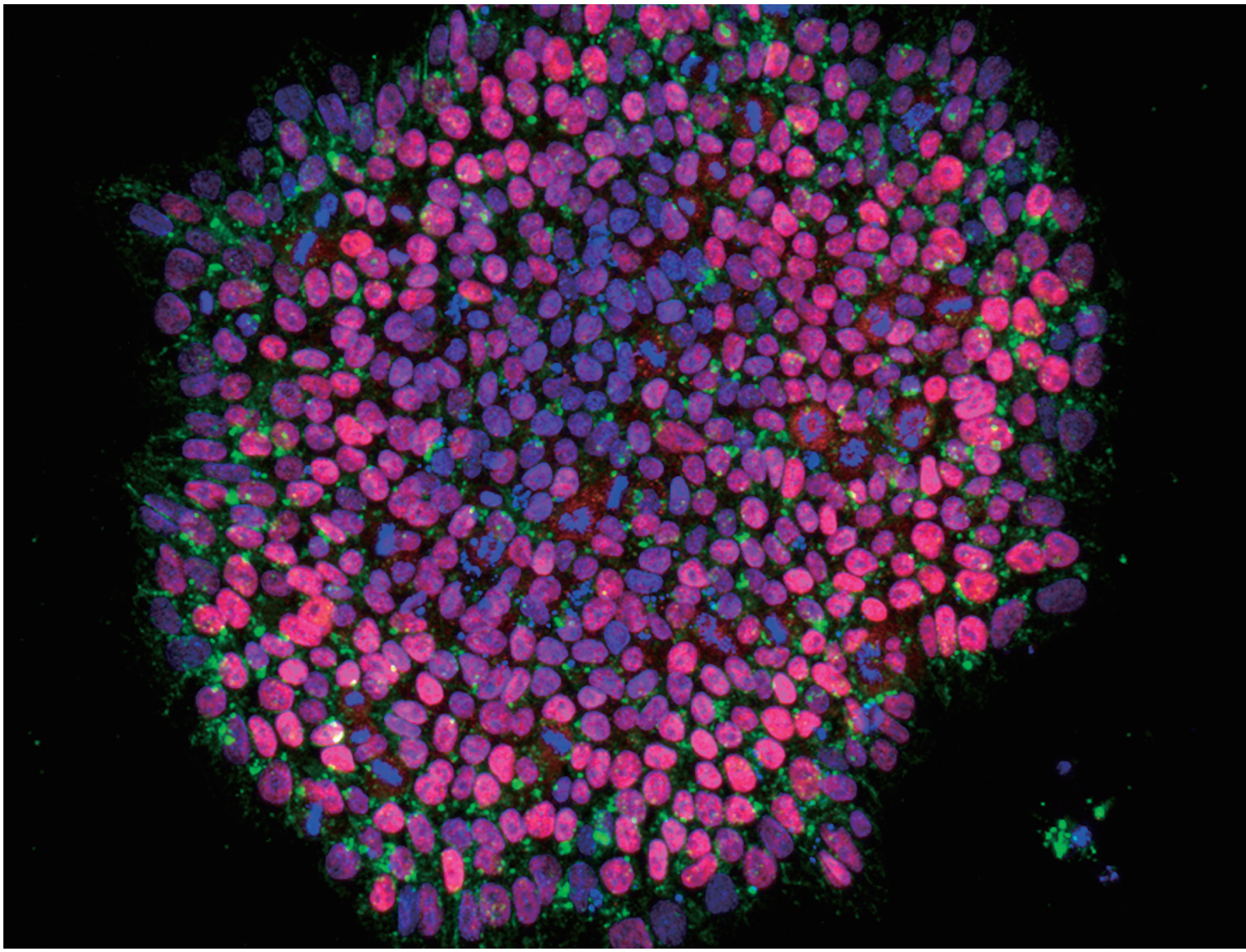


Schizophrenia patient-derived induced pluripotent stem cells. Blue, nuclei; red and green, OCT4 and TRA-1-60 (pluripotent markers), respectively.

# Psychiatry & Behavioral Sciences

Project Leader
**Makoto ARAI**

Makoto Arai has been working as a reader in the schizophrenia research project in the Institute since April of 2015. After obtaining Master's and Doctoral Program of the Department of Biological Science and Technology, Faculty of Industrial Science and Technology, Tokyo University of Science. He received Ph.D. of Engineering from Tokyo University of Science in 2002. He shifted his focus to research for molecular mechanisms of schizophrenia under the supervision of Dr. Masanari Itokawa as a postdoctoral fellow position in 2002 and has been working on how genetic and environmental factors are involved in schizophrenia. Currently, he is interested in mechanisms of glycation and oxidative stress associated with phenotypes of psychiatric disorders during life stage. Advancement of studies made using specific biomarkers will highlight the innovative ideas underlying recovery from psychiatric disorders.

