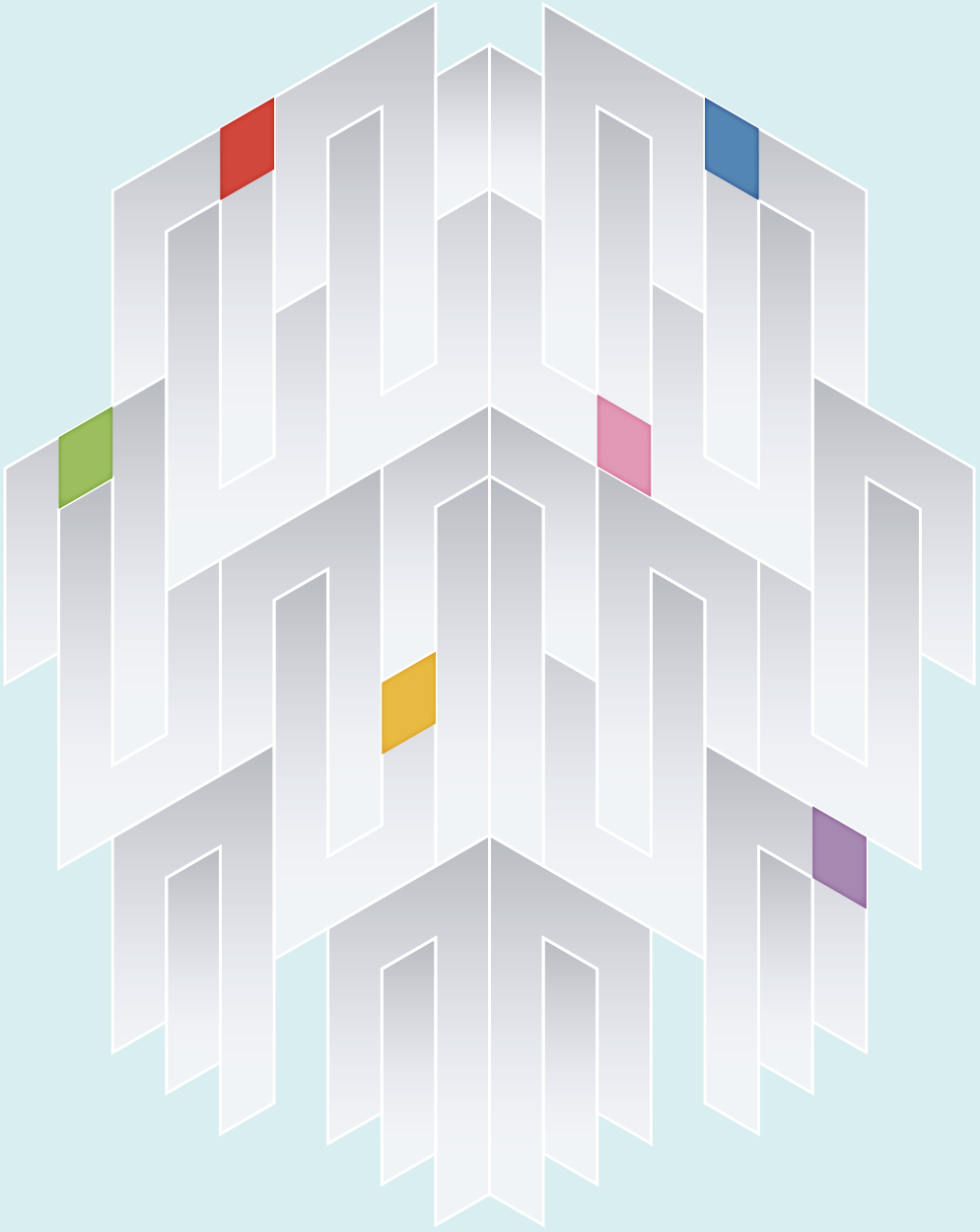


BRAIN RESEARCH INSTITUTE
NIIGATA UNIVERSITY 2020

新潟大學腦研究所

Message from the Director

BRI in the time of coronavirus

Osamu Onodera
Director, Brain Research Institute, Niigata University

My name is Osamu Onodera, BRI professor of Neurology. I became a new director in February 2020. The coronavirus pandemic emerged shortly after my appointment and we have been struggling to deal with various issues arise from the pandemic ever since. I imagine we will have to live with the coronavirus for the next few years at least. Additionally, there seems to be no going back to a previous lifestyle from a new normal. For better or worse, we have come to acknowledge many things in the unprecedented experience. One is the concept of higher education. After experiencing the pandemic time, there will be a paradigm shift in the perceptions of those receiving higher education. Until now, universities have provided a physical space for education and screened those who enter the place. But the online classes, swiftly implemented in response to the pandemic, have virtually eliminated the limitations of the physical space on their own. This is nothing less than the unprotected exposure of higher education, which has been secured by the physical element of space, to the world. There is a big change that will allow students to choose any class in the world. In an age where automatic translation is possible, language barriers are no longer an issue. It's a huge upheaval for learners. When the education providers lose the superiority of the physical space, what can the providers use as a source of strength to maintain its form?

The nature of our learning is called into question in such a time. In this context, I believe that the importance of learning that shares the space in which we get together will become even more important. In the new normal, there may be an even greater screening for the education with which we share the space.

In recent neuroscience research, large-scale analysis has become the mainstream and the in-situ nature of research is being lost. While some suggest building a virtual form of research like network-based laboratories, a standard form of physically constrained institute may need to change. However, the traditional idea still exists in me, which genuine discoveries and excitements are nurtured in the context of the physical space. I believe that the greatest advantage of the institute is that it provides a "place" of chaos, a space for learning. In a post-pandemic world, the way the institute is run and the way it is taught could change drastically. We will be assessed in such a situation. I think the nature of the importance of people gathering closer to have academic discussion won't go away in any era. As a research institute of brain, we will make an effort to develop such a space in the new academic system of the post-coronavirus era.

