TMiMS

Annual Reports 2023

Contents

Message from the Chairperson

Chairperson
Keiji TANAKA

Tokyo is the political, economic, and cultural center of Japan. Thus, improving the health and welfare of the residents of Tokyo is an important step toward building a prosperous future for Japan. The mission of the Tokyo Metropolitan Institute of Medical Science (TMIMS) is to promote research in the life and medical sciences to improve the lives of the citizens of Tokyo. It is well-known that Japan has the most rapidly aging society in the world. Tokyo, which reflects Japan itself, is undergoing a steady increase in cancers, infectious diseases, lifestyle-related illnesses, neural and mental disorders, and various other health problems. Naturally, curing all of these diseases is a common goal for all humankind, and considerable efforts have been made at the national level. However, it is also essential for the Tokyo Metropolitan Government to take the initiative in this endeavor. Tokyo has numerous problems unique to megacities. For example, high population densities can contribute to social and mental disorders not commonly seen in other environments or can breed diseases that can spread explosively throughout the dense population. TMIMS has been actively working on these and other important problems, addressing health-related issues with the aim of protecting the health of all Tokyo citizens.

From early 2020 to the spring of 2023, the highly contagious COVID-19 disease spread throughout the world causing unprecedented damage at all levels of society. Combatting this disease became a top priority. Four years ago, we set up a "Coronavirus Countermeasures Special Team," and in cooperation with the Tokyo Metropolitan Government, we have been making every effort to develop effective strategies to eliminate this disease. Particularly, epidemiological studies such as monitoring of the resident population in the major downtown areas of Tokyo have contributed greatly to the Tokyo Metropolitan Government's countermeasures against COVID-19 disease, and we have also pursued our own highly original vaccine development research against SARS-CoV-2. Today the number of people infected with SARS-CoV-2 has dropped dramatically, the threat of COVID-19 disease has greatly diminished, and social and economic activities have recovered greatly. For the past four years, many academic interactions have been through web conferences, but now they are being transformed back to on-site meetings. However, although it has decreased dramatically, the spread of COVID-19 is still on-going, and TMIMS will need to continue fundamental research in order to develop effective countermeasures to combat the disease in 2024.

Throughout history there has always been an ongoing struggle between humans and diseases. In the 21st century, globalization and international human interactions have greatly accelerated academic development and the elucidation and dissemination of new knowledge. However, globalization has also allowed the spread of infectious diseases around the world. Thus, it is critically important for people in the modern world to have effective strategies for preventing or minimizing the spread of infectious diseases and developing effective cures without curtailing international interactions. This has generated a strong social demand for medical advances and solutions. With this goal in mind, scientists at TMIMS will continue to dedicate themselves to advancing basic and clinical research.

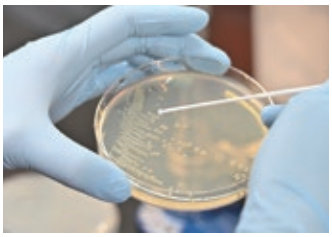
I am of the opinion that scientific research is a symbol of culture. A society cannot be considered cultured if it has no interest and knowledge of science and research. Accordingly, TMIMS aims to be acclaimed both academically and culturally for the knowledge and wisdom of its excellent researchers. Our goal is to become a symbol of the culture of Tokyo, the foremost megalopolis in the world. Academic research is often roughly divided into top-down, exit-oriented, applied research (of immediate use), and bottom-up, future-oriented basic research (seemingly not of immediate use). Balancing these two research strategies, TMIMS endeavors to operate in a flexible manner in order to achieve additive and synergistic effects. Top-down and bottom-up research strategies are not incompatible, but can work in a cooperative and harmonious manner. Throughout the history of science, we can find numerous examples of seemingly useless research suddenly becoming useful, resulting in great service to society.

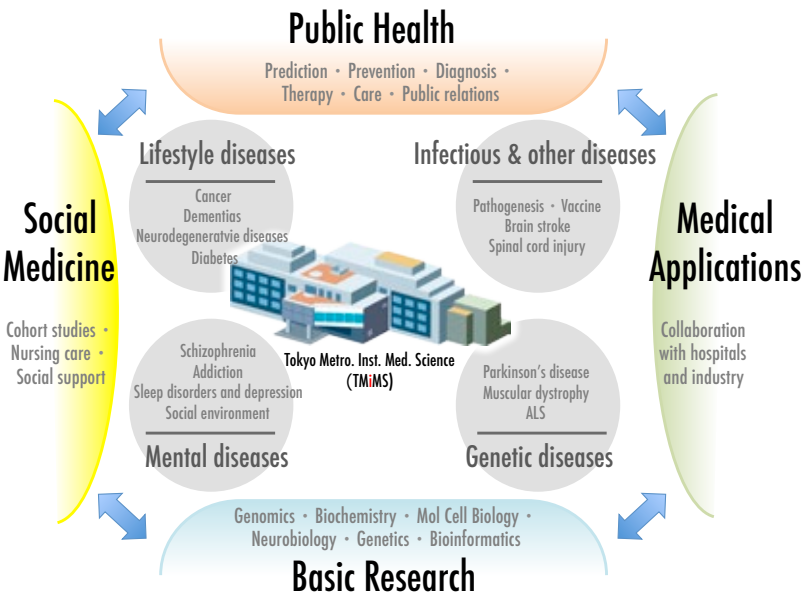
Our medical researchers are energetically pursuing their research to develop preventive medicine and new therapeutic methods to protect citizens' health. During this process, TMIMS also plays an important role in educating young researchers who will continue to develop human knowledge and contribute to social prosperity. All staff members of TMIMS are working on research in the life sciences, ranging from fundamental to practical, using cutting-edge technologies to achieve their goals.