# Schizophrenia Research

Laboratory HP: https://www.igakuken.or.jp/schizo-dep/english.html

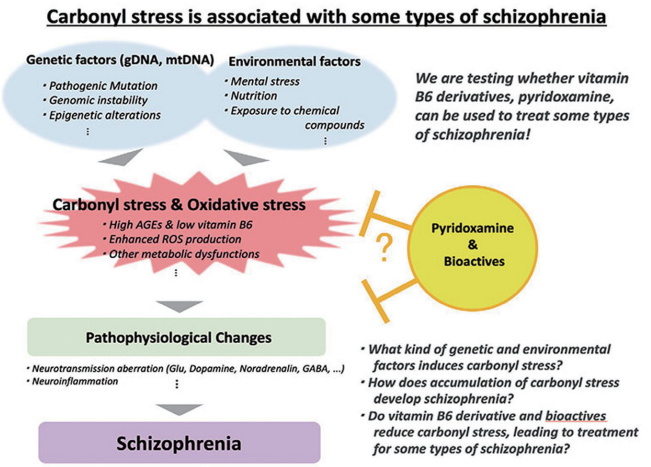
## Staff

| Researchers | Research Assistants | Students |
|---|---|---|
| Masanari ITOKAWA | Ikuyo KITO | Tianran WANG |
| Yasue HORIUCHI | Nanako OBATA | Riko AGARIE |
| Mitsuhiro MIYASHITA | Izumi NOHARA | Mai ASAKURA |
| Kazuya TORIUMI | Mai HATAKEYAMA | Kyoka IINO |
| Hiroaki ISHIDA | Chikako ISHIDA | Azuna OZAWA |
| Akane YOSHIKAWA | Akiko KOBORI | Chinatsu SUGIMURA |
| Kazuhiro SUZUKI | Tomoko INOUE | Yasufumi TOMITA |
| Yasuhiro MIYANO | | Mayuk MASADA |

## Research Summary

Profiling of the peripheral metabolic system is a viable schizophrenia research strategy that can lead to earlier diagnostic methods, elucidation of molecular mechanisms, and novel strategies for the prevention and treatment of schizophrenia.

We focus on, 1) developing individualized medicine for treating schizophrenia, 2) investigating factors involved in disease onset, and 3) understanding the molecular pathology by using biomarkers to overcome the barrier of heterogeneity. Our research outcomes will be applied to drug development by establishing a new biomarker-based field of research in molecular psychiatry. Data obtained from metabolomics, genomics, induced pluripotent stem (iPS) cell models, animal models, post-mortem brain analyses, neuropsychology, and genetic counseling research will be consolidated to elucidate the genetic and environmental factors relevant to psychiatric disorders such as schizophrenia.




The biomarker-based approach is an innovative and creative strategy for identifying the metabolic changes associated with schizophrenia, independent of conventional pathological hypotheses. Verification in cellular and animal models can shed light on the molecular mechanisms underlying the utility of naturally-derived substances in trading schizophrenia, and is expected to lead to the future development of much safer treatments and prophylactic methods.

## Selected Publications

Son S, et al. (2020) "Enhanced carbonyl stress and disrupted white matter integrity in schizophrenia." ***Schizophr Res***. S0920-9964(20)30435-7.

Mizutani R, et al. (2019) "Three-dimensional alteration of neurites in schizophrenia." ***Transl Psychiatry.*** 9: 85

Itokawa M, et al. (2018) "Pyridoxamine: A novel treatment for schizophrenia with enhanced carbonyl stress." ***Psychiatry Clin. Neurosci.*** 72: 35-44.

Miyashita M, et al. (2016) "The regulation of soluble receptor for AGEs contributes to carbonyl stress in schizophrenia." ***Biochem. Biophys. Res. Commun.*** 479: 447-452.

Miyashita M, et al. (2014) "Clinical Features of Schizophrenia With Enhanced Carbonyl Stress." ***Schizophr. Bull.*** 40: 1040-1046.

Arai M, et al. (2010) "Enhanced Carbonyl Stress in a Subpopulation of Schizophrenia." ***Arch. Gen. Psychiatry.*** 67: 589-597.

Project Leader
Yoshitaka TATEBAYASHI

# Affective Disorders Research

Yoshitaka Tatebayashi has been the head of the Affective Disorders Research Project since 2014. He obtained his MD from Osaka University School of Medicine in 1989 and worked at Osaka University Hospital from 1989 to 1990, the Graduate School of Medicine at Osaka University from 1990 to 1994, and the Department of Neurology at Nippon Life Hospital from 1994 to 1996. He then worked as a research scientist at the Institute for Basic Research in Developmental Disabilities from 1996 to 2000, and at RIKEN Brain Science Institute from 2000 to 2004. He was the director of the Depression Laboratory at the Tokyo Institute of Psychiatry from 2004 to 2011, and the director of the Depression Laboratory at TMIMS from 2011 to 2014.