History

1957
Research Facility of Neurosurgery at School of Medicine, the origin of Brain Research Institute is founded.

1967
Research Facility of Neurosurgery, School of Medicine is transformed into Brain Research Institute. Faculty of Morphology is renamed Faculty of Neuropathology.

1971
Brain Disorder Specimen Center is set up.

1976
New Research Building opens. (3,467m²)

New Brain Disorder Specimen Center opens. (531m²)

1977
Research Building extension is completed; 1,018m² of animal testing laboratory and other laboratories are added.

1986

1995
Reorganization results in BRI's new structure of 3 big branches: Basic Neuroscience Branch (Depts. of Molecular Neurobiology, Cellular Neurobiology, Neurophysiology, and Developmental Neurobiology), Pathological Neuroscience Branch (Depts. of Pathology and Molecular Neuropathology), and Clinical Neuroscience Branch (Depts. of Neurosurgery and Neurology). Brain Disorder Specimen Center is renamed Brain Disorder Analysis Center.

MEXT Joint Usage / Research Center

The Collaborative Research Center for Brain Diseases Utilizing Neuropathological Resources

BRI was certified as a joint usage/research center by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) in 2010. Our extensive collection of brain disease materials and expertise have been open to the neuroscientists' community in Japan. BRI's diverse joint researches in neuropathology and related fields have brought out a great deal of achievement in relation to unravelling the pathological mechanism of brain disease. Given the MEXT's recognition for such achievements, BRI has renewed the certification of a joint usage/research center in FY 2016.

BRI has the world-class collections of neuropathological specimens and advanced imaging analysis technique. BRI is committed to tackling tasks such as neuropathological analysis on brain disorders like Alzheimer's disease, development of early diagnostic technique, and translational research on the treatment for reducing disease progression.

By utilizing the specimens of human brain disease and the animal model resources along with the underpinning of translational research for clinical application, BRI's collaboration with researchers across the world offers a prospect of reducing the burden of intractable neurological disease. Expected outcomes include the followings: to shed light on the disease pathology, to establish early imaging diagnostics, and to discover new treatment that slows disease progression.

