that with Tübingen University will be held in Tübingen University.

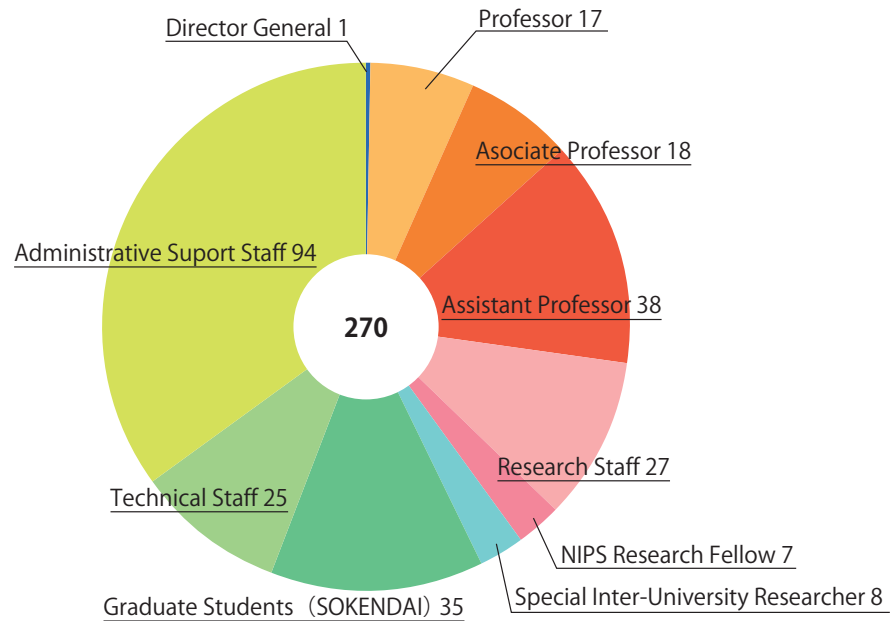
Besides these, many international research collaborations of high quality are performed at the individual researchers' level, supported by the budget of NIPS and also research grant from outside.

## Number of Foreign Researchers



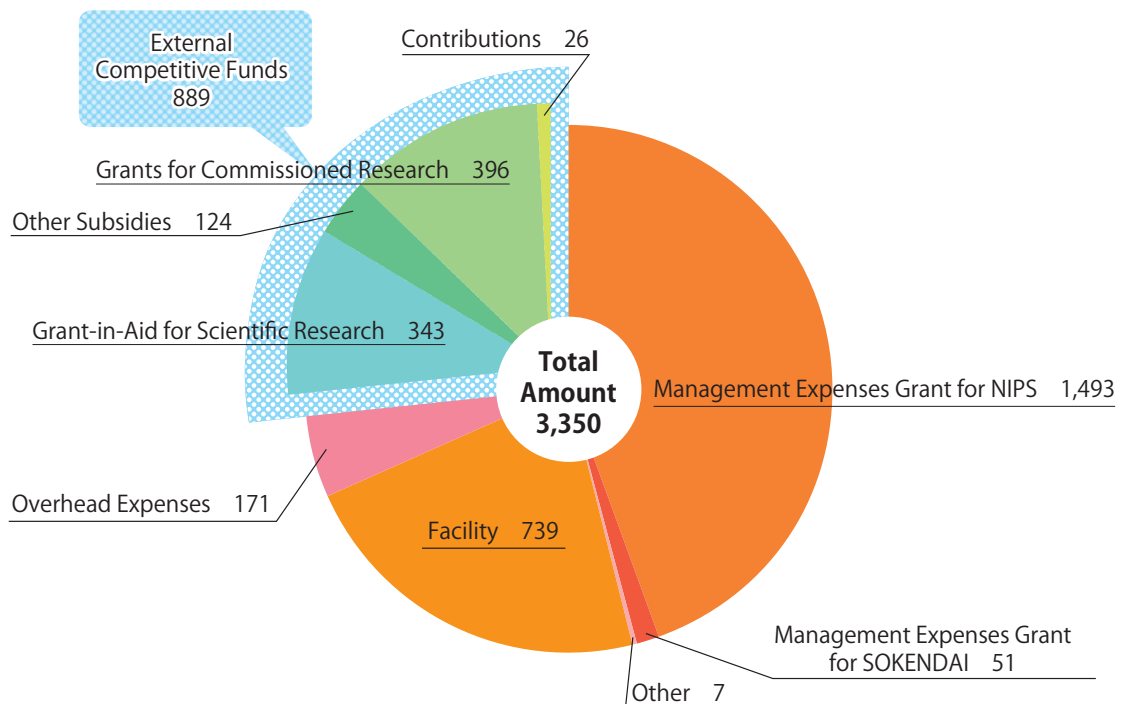
## Current State

### Staffs



### Budget

numbers are in million yen/As of May, 2019



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.