Laboratory HP: https://www.igakuken.or.jp/affective/english/reserch-1.html

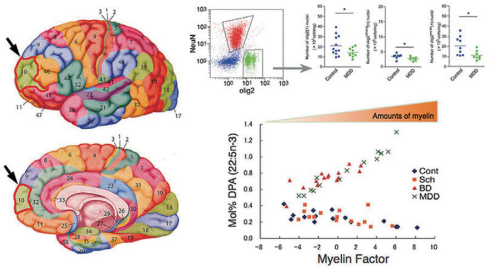
## Staff

**Researchers**

Naomi KIKUCHI-NIHONMATSU
Yoshiki MATSUDA
Kazuhisa AOKI
Takiko SHINOZAKI
Nobuyuki OZAWA

## Research Summary

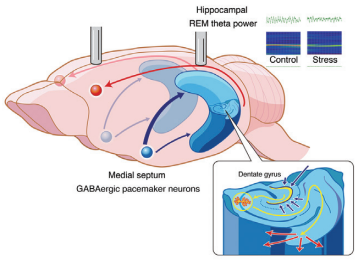
Major depressive disorder (MDD) and bipolar disorder (BD), collectively known as affective disorders, are relapsing and remitting disorders of affect with nearly full recovery between episodes. We use human postmortem brains and animal and cell culture models to identify the processes in which stress or aging causes changes in the brain to induce these disorders. An initial focus of our work was stress-induced or age-related changes in cellular structure and lipid composition, particularly in oligodendrocyte cells within the brain's mood circuitry. We are also interested in the biological relationship between affective disorders and dementias such as Alzheimer's disease.




We recently established a novel rat social defeat stress (SDS) model that develops prolonged MDD-like maladaptive social avoidance and sleep abnormalities. These abnormalities were associated with changes in electroencephalography (EEG) spectral powers, including reduced REM sleep theta power. Chronic treatment with two different classes of antidepressants (ADs), imipramine and fluoxetine, as well as preventative use of ergothioneine, a metabolite of the gut bacterium Lactobacillus reuteri, significantly ameliorated these behavioral, sleep, and EEG abnormalities.

Interestingly, REM theta power was normalized by chronic but not acute AD administration. We speculate that the septohippocampal pathway, including the medial septum and hippocampus, may be partially or largely impaired by SDS, resulting in both emotional and/or cognitive symptoms in our model.

Inflammation may be involved in this process since ergothioneine has a strong anti-oxidative as well as anti-inflammatory effects.




## Selected Publications

Matsuda Y, et al. (2020) "Ergothioneine, a metabolite of the gut bacterium Lactobacillus reuteri, protects against stress-induced sleep disturbances." ***Transl. Psychiatry*** 10:170.

Bauer M, et al. (2014) "Relationship between sunlight and the age of onset of bipolar disorder: an international multisite study." ***J. Affect. Disord.*** 167:104-111.

Nihonmatsu-Kikuchi N, et al. (2013) "Depression and Alzheimer's disease: novel postmortem brain studies reveal a possible common mechanism." ***J. Alzheimers Dis.*** 37: 11-21.

Tatebayashi Y, et al. (2012) "Abnormal fatty acid composition in the frontopolar cortex of patients with affective disorders." ***Transl. Psychiatry*** 2:e204.

Hayashi Y, et al. (2012) "Neuropathological similarities and differences between schizophrenia and bipolar disorder: a flow cytometric postmortem brain study." ***PLoS One*** 7: e33019.

Hayashi Y, et al. (2011) "A novel, rapid, quantitative cell-counting method reveals oligodendroglial reduction in the frontopolar cortex in major depressive disorder." ***Mol. Psychiatry*** 16: 1155-1158.

Project Leader
## Makoto HONDA

Makoto Honda has been the leader of the Sleep Disorders Project since 2009. After graduation from School of Medicine, University of Tokyo in 1989, he worked as a psychiatrist in Tokyo University Hospital, Tokyo Metropolitan Matsuzawa Hospital in parallell with the training of molecular genetics under Prof. Tatsuhiko Kodama. He received Ph.D in 1998 from the Graduate School of Science, Univ. of Tokyo. In 2001 after the discovery of hypocretin/orexin loss in narcolepsy, he moved to the Narcolepsy Center in Stanford University, USA, as a post-doctoral student / research fellow. Since then he has been working in sleep research fields. His primary interest is to understand the pathophysiology of sleep disorder narcolepsy and idiopathic hypersomnia and to find better markers/treatment options for them. He also works as a sleep physician to push forward clinical research.

# Sleep Disorders

Laboratory HP: https://www.igakuken.or.jp/sleep/

## Staff

**Researchers**
Taku MIYAGAWA
Akiyo NATSUBORI

**Research Assistants**
Takashi KOJIMA
Yasuko SEKI
Yoshiko HONDA

**Visiting Scientist**
Mihoko SHIMADA

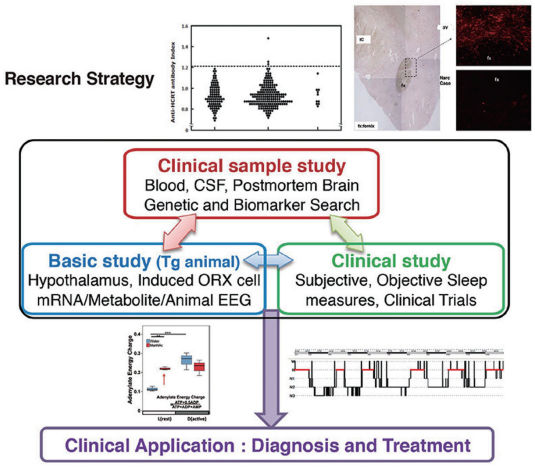
**Students**
Momoka MIYAZAWA
Takuma OGAWA
Shun SUZUKI

## Research Summary

**Our goal is to find the causes and develop better treatments for Narcolepsy and Hypersomnia.**
Narcolepsy is a sleep disorder of abnormal intrinsic sleep-wake regulation, resulting in unique symptoms including frequent lapses into sleep, nocturnal sleep instability, and REM sleep related manifestations such as cataplexy (abrupt loss of muscle tone triggered by emotion), sleep paralysis, and hypnagogic hallucination.