Major Research Projects

Drug discovery for Alzheimer's disease

(MEXT Joint Usage / Research Center reinforcement project)

20 years of research efforts at Center for Integrated Human Brain Science has successfully developed non-invasive imaging method for preclinical diagnosis of Alzheimer's disease (AD), and has also demonstrated that disturbance in aquaporin-4 (AQP4) functionality, which hinders proper clearance of β-amyloid, plays a significant role in the pathogenesis of AD. The project aims to apply such a developed diagnostic technique in preventing AD: together with establishing an early diagnostic method for AD using magnetic resonance imaging (MRI) and positron emission tomography (PET), the project will target discovery of the new drug designed to modulate AQP4 function and prevent impairment in clearance of β-amyloid.

Clinical research promotion project for neurological disease by establishing the system neuropathology: Establishing a platform for clinical research utilizing neuropathological resources (MEXT education and research activities project)

In therapeutic research of brain disease, the diagnostics bound by the traditional theory of localization of brain function appears no longer sufficient. In order to overcome brain disease, there has been an increasing demand for a new academic discipline, which allows us to understand brain disease in accordance with the functional connectivity of each part of the brain. Niigata University launched a project aimed at setting a new pathological assessment method, naming such neuropathology as "System Pathology for Neurological Disorders." Conducting interventional trials based on the knowledge will pave a way to overcome brain disease. Connecting the collective expertise in brain at BRI, a number of research projects on neurology at School of Medicine and the medical care system at University Hospital together, the project aims to ensure a seamless environment that will readily translate basic scientific findings into therapeutic interventions for patients. The project seeks to launch a clinical research center, which will serve for translational research on brain disease.

1996

Ultra-high Magnetic Field MRI Research Building opens. (251m²)

2002

Brain Disorder Analysis Center is transformed into 2 Centers: Center of Integrated Human Brain Science and Center for Bioresource-based Researches. The latter merges with Genetic Research Facility of Niigata University and Animal Testing Facility, School of Medicine.

2003

Center for Integrated Human Brain Science (CIHBS) Building opens. (3,969m²)

2006

Reformed Center for Bioresource-based Researches consists of 2 Branches: Bioresource Science Branch and Brain Science Branch. Dept. of Project Programs is added to Brain Science Branch. Depts. of Molecular Neuropathology (Pathological Neuroscience Branch) and Bioinformatics (CIHBS) are transformed into Depts. of Digital Pathology and Digital Medicine respectively. CIHBS PET Building opens. (416m²)

2008

Center for Bioresource-based Researches extension is completed. (200m²)
BRI is certified as a Joint Usage/Research Center by the Ministry of Education, Culture, Sports, Science and Technology (MEXT). ("the Advanced Collaborative Research Center for Brain Diseases Utilizing Neuropathological Specimens", start date: April 1, 2010)

2016

BRI renews MEXT's certification on the Joint Usage/Research Center, which is renamed "Collaborative Research Center for Brain Diseases Utilizing Neuropathological Resources".