Ohsumi Conference Hall (capacity of 208)

Conference Room B (capacity of 112)

Conference Room C (2 rooms, capacity of 50 each)



Ohsumi Conference Hall



## ► 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	12
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 Three Okazaki

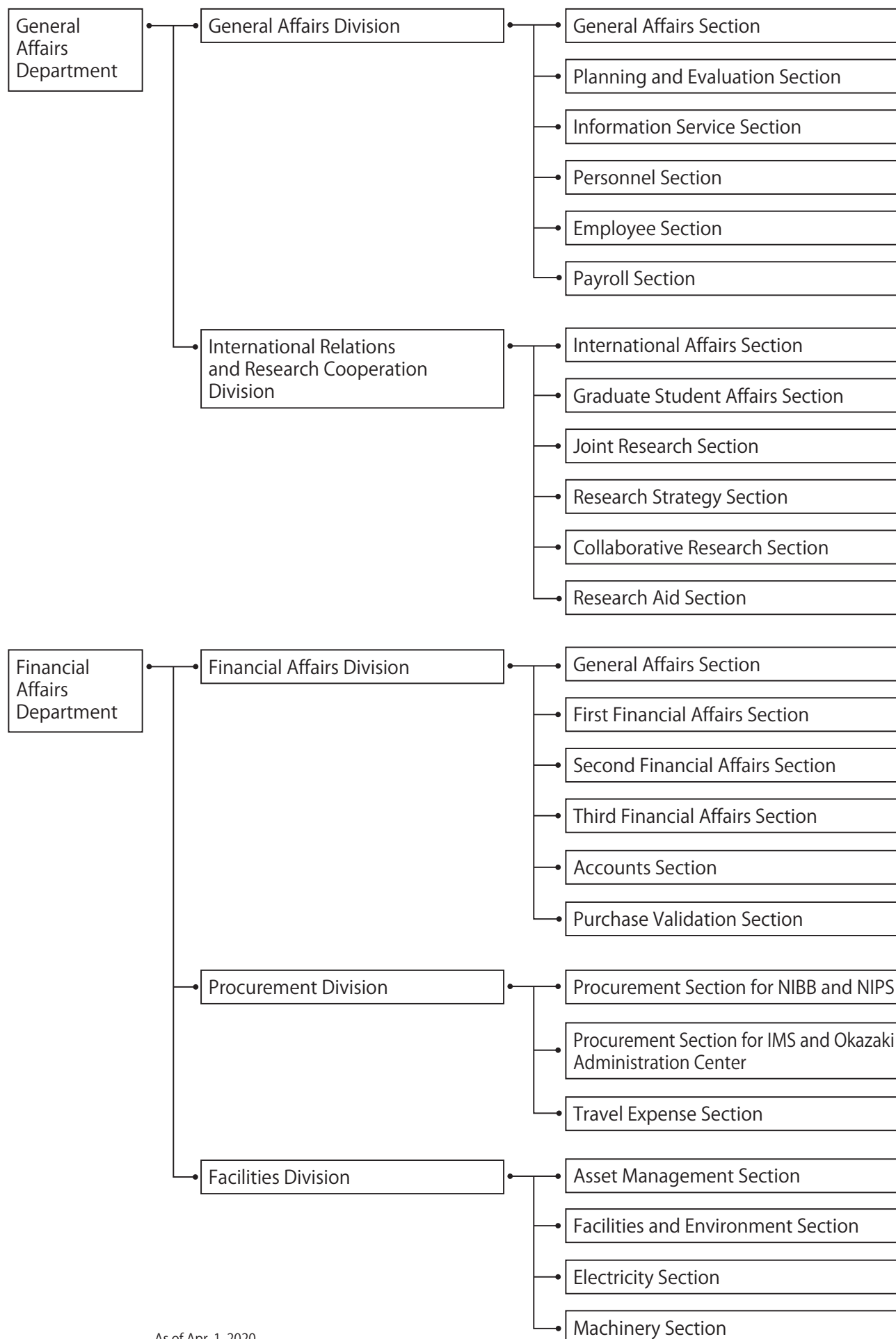
Institutes Opening day: From Monday to Friday