Narcolepsy is associated with a deficiency of wake-promoting orexin/hypocretin producing neurons localized in the hypothalamus, and virtually all the patients carry human leukocyte antigen (HLA)-DQB1*06:02.

**We are trying to solve the mystery of narcolepsy**
Narcolepsy is associated with a variety of physical and psychiatric comorbid conditions. Since appropriate wakefulness is essential for higher brain functions, abnormal sleep-wake regulation can lead to various associated features. Despite the progress in sleep research fields, we currently have inadequate symptom-based treatments for sleep disorders, including narcolepsy. We are trying to elucidate the pathophysiology of narcolepsy with multifaceted problems to improve the QOL of hypersomnia patients.




## Selected Publications


Natsubori A,et al (2020) "In vivo state-dependent dynamics of cellular energy status in cortical neurons". ***Communications Biol*** 3 491

Shimada M et al (2020) Metabolome analysis using cerebrospinal fluid from narcolepsy type 1 patients. ***Sleep*** zsaa095.

Shimada M et al. (2020) "Epigenome-wide association study of narcolepsy-affected lateral hypothalamic brain and overlapping DNA methylation profiles between narcolepsy and multiple sclerosis". ***Sleep*** 43(1):zsz198

Miyagawa T et al (2019) "A missense variant in PER2 is associated with delayed sleep-wake phase disorder in a Japanese population". ***J Hum Genetics***, 64(12):1219-1225

Shimada M, et al. (2018) "Epigenome-wide association study of DNA methylation in narcolepsy: an integrated genetic and epigenetic approach." ***Sleep*** 41:zsy019

Toyoda H, et al. (2017) "Narcolepsy susceptibility gene CCR3 modulates sleep-wake patterns in mice." ***PLoS ONE*** 12:e0187888

Miyagawa T, et al. (2013) "Effects of oral L- carnitine administration in narcolepsy patients: a randomized, double-blind, cross-over and placebo-controlled trial." ***PLoS ONE*** 8:e53707.

Miyagawa T, et al. (2011) "Abnormally low serum acylcarnitine levels in narcolepsy patients." ***Sleep*** 34:349-353.

Project Leader
## Kazutaka IKEDA

Kazutaka Ikeda, the head of Department of Psychiatry and Behavioral Sciences since 2015, has been the leader of the Addictive Substance Project since 2005. He graduated Faculty of Engineering, the University of Tokyo in 1989. After that, he studied under Dr. Kenji Sobue, Dr. Masayoshi Mishina and Dr. Toshiro Kumanishi as a graduate student. He received Doctor of Medical Science in 1995 from Graduate School of Medical Science, Niigata University. He started to work at RIKEN as a researcher under the supervision of Dr. Masao Ito, Dr Ryoji Yano and Dr Hiroaki Niki in 1995. He moved to Tokyo Metropolitan Institute of Psychiatry in 2000 and has leaded a project team since 2002. His current interest is to improve treatment, prevention, and understanding of addiction, pain, and developmental disorders through revealing of mechanisms underlying addictive substance effects.

# Addictive Substance

Laboratory HP: https://www.igakuken.or.jp/abuse/

## Staff

**Researchers**
Shinya KASAI
Daisuke NISHIZAWA
Masayo FUJITA
Soichiro IDE
Seii OHKA
Hiroko KOTAJIMA
Yuki MORIYA

**Research Assistants**
Yoko HAGINO
Junko HASEGAWA
Etsuko KAMEGAYA
Yukiko MATSUSHIMA
Yuki SERITA
Yuko EBATA
Kyoko NAKAYAMA

**Students**
Yuiko IKEKUBO
Yukiko OCHIAI
Yoshihisa KATO
Aimi YAMAGISHI
Yoshihiko KOSAKI
Moe SOEDA
Rie INOUE
Shoka MATSUYAMA

## Research Summary

Addiction to various substances (e.g., drugs, alcohol, and tobacco) and behaviors (e.g., internet and gambling) is a serious public health problem. The use of illegal drugs has been increasing in Japan in recent years. Thus, preventing and solving problems that are related to addiction are important.