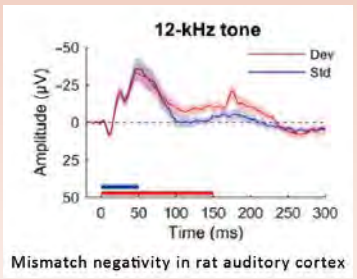
Organization

As of July 1 2020

Basic Neuroscience Branch		Dept. of Molecular Neurobiology	Prof.	Hiroyuki Nawa
			Assist. Prof.	Hisaaki Namba
		Dept. of Brain Tumor Biology	Assoc. Prof	Nobuyuki Takei
			Assist. Prof	Yuriko Iwakura
		Dept. of Cellular Neuropathology	Prof.	Takayasu Mikuni
			Assoc. Prof.	Motokazu Uchigashima
			Assist. Prof.	Hitoshi Uchida
		Dept. of System Pathology for Neurological Disorders	Prof.	Kazuki Tainaka
			Prof.	Masaki Ueno
Pathological Neuroscience Branch		Dept. of Pathology	Prof.	Akiyoshi Kakita
			Assoc. Prof.	Hiroshi Shimizu
		Dept. of Molecular Pathology	Prof.	Koichi Wakabayashi
			Assoc. Prof.	Fumiaki Mori
Clinical Neuroscience Branch		Dept. of Neurosurgery	Prof.	Yukihiko Fujii
			Assoc. Prof.	Makoto Oishi
			Assist. Prof.	Tetsuya Hiraishi
			Assist. Prof.	Manabu Natsumeda
		Dept. of Neurology	Prof.	Osamu Onodera
			Assoc. Prof.	Masato Kanazawa
			Assist. Prof.	Takuya Konno
Center for Integrated Human Brain Science		Dept. of Integrated Neuroscience	Assoc. Prof.	Hitoshi Matsuzawa
		Dept. of Biological Magnetic Resonance	Prof.	Hironaka Igarashi
			Assist. Prof.	Masaki Watanabe
		Dept. of Functional Neurology & Neurosurgery	Assoc. Prof.	Yuji Suzuki
			Assoc. Prof.	Ken-ichi Yamada
			Assist. Prof.	Satoshi Ueki
Center for Bioresouce-based Researches	Bioresource Science Branch	Dept. of Molecular Genetics	Prof.	Takeshi Ikeuchi
			Assoc. Prof.	Akinori Miyashita
			Assist. Prof.	Kensaku Kasuga
		Dept. of Comparative & Experimental Medicine	Prof.	Toshikuni Sasaoka
			Lecturer	Nanaho Fukuda
			Assist. Prof.	Kanako Oda
		Dept. of Animal Model Development	Prof.	Toshikuni Sasaoka
			Assoc. Prof.	Manabu Abe
			Assist. Prof.	Ena Nakatsukasa
	Brain Science Branch	Dept. of Pathology Neuroscience	Prof.	Akiyoshi Kakita
			Assoc. Prof.	Mari Tada
			Assist. Prof.	Rie Saito
		Dept. of Molecular Neuroscience	Prof.	Osamu Onodera
			Assist. Prof.	Akihiro Sugai
		Dept. of Neuroscience of Disease	Prof.	Hideaki Matsui
			Assoc. Prof.	Ryuichi Hishida
			Assoc. Prof.	Atsushi Sugie
		Dept. of Translational Research	Assoc. Prof.	Kouichirou Okamoto

Prof.
Hiroyuki Nawa

Dept. of Molecular Neurobiology

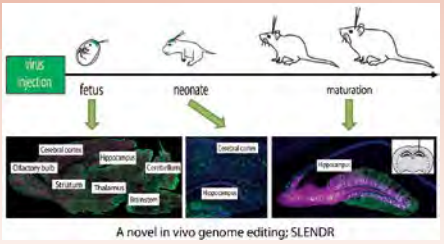


Mismatch negativity in rat auditory cortex

Neurons and glial cells communicate to each other not only via neurotransmitters but also using various bioactive proteins, namely neurotrophic factors and cytokines. Our long-term objective is to elucidate the molecular and pathologic mechanisms of how these bioactive proteins regulate brain development or perturb neural functions related with neuropsychiatric diseases. We have established animal models for schizophrenia by perturbation of cytokine signals during neonatal development. Using these models, we aim to clarify neuropathological and therapeutic mechanisms of the disease. Our efforts have been paid to the following projects: (1) the molecular and system neuropathology of schizophrenia and its animal modeling (hallucination, auditory-evoked potential, social withdrawal), (2) the cytokine-dependent regulation of monoaminergic development and function (EGF, NRG1, EGFR, ErbB4), and (3) the specificity and functionality of the intracellular signaling driven by these bioactive proteins and their possibility as therapeutic targets for schizophrenia. Currently we are addressing these questions employing all types of biological approaches including molecular genetic, biochemical, cell biological, electrophysiological, pharmacological, and behavioral tools and techniques. We hope these studies will lead to the understanding of how bioactive factors control the onset and progression of developmental brain diseases such as schizophrenia, which might hint at developing new drugs.