We are working to advance and enrich TMIMS' research power to make it a world-premiere research institute that provides wide-ranging contributions to society. To this end, the entire staff of TMIMS strives to help pursue incomparable fundamental research and pass the benefits of this research on to society. At the same time, we are continuing to recruit and educate talented people to increase our momentum. Thank you for your support, which is indispensable for the further development of TMIMS.

Our Mission

The mission of TMIMS is to pursue research that will provide solutions for health-related problems commonly observed in large urban areas and developed countries. We pursue basic research to understand molecular and cellular mechanisms of biological pathways and disease pathology, and collaborate with municipal hospitals and clinics to translate basic research findings into technologies that can be used to predict, prevent, and treat health problems. Toward this goal, we try to identify causes of unsolved diseases in order to develop novel drugs and therapies. We study mental diseases to find effective treatment, and investigate social factors that affect mental health of people in urban area. We also contribute to improved care for those suffering from incurable diseases such as ALS to better patients' quality of life.





Message from the Director: TMIMS 2023

Director
Hisao MASAI

Despite the hope for peace in the world, 2023 witnessed another war that brought devastation to people hoping for a happy life with their loved ones. It was tragic to see so many innocent people including small children dying every day. For us living so far away from the wars, it is easy to bury our heads in the sands and pretend all this is occurring in another world, but these tragedies are happening in real time on our planet and we must all take responsibility and work towards peace and the alleviation of suffering.

In 2023, the COVID pandemic abated and life has somewhat returned to normal. Face-to-face meetings have resumed, and parties are back. We are very happy to be able to attend real meetings where we can network, have in-person discussions, and develop new collaborations.

TMIMS 2023

The Center for Medical Research Cooperation made great strides in promoting collaborative research with Tokyo Metropolitan hospitals. It developed a close association with The Tokyo Metropolitan Hospital Organization, which was established in July 2022, and embarked on new collaborative projects with hospitals. This year, 9 joint research proposals were supported by our seeds-exploring and joint research programs.

Three special projects (liver cirrhosis, neural prosthesis technology and vaccine development) endorsed by the Tokyo Metropolitan Government were conducted. Three programs commissioned by the Tokyo Metropolitan Government (dementia care, child abuse prevention and visiting nurse training for patients with intractable diseases) were also conducted and contributed to the policy making by the government.

There were two TMiMS International Symposia in 2023. The 24th TMIMS International Symposium, "Early Detection and Social Intervention for Psychosis and Suicide," was organized by Dr. Atsushi Nishida and held on March 17, 2023, and the 25th TMIMS International Symposium, "Cells and Chromosomes," was organized by me and held on October 16, 2023. Both were held in-person, as opposed to online, and and included three and six invited, foreign speakers. The presentations were followed by active discussions. Other public relation-related activities conducted in 2023 are listed on page 54.

Two years ago, we created a program for inviting prominent foreign scientists to visit and work at the institute for up to one year. The program started operating in 2022, and this year, four scientists, Professor Krassimir Yankulov (University of Guelph, Canada), Professor Steve Perlmutter (Medical School, University of Washington, USA), Professor Robert Barry (Massachusetts General Hospital and Harvard Medical School, USA), and Dr. Sung Q Lee (Electronics and Telecommunications Research Institute, South Korea) worked and collaborated with us through this program.

Research achievements from our institute in 2023

We are currently in the fourth year of the 4th project term, and have published many papers in 2023. Most notably, Dr. Tomoyuki Miyashita and Dr. Minoru Saitoe in the Learning and Memory Project discovered that glial cells actively transmit sensory information to higher brain regions in the fruitfly. This transmission is necessary for learning and memory, and currently Dr. Miyashita is studying whether similar types of transmission occur in mammals. This study reveals novel roles of glia in information transfer and was published in *Science.* Dr. Akiyo Natsubori from the Sleep Disorders Project found that when animals awaken from sleep, serotonergic neurons in the dorsal raphe nucleus induce cortical astrocytes to release more lactate, thus increasing ATP production in cortical pyramidal neurons. In general, neurons use more energy when an animal is awake compared to when it is asleep, and Dr. Natsubori's work, published in *iScience*, describes a mechanism through which neurons obtain more energy when animals awaken. Dr.Tetsuya Hirabayashi from the Laboratory of Biomembrane identified a novel metabolic pathway for the production of methyl donors from phosphatidylcholine in the liver. Methyl insufficiency in mice lacking enzymes involved in the breakdown of hepatic phosphatidylcholine causes various adverse effects including growth retardation, reduced weight, hypoglycemia, hypolipidemia, increased energy consumption and altered histone/DNA methylation, demonstrating the functional importance of this pathway in the availability of methyl