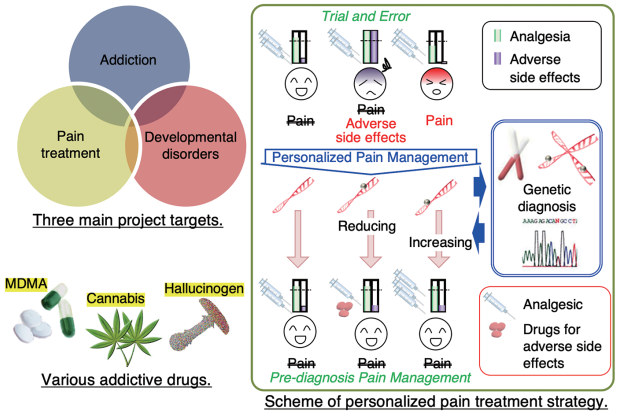
Some addictive drugs are also widely used as analgesics and for the treatment of developmental disorders. Some molecules that are involved in the actions of addictive drugs may be shared between analgesia and developmental disorders. The goals of our project are the following:

(1) Developing novel treatments for addiction and prevention. We study action mechanisms of opioids, dopamine, and hallucinogens such as phencyclidine to reveal the onset of addiction using several mouse models and behavioral pharmacological study. In parallel with the basic research, we also develop and verify a scale to addiction severity.

(2) Improving personalized pain treatment. Sensitivity of opioid analgesics is associated with polymorphisms of several genes. Based on the genome information, we develop personalized pain treatment.

(3) Developing novel treatments for developmental disorders. We mainly focus on autism and attention deficit hyperactivity disorder (ADHD). In our project, tuberous sclerosis complex 1 and 2 hetero knockout mouse and dopamine transporter knockout mouse are mainly used as models of autism and ADHD, respectively. We are finding novel treatments for autism.

Attaining these goals will make significant contributions to society. We seek to accomplish these goals by studying the actions of addictive drugs using molecular biological, behavioral pharmacological, human genomic, and clinical approaches.



Scheme of personalized pain treatment strategy.

## Selected Publications


Fujita M, et al. (2020) "Increase in excitability of hippocampal neurons during novelty-induced hyperlocomotion in dopamine-deficient mice." ***Mol. Brain.*** 13: 126.

Kotajima-Murakami H, et al. (2018) "Effects of rapamycin on social interaction deficits and gene expression in mice exposed to valproic acid in utero." ***Mol. Brain*** 12:3

Sugaya N, et al. (2018) "A randomized controlled study of the effect of ifenprodil on alcohol use in patients with alcohol dependence." ***Neuropsychopharmacology Rep.*** 38(1):9-17.

Ide S and Ikeda K. (2018) "Mechanisms of the antidepressant effects of ketamine enantiomers and their metabolites. " ***Biol. Psychiatry***. 84:551-552.

Nishizawa D, et al. (2014) "Genome-wide association study identifies a potent locus associated with human opioid sensitivity." ***Mol. Psychiatry***. 19: 55-62.

Sato A, et al. (2012) "Rapamycin reverses impaired social interaction in mouse models of tuberous sclerosis complex" ***Nat. Commun.*** 3: 1292.

Laboratory Head
## Kanato YAMAGATA

Kanato Yamagata graduated from Kanazawa University School of Medicine and received M.D. in 1985. He was engaged in the research on the photoreceptor-specific protein at Cancer Research Institute in Kanazawa University as a graduate student. After receipt of Ph.D. in 1989, he moved to the Johns Hopkins University and started to work on "activity-regulated gene expression in the brain" under the supervision of Prof. Daniel Nathans. After coming back to Japan, he continued to investigate the roles of these gene products in synaptic plasticity and has clarified most gene products are involved in the pathogenesis of various brain diseases. His current interest is a development of new therapeutics for developmental disorders accompanied intellectual disability and autism.

# Synaptic Plasticity

Laboratory HP: https://www.igakuken.or.jp/plasticity/

## Staff

**Researchers**
Tadayuki SHIMADA
Chihiro HISATSUNE
Hiroko SUGIURA
Keiko MORIYA-ITO

**Research Assistants**
Fumie MASUDA
Tomoko KAWANO

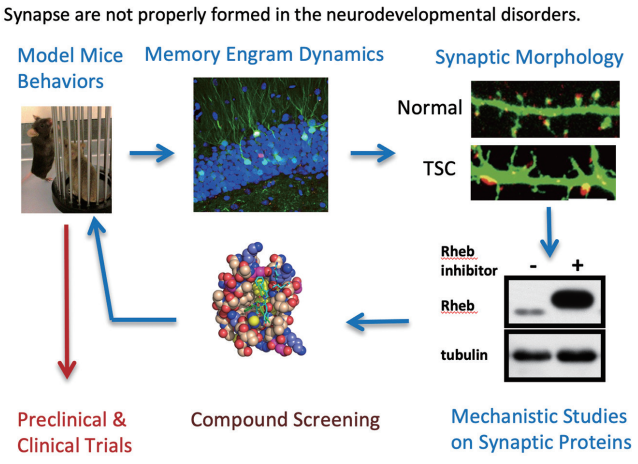
**Students**
Hirono KOBAYASHI
Yuka KAWAMOTO
Shiho SAKAI

## Research Summary

We study the molecular basis of activity-dependent synaptic plasticity. In particular, we have cloned a set of immediate early genes (IEGs) that are rapidly transcribed in neurons involved in information processing, and that are essential for long term memory. IEG proteins can directly modify synapses and provide insight into cellular mechanisms that support synaptic plasticity. Furthermore, these IEG products have been shown to be involved in developmental brain disorders, including refractory epilepsy, intellectual disability and/or autism.