Prof.
Takayasu Mikuni

Dept. of Cellular Neuropathology

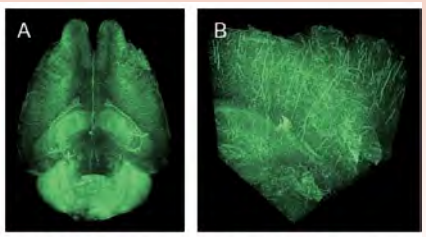


A novel in vivo genome editing; SLENDR

Our goal is to understand the physiology and pathophysiology of the brain at the cellular and molecular levels. We established "SLENDR", a technique based on in vivo genome editing, to image endogenous proteins with high specificity, resolution and contrast in single cells in mammalian brain tissue (Cell, 2016). In addition, we recently developed "vSLENDR", a genome editing method to target virtually any cell-types, areas and ages across the brain, widely expanding the applicability of genome engineering technologies in the broad field of neuroscience (Neuron, 2017). Using "SLENDR" and "vSLENDR", we will explore the cellular and molecular mechanism underlying long-lasting memory, and further investigate how the mechanism is impaired in memory disorders to provide new therapeutic strategies.

Prof.
Kazuki Tainaka

Dept. of System Pathology for Neurological Disorders

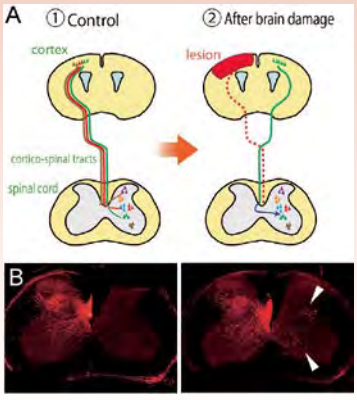


Whole 3D brain imaging by light-sheet microscopy

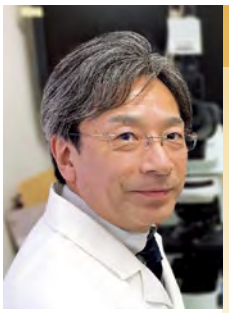
Current biopsy and histology have long relied on thin-sectioned 2D images with several chemical staining methods and specific immunohistochemistry. Facile 3D visualization of human brain tissue with single-cell resolution would provide a novel concept of the neuropathological diagnosis and contribute our understanding of pathological mechanisms based on comprehensive and quantitative analysis of individual biomarker. In this laboratory, we aim at establishing a novel 3D neuropathology by developing a highly efficient clearing protocol for human brain tissue and combining with a rapid 3D imaging using light-sheet fluorescence microscopy.

Prof.
Masaki Ueno

Dept. of System Pathology for Neurological Disorders



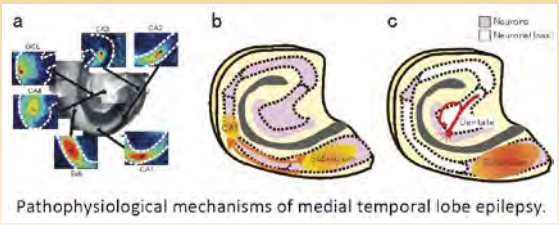
Central nervous system injuries due to stroke or trauma disrupt neural circuits and result in severe deficits of functions. The brain and spinal cord have very limited capacity to reconstruct the circuit once it is damaged, and therefore none of effective therapeutic methods have been developed so far. We previously demonstrated that spared motor and autonomic circuits are dynamically reorganized after injuries and influence the recovery process of functions. These results suggest that controlling the rewiring of the circuit would lead to make proper neuronal connections that achieve functional recovery. The goal of our study is to understand the process of rewiring and its underlying molecular mechanisms and neural functions. Toward this aim, we are analyzing neural systems of both normal and injured brain and spinal cord, using cutting-edge techniques including, mouse genetics, viral tracers, optogenetics, chemogenetics, and 3D behavior analysis. We believe that this study paves the way to develop novel strategies to regenerate circuits and restore neural functions.