Opening time: From 8:00 to 19:00 (maximum extension

20:00) Childcare form: Regular childcare, temporary childcare



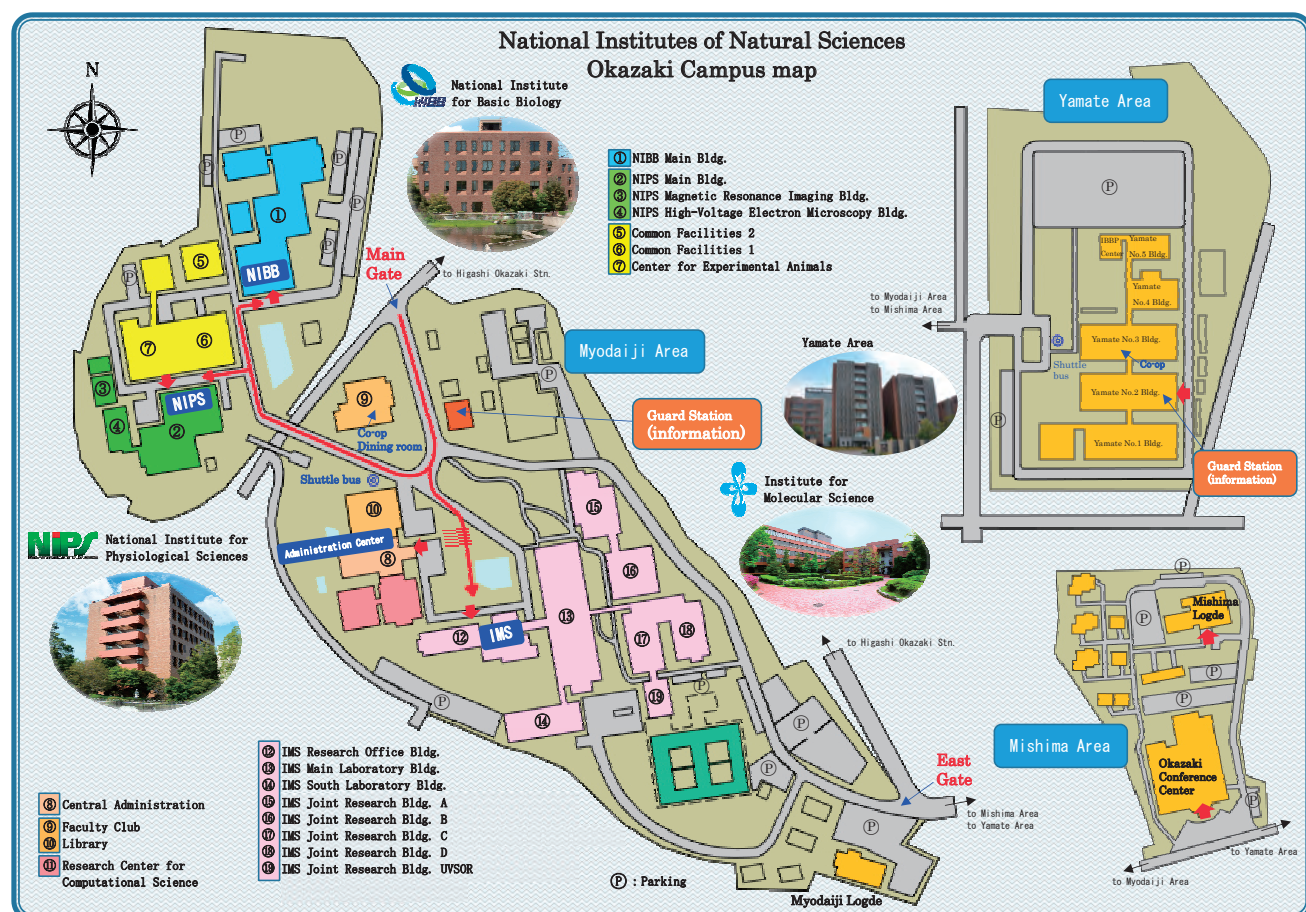
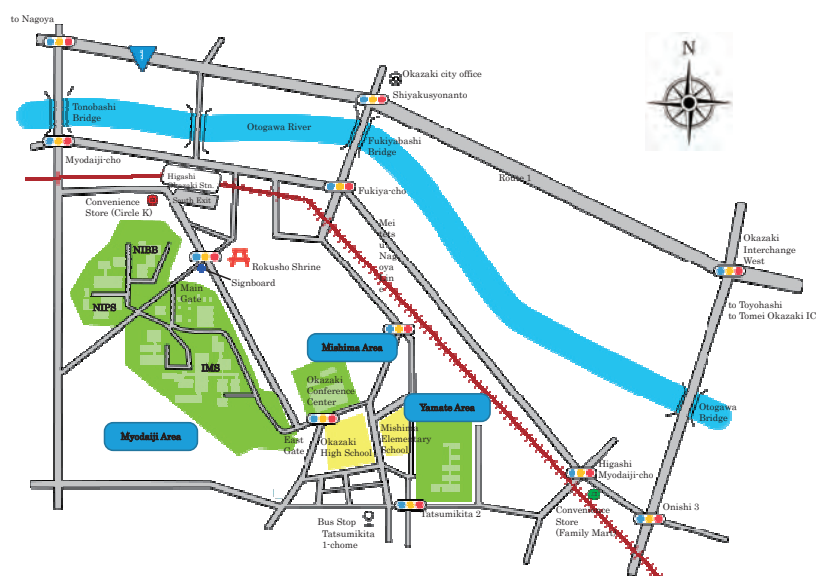
# Okazaki Administration Center