For example, COX-2 and mPGES-1 are prostaglandin synthases that exacerbate neuronal cell death after seizures, leading to intractable epilepsy. Arcadlin is a protocadherin that induces spine shrinkages after seizures, resulting in developmental delay or amnesia. Rheb regulates excitatory synapse formation via syntenin. Constitutive activation of Rheb causes TSC (tuberous sclerosis complex), which is accompanied by epilepsy, mental retardation and autism. Finally, neuritin is a secreted or membrane-anchored protein and induces neurite branching. It may be involved in temporal lobe epilepsy. Thus, analysis of rapid de novo transcription provides novel insights into the cellular and neural network basis of behavioral plasticity.

We are also exploring the possibility that these IEG products could be therapeutic targets for developmental disorders. We are making genetic mouse models of developmental disorders and are testing the effects of several drug inhibitors against IEGs.




## Selected Publications


Takeuchi C, et al. (2020) "Dendritic Spine Density is Increased in Arcadlin-deleted Mouse Hippocampus." ***Neuroscience*** 442:296-310.

Shimada T, et al. (2019) "Syntenin: PDZ Protein Regulating Signaling Pathways and Cellular Functions " ***Int. J. Mol. Sci.*** 20(17):4171.

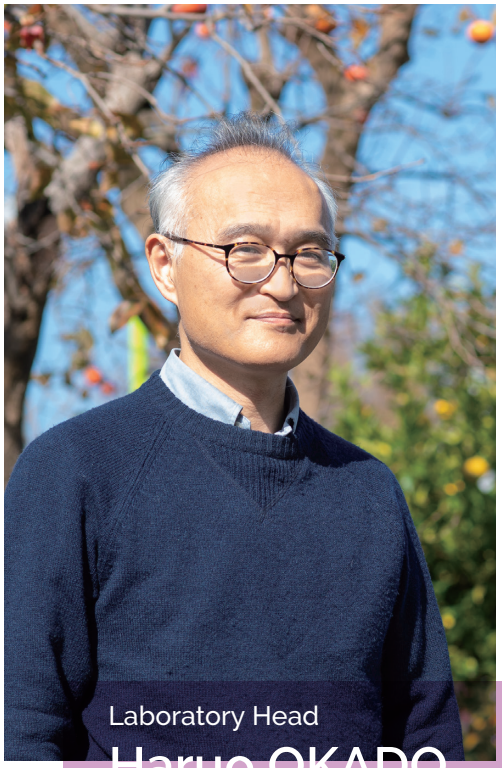
Shimada T and Yamagata K. (2018) 442:296-310. "Pentylenetetrazole-Induced Kindling Mouse Model." ***JoVE*** (136).

Shimada T, et al. (2016) "Neuritin Mediates Activity-Dependent Axonal Branch Formation in Part via FGF Signaling." ***J. Neurosci.*** 36(16):4534-4548.

Sugiura H, et al. (2015) "Rheb activation disrupts spine synapse formation through accumulation of syntenin in tuberous sclerosis complex." ***Nat. Commun.*** 6:6842.

Masui K, et al. (2015) "Glucose-dependent acetylation of Rictor promotes targeted cancer therapy resistance." ***Proc. Natl. Acad. Sci. USA*** 112(30):9406-9411.

Yasuda S, et al. (2014) "Activation of Rheb, but not of mTORC1, impairs spine synapse morphogenesis in tuberous sclerosis complex." ***Sci. Rep.*** 4:5155.



Laboratory Head
## Haruo OKADO

Haruo Okado, the laboratory head of Neural Development Laboratory. After graduation from medical school of University of Tokyo in 1986, he conducted developmental biology using ascidian embryos under Dr. Kunitaro Takahashi at Brain institute of Univ. of Tokyo as a graduate student, and received Ph.D in 1991. After abroad study about regulatory expression of glutamate receptors under Dr. Stephan Heinemann in the Salk Biological Institute, he has been working how brain is developing and function using mice in the Tokyo metropolitan institute for neurosciences, and from 2011 in Tokyo metropolitan institute of medical science. In particular, he focus on the function of the transcription repressor RP58 on brain development and function. In recent, he and colleagues are interested in the interaction of genetic factor and environmental factor in the development of the brain.