Prof.
Akiyoshi Kakita

Dept. of Pathology / Dept. of Pathology Neuroscience

Mission:
To provide the highest quality pathology services and scientific evidence focused on the advancement of developments in the field of neuropathology.



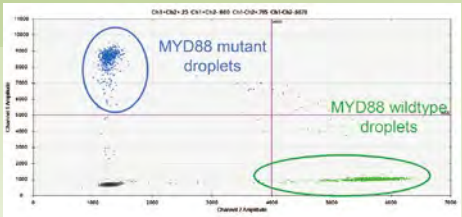
Pathophysiological mechanisms of medial temporal lobe epilepsy.

Vision:
As an academic pathology department, we aim to deliver a high degree of professionalism in clinicopathological diagnostic services and neuropathology research, utilizing comprehensive and innovative approaches and building departmental competence to meet the needs of patients, institutions, and society.

Our approach will involve taking full advantage of opportunities to advance both the science and practice of neuropathology through individual and collaborative research, which hopefully will produce leading practitioners and researchers.

Prof.
Yukihiko Fujii

Dept. of Neurosurgery

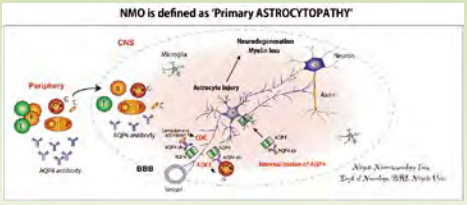


Digital Droplet PCR system for detection of the MYD88 DNA mutation

Department of Neurosurgery, University of Niigata was founded by Professor Mizuho Nakata, "the father of Neurosurgery in Japan", in 1953, becoming the first independent Department of Neurosurgery in Japan. Since then, the department has led the field of preclinical research and surgery for brain tumors, cerebral vascular disease, brain trauma, and functional surgery. Also, the department is unique in that it is affiliated with the Brain Research Institute, enabling collaboration with many basic neuroscience laboratories within the Institute. Answering clinical questions through basic research and using the results to improve clinical medicine, is precisely what Professor Nakata envisioned when he founded the Brain Research Institute. It is our obligation to carry on this spirit, and all staff is dedicated in discovering new insight into neurosurgical practice.The main research areas we are currently focusing on include: (1)establishing brain tumor cell lines and intracranial xenografts to develop the best strategies to treat each tumor, (2) diagnosing brain tumors by detecting driver mutations from cell free DNA of cerebrospinal fluid (Fig 1), (3) developing assistive surgical technology to enable accurate simulation for complex neurosurgery cases and education of young neurosurgeons, (4) collaboration with Nishi-Niigata Chuo National Hospital to elucidate the complex pathophysiology of epilepsy.

Prof.
Osamu Onodera

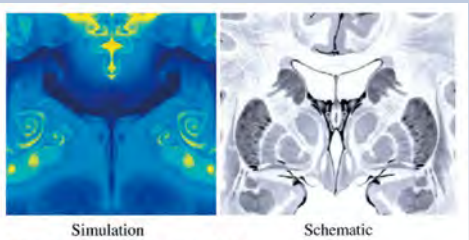
Dept. of Neurology / Dept. of Molecular Neuroscience



The Niigata University Brain Research Institute possesses not only a basic neuroscience branch but also a clinical neuroscience branch: Departments of Neurology and Neurosurgery. Thus, the aim of our Institute is to overcome brain diseases. We study a wide variety of brain diseases by using genetic, biochemical, cell biological, histological, and imaging approaches, in collaboration with other departments in the Institute.
In the past 50 years, we have produced favorable results of clinical and basic research. In the beginning, we revealed Niigata Minamata and SMON diseases, which are caused by toxic reagents, making us to have profound connections with society. Up to now, we established entities of novel brain diseases and elucidated their etiologies and disease mechanisms by genetic, biochemical, and histological approaches.
We have also educated a large number of neurologists. Careful observation of patients by the excellent neurologists brought us fruitful success in a new discovery. Our research is attributable to the support of patients and clinicians, and we will keep tight connection with them.
Neurologists need comprehensive knowledge of medicine and a wide range of social skills including communication, leadership, and problem-solving skills. We actively train young doctors to acquire the knowledge and skills to become a specialist in various fields from a cutting-edge basic neuroscience to practical neurology. We are professional for brain diseases and will ensure the best possible support for our patients.