As of Apr. 1, 2020

# 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)

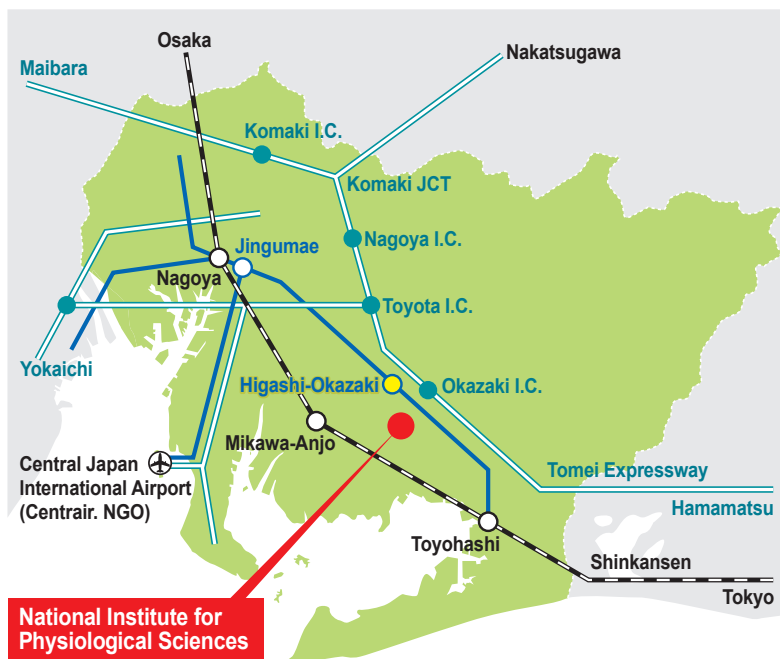
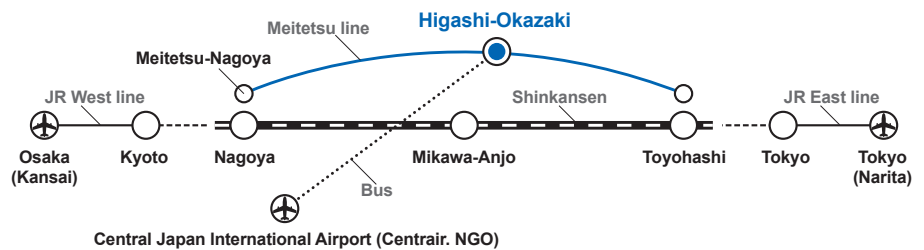
### A) By plane (\*Recommended)

Transfer to Central Japan International Airport

### B) By train




















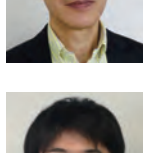


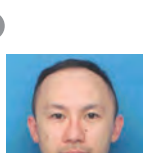




Take the JR Narita Express airport shuttle train from Narita to Tokyo Station (approximately 60 minutes) and change trains to the Tokaido shinkansen (bullet train).

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.



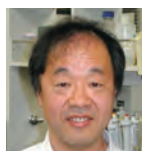


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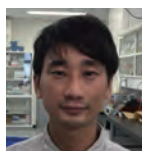
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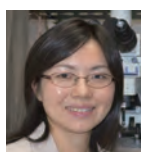
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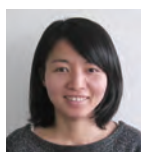
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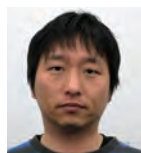
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