# Neural Development

Laboratory HP: https://www.igakuken.or.jp/differentiation/

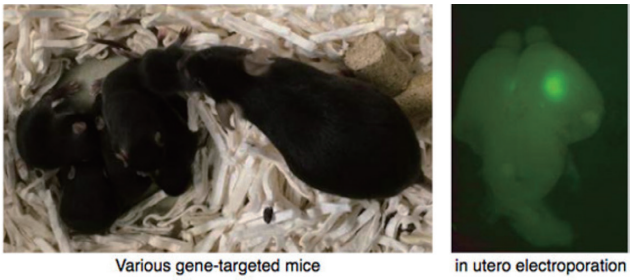
## Staff

**Researchers**
Shinobu HIRAI
Tomoko TANAKA

**Research Assistants**
Katsuko TAKASAWA
Hiroko SHIMBO
Fumika KAWANO

## Research Summary

Various factors control differentiation of neural stem cells and survival of the resulting neurons, and aberrancy in these processes are associated with intellectual disability, age-related brain disorders, and brain tumors. We aim to elucidate the mechanisms of development and maintenance of brain functions, ultimately to develop methods for the prevention and treatment of intractable cranial nerve diseases.



Various gene-targeted mice　　in utero electroporation

Our major projects include

1. Understanding how the transcriptional repressor, RP58, regulates brain development and maintenance. From several findings, I propose three hypotheses: first, artificial or evolutional regulation of RP58 regulation can increases neurons in number by promoting the formation of the outer SVZ. Second, a decrease in RP58 expression in aging contributes to brain dysfunction in aging. Third, the quantity of RP58 is involved in the recognition function and development of glioma, and artificial regulation of RP58 can control and useful treatment for cognitive dysfunction and glioma.

2. Altering the nutritional environmental factors to manipulate brain development and functions. We demonstrate that a high-sucrose diet during adolescence induces psychosis-related phenotypes, such as hyperactivity, poor working memory, impaired sensory gating, and disrupted interneuron function, particularly in mice deficient for glyoxalase-1, an enzyme involved in detoxification of sucrose metabolites. Further, the high-sucrose diet induced microcapillary impairment and reduced brain glucose uptake. We proposed that psychiatric disorders are associated with microvascular brain damage, possibly due to various environmental stresses including metabolic stress.

3. Understanding the roles of environmental factors in development and aging of brain functions. We established that postnatal maternal separation facilitates the impairment of spatial cognitive function and the formation of amyloid beta plaque in Alzheimer's disease (AD) model mice, with disruption of micro-capillaries, and we verified that early-life stress constitutes a risk factor for AD. Furthermore, we found that morphological and functional changes to microglia are early symptoms in our experimental model, and suggest the possibility that impairment of the cerebral vascular system caused by interactions between microglia and vasculature induces dysfunction in the BBB, thereby facilitating the clinical condition of AD.

## Selected Publications


Okado H (2019) Regulation of brain development and brain function by the transcriptional repressor RP58. ***Brain Res.*** 1705:15-23.

Hirai S, et al. (2018) "Developmental Roles and Evolutionary Significance of AMPA-Type Glutamate Receptors." ***BioEssays.*** 2018 2018 Sep;40(9):e1800028.

Hirai S, et al. (2017) "AMPA glutamate receptors are required for sensory-organ formation and morphogenesis in the basal chordate." ***Proc. Natl. Acad. Sci. USA.*** 114: 3939-3944.

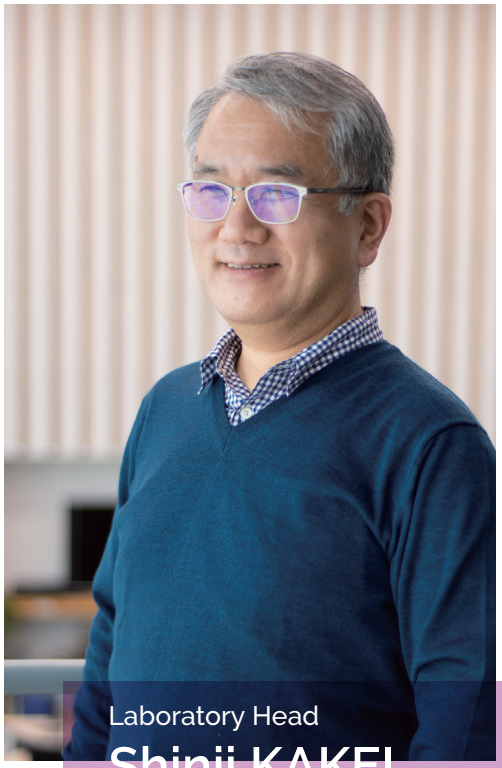
Nakajima K, et al. (2015) "Benzodiazepines induce sequelae in immature mice with inflammation-induced status epilepticus." ***Epilepsy & Behavior*** 52: 180-186.

Ohtaka-Maruyama C, et al. (2013) "RP58 regulates the multipolar-bipolar transition of newborn neurons in the developing cerebral cortex." ***Cell Rep.*** 3: 458-471.

Hirai S, et al. (2012) "RP58 controls neuron and astrocyte differentiation by downregulating the expression of Id1-4 genes in the developing cortex." ***EMBO J.*** 31: 1190-1202.

Ohtaka-Maruyama C, et al. (2012) "The 5'-flanking region of the RP58 coding sequence shows prominent promoter activity in multipolar cells in the sub- ventricular zone during corticogenesis." ***Neuroscience*** 201: 67-84.