Prof.
Hironaka Igarashi

Dept. of Biological Magnetic Resonance

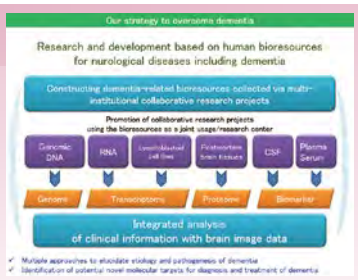


Simulation of brain morphology
The results of numerical simulation with thermal convection as a dominant equation.

Continuous technological development represents an indispensable component of the recent remarkable advancements in the state of our knowledge of human brain function. Magnetic resonance is a field which provides a number of versatile non-invasive methodologies applicable to the analysis of human specific brain function. The Department of Biological Magnetic Resonance focuses on the research, development and education of magnetic resonance technologies as well as the research and education of human brain function based on integrated knowledge of advanced engineering and non-linear computational analysis.

Prof.
Takeshi Ikeuchi

Dept. of Molecular Genetics



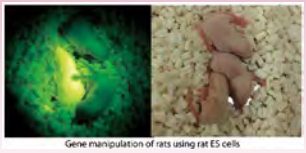
Recent research and development of dementia has drastically changed. Therapeutic approach to dementia has shifted from symptomatic drugs to disease-modifying drug. More attention has been paid in dementia to pathophysiological diagnosis based on biomarker rather than symptom-based diagnosis. Prospering in research by virtue of paradigm shift, we have pioneered research that will bring revolution in clinical practice of dementia. Our mission has two elements; one is biomarker development, and the other is genome research of dementia. We attempt to see through pathological changes occurring in the brain affected with dementia using blood and cerebrospinal fluid samples from preclinical phase to symptomatic phase. We have established large sample collection of genomic DNA for dementia disorders. Whole genome/exosome analyses have been applied in the genome analysis of dementia to explore novel genetic factors in Japan. We have provided a clinical sequence examination for physicians across Japan for genetic diagnosis of dementia. By this effort, we will contribute to the realization of genome medicine of dementia in Japan. Even though the environmental surrounding of dementia research has been drastically moving, we keep pioneering the dementia research without forgetting our mission that we will deliver a bright future to patients with dementia.

Prof.
Toshikuni Sasaoka

Dept. of Comparative & Experimental Medicine

Dopamine is thought to play an important role in motor control, memory, learning and motivation. We focus on motor symptoms of Parkinson's disease (PD) which is one of the important neurological diseases, and as a PD model animal, develop a genetically engineered mouse for dopamine receptors and related molecules that convey dopamine information. By analysis of animal behavior regarding learning and memory and analysis of the function of neural circuit, we aim to clarify mechanism of motor control, learning and memory, and develop therapeutic method for PD. At the same time, we are conducting research into the search and analysis of RNA-binding proteins that are responsible for development and maintenance of neural circuit as well as function of neural circuit. Recently, we are focusing on development of an innovative embryo manipulating system for the generation of genetically modified marmosets in collaboration with Dept. of Animal Model Develoment. Simultaneously, we are in charge of administration and management of core facility for animal experiments in Niigata University with mice, rats, rabbits, guinea pigs, dogs, pigs, Japanese monkeys, marmosets, medaka etc as experimental animals to promote advanced animal experiments. In addition to setting up the experimental environment, we support research using developmental and reproductive engineering technologies such as in vitro fertilization, embryo transfer, cryopreservation of embryos and spermatozoa. In addition, we are rapidly advancing the creation of genetically modified animals by incorporating rapidly progressing genome editing technology. Using these experimental techniques, we maintain the animal experiment environment in the Specific Pathogen Free (SPF) environment, and also contribute to the implementation of efficient research through planned animal production.

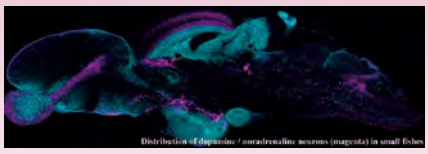
Dept. of Animal Model Development


Gene manipulation of rats using rat ES cells

Our research efforts are focused on understanding of molecular mechanisms of higher brain functions such as learning and memory. Making good use of current methods in molecular biology and developmental engineering, we are now engaged in the following projects: 1) functional assay of neurotransmitter receptors and related molecules with gene-targeting techniques, 2) generation and analysis of animal models for human nervous diseases, 3) establishment of germ line-competent embryonic stem cells derived from rat embryos, and 4) development of basic methods for generation of gene-modified animals using gene-editing technology.

Prof.
Hideaki Matsui

Dept. of Neuroscience of Disease


Distribution of dopamine / noradrenaline neurons (magenta) in small fishes

There exist approximately 100,000,000,000 neurons in each human brain, and the number of glia cells is much more than that of neurons. Supposed that each neuron is a star in the Universe, we could compare the brain to a small Universe within. However, things are more complicated because each neuron extends long fibers to other neurons for communicating signals. In one sense, the brain, a small Universe, is much more complicated than the Universe itself.

It is theoretically, technically and physically impossible to study all the twinkling stars in the sky. But we could estimate the characters of stars or planets by carefully observing and analyzing the sun and planets in the solar system. It is also impossible to elucidate functions, anatomies and networks of all the neurons one by one, but we are able to reach a right conclusion if we handle a miniature brain and deduce common principles from the mini-brain.

This is the way that we have followed. We will disclose the phenomenon occurring in human brain by studying Fish brain. Especially our aim is to elucidate the mechanism of neurological diseases and disorders, deepening scientific and social understanding for some, or finding a drug for others. We human beings have evolved exactly from Fish, and most of the functions and structures in the human brain are preserved in Fish brain. Our laboratory has tried uncovering the physiological functions and pathophysiology of the human brain by comparing Fish and human brains, and we will surely find therapies for neurological diseases and disorders.

Global Partnerships

Global partnerships can bring together complementary strengths and deepen the impact of joint research. BRI is committed to forming such partnerships and will further develop existing partnerships. The institute regularly welcomes scientific visitors from around the world and signs MOUs and agreements with overseas research institutions. BRI also annually hosts international symposia, which feature fascinating lectures by distinguished scientists from across the world.

Medical Practice and Education

BRI's mission is to advance scientific research on the nervous system of the brain. BRI has a historical background that has developed through the clinical care of neurosurgical cases in the School of Medicine. BRI offering an integrated approach to its research, along with clinical and educational activities, is therefore a great strength. The research at BRI covers a wide spectrum from Basic Neuroscience to Clinical Neuroscience related research to human brain disease. Pathological Neuroscience that bridges these two areas and the integrated research of these three areas brings greater progress, making BRI one of the most desirable institutes for research on brain disease in Japan. In order to continue to engage in cutting-edge research, BRI is dedicated to training competent researchers. BRI is also dedicated to research in the clinical area to advance medicine.




NU Junior Doctor Training School

BRI hosted a hands-on science experience class in August 2019 as the 4th session of the master's program of "the Niigata University Junior Doctor Training School", a STEM education program aiming at fostering the budding scientists. 41 pupils, from the 5th grade of elementary school to junior high, participated in BRI lab tours and lectures.


Niigata Summer Seminar for Neuroscience

Every summer, BRI offers a seminar for young researchers across Japan to learn and explore topics at the forefront of neuroscience. Participants learn cutting-edge knowledge on specific topics from both BRI and external scientific experts at the forefront of neuroscience research through lectures and discussions. The seminar also features an on-site training course that provides an opportunity to participate in current experiments.


Science Education

Partnering with the local Super Science High Schools specified by MEXT, BRI provides opportunities including study tours at the institute and lectures that BRI scientists travel to the schools to give. BRI is working to nurture the next generation of global researchers by introducing the attractive world of neuroscience.

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