Okado H, et al. (2009) "Transcriptional repressor RP58 is crucial for cell-division patterning and neuronal survival in the developing cortex." ***Dev. Biol.*** 331: 140-151.



Laboratory Head
## Shinji KAKEI

Dr. Kakei graduated from Tokyo Medical and Dental University, School of Medicine, to receive M.D. degree in 1986. Then, he moved on to the Ph.D. course to make physiologic and morphologic studies of the cerebro-cerebellar communication loop at a single-cell level under the supervision of Prof. Yoshikazu Shinoda. In 1996, he moved to the United States to be a postdoc in the laboratory of Prof. Peter L. Strick at State University of New York. There, he designed a novel experimental paradigm to dissociate intrinsic (i.e., muscle and joint) and extrinsic (i.e., spatial) coordinate frames for neuron activities in behaving monkeys. They published a series of influential papers that outlined sensorimotor transformation in cortical motor areas (Kakei et al. Science, 1999; Nat Neurosci, 2001, Neurosci Res 2003). After returning to Japan, he first set up his lab at Tohoku University to study information processing in the cerebro-cerebellar communication loops. More recently, he is trying to integrate neuron recording studies in animals and movement analysis in patients with neurological disorders aiming at a synergistic effect.

# Movement Disorders

Laboratory HP: https://www.igakuken.or.jp/motor-control/

## Staff

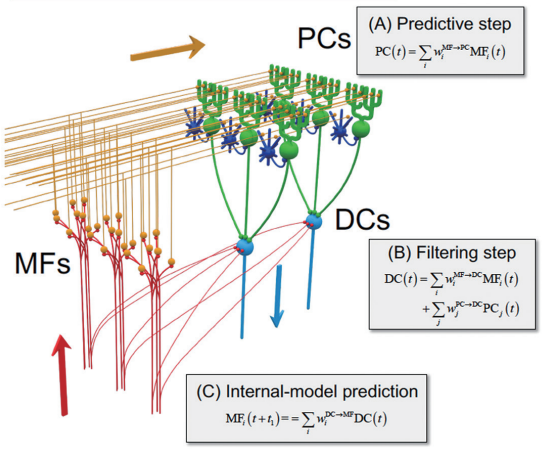
**Researchers**
Kyuengbo MIN
Takahiro ISHIKAWA
Takeru HONDA

**Students**
Masaya WATANABE

## Research Summary

We try to understand how the brain controls our movements in the real world. We study the process of action generation at a single neuron level using animal models to understand how movements are processed in the brain. We also study actions of healthy people, as well as those with neurological disorders, such as cerebellar disorders, Parkinson's disease, or strokes. We look for building-blocks of motor control with multidisciplinary approaches. Our tools include various neurophysiological recording techniques (single unit recording, electromyography (EMG) and electro-encephalography (EEG)), brain stimulation, neuroimaging, analysis of movement kinematics and a large-scale modeling. We have two long-term goals: 1) to understand the basic function of the motor structures of the brain including the cerebellum, the basal ganglia, and the motor cortex; and 2) to understand how our brain controls our movements on the basis of the findings in 1).

**The Cerebellum as a Kalman Filter**




This figure summarizes our cutting edge finding that the cerebellum function as a Kalman filter. MF: mossy fiber (red), PC: Purkinje cell (green), DC: dentate cell (light blue). Granule cells (orange) and inhibitory interneurons (blue) are included to show the basic structure of the cerebellar neuron circuitry. Three stages of linear computation: (A) Predictive step, (B) Filtering step, (C) Internal model prediction, are accompanied with the three types of computation of Kalman filter.
(Tanaka, Ishikawa and Kakei Cerebellum 2019).

## Selected Publications


Tanaka H, et al. (2020) "The Cerebro-Cerebellum as a Locus of Forward Model: A Review." ***Front Syst Neurosci.*** 14:19. doi:10.3389/fnsys.2020.00019.

Honda et al. (2020) "Assessment and rating of motor cerebellar ataxias with the Kinect v2 depth sensor: Extending our appraisal." ***Front Neurol.*** 2020 11:179. doi: 10.3389/fneur.2020.00179.

Kakei S, et al. (2019) "Contribution of the Cerebellum to Predictive Motor Control and Its Evaluation in Ataxic Patients." ***Front Hum Neurosci.*** 13:216.

Tanaka H, et al. (2019) "Neural Evidence of the Cerebellum as a State Predictor." ***Cerebellum.*** 18(3):349-371.

Tomatsu S, et al. (2016) "Information processing in the hemisphere of the cerebellar cortrexfor motor control of wrist movement." ***J. Neurophysiol.*** 115:255-270.

Ishikawa T, et al. (2016) "The cerebro-cerebellum:Could it be loci of forwardmodels?" ***Neurosci. Res.*** 104:72-79.

Lee J, et al. (2015) "A new method for functionalevaluation of motor commands inpatients with cerebellar ataxia." ***PLoS One*** 10:e0132983.

Ishikawa T, et al. (2014) "Releasing dentatenucleus cells from Purkinje cellinhibition generates outputs fromthe cerebrocerebellum." ***PLoS One*** 9:e108774 (pp.1-16).