groups. This work was published in Cell Reports. Dr. Daisuke Yamane from the Viral Infection Control Project discovered a novel biochemical mechanism controlling activity of interferon regulatory factor 1 (IRF1), a critical factor in immunity. He found that CSNK2B, a regulatory subunit of casein kinase 2, binds directly with IRF1 to regulate downstream effector genes that inhibit replication of pathogenic hepatitis viruses and flaviviruses (reported in *Nucleic Acids Research*). Kazuya Toriumi in the Schizophrenia Research Project identified a novel precursor of pentosidine, an advanced glycation end-product associated with Schizophrenia. Identification of this precursor, glucuronic acid, suggests novel causes and possible treatments for Schizophrenia and was published in *Redox Biology*. Dr. Masato Hasegawa of the Dementia Research Project has been studying the connection between amyloid filaments and age-dependent neurodegenerative diseases and contributed to a report in Nature on the discovery on age-dependent formation of novel amyloid filaments of a protein, TMEM106B. Other interesting papers published this year are listed on our Home Page (https://www.igakuken.or.jp/topics/topics2022.html).

Science in 2023

The fight against COVID-19 has continued for over four years and we are finally seeing an exit from the long depressing days of isolation, no contact, no direct, face-to-face communication and no parties! At the onset of the outbreak, the immediate need for vaccines was obvious, but nobody expected that people would begin to be vaccinated a year later. This was made possible by the application of mRNA therapy technology. Although the idea for this type of therapy was there as early as 1980s, its application was hampered by strong inflammatory responses by injected mRNAs. Katalin Karikó noted that, compared to mRNAs, tRNAs do not cause significant inflammation when injected. What characterizes tRNAs is the presence of varieties of modified bases. This gave Karikó the idea that converting mRNAs to be more tRNA-like might help reduce inflammatory responses. She introduced a base modification, pseudo uridine, into an injected mRNA and observed very little inflammation. Later she found that the modified mRNA produced much more protein compared to normal mRNA. These discoveries eliminated the obstacles to using mRNA for therapy. In 2020, this technology was used to develop vaccines against SARS-CoV-2, and world-wide vaccination against COVID-19 in less than a year saved millions of lives and prevented serious cases for many more. The 2023 Nobel Prize in Physiology or Medicine was awarded to Katalin Karikó as well as to Drew Weissman for their discoveries concerning nucleoside base modifications that enabled the development of effective mRNA vaccines against COVID-19.

I was deeply moved and amazed by the speed with which goals were set and achieved in the development of these vaccines. Many factors contributed to this success. Among all, global collaboration among the scientific community, pharmaceutical companies, and governments was key. The urgency of the pandemic prompted governments and organizations to allocate significant funding and resources to vaccine development. Regulatory agencies like the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) implemented expedited review processes for COVID-19 vaccines, which helped in accelerating the approval and distribution of vaccines. The organized effort through the collaboration of academic, private, and governmental sections and streamlined efforts with goal-oriented, rapid decision-making facilitated the process.

Dream for Science

While I was writing this article, the news came out that two-way star Shohei Ohtani has agreed to a record $700 million (\101 billion), 10-year contract with the Los Angeles Dodgers. This is certainly a genuine dream-come-true story. It feels like ages ago, but in March 2023, the entire country was crazy about the WBC (World Baseball Classic). All the games gave so much joy and excitement to children and adults alike. When big baseball stars, like Nomo, Matsui, Ichiro and Ohtani, left the Japanese Baseball League and went to Major Baseball League, baseball critiques here lamented the loss of quality players and worried about the decline of the JBL. However, the outcome was the completely opposite. Looking at Nomo and Matsui as models, children strove to become star baseball players, and talented athletes continued to emerge from the JBL to make their own dreams come true.

We need similar dreams in Science. The lack of face-to-face communication during the COVID-19 pandemic deprived teachers and professors of the opportunity of passing on their dreams to children and students. When Hayabusa returned to Earth with samples collected from the surface of the asteroid, Itokawa, many, including children, were fascinated with space, asteroids, and the long and lonely journey that Hayabusa had taken. This successful 1st mission was followed by the Hayabusa2, which landed on the asteroid, Ryugu, and again returned successfully with many more samples. The enthusiasm in Japan was so great that many people applied during recruitment of astronauts, and the chance of passing the screening was one out of 2000.

How about our field? Students are not very inclined to follow the academic path in Japan, seeing their seniors who are struggling in renewing their positions which last only for 5 years. They do not see a bright future or "dream" in staying in academia. We need to inspire young students and convince them that excitement in Science is something that they can devote your life to and succeed at.

Outlook for 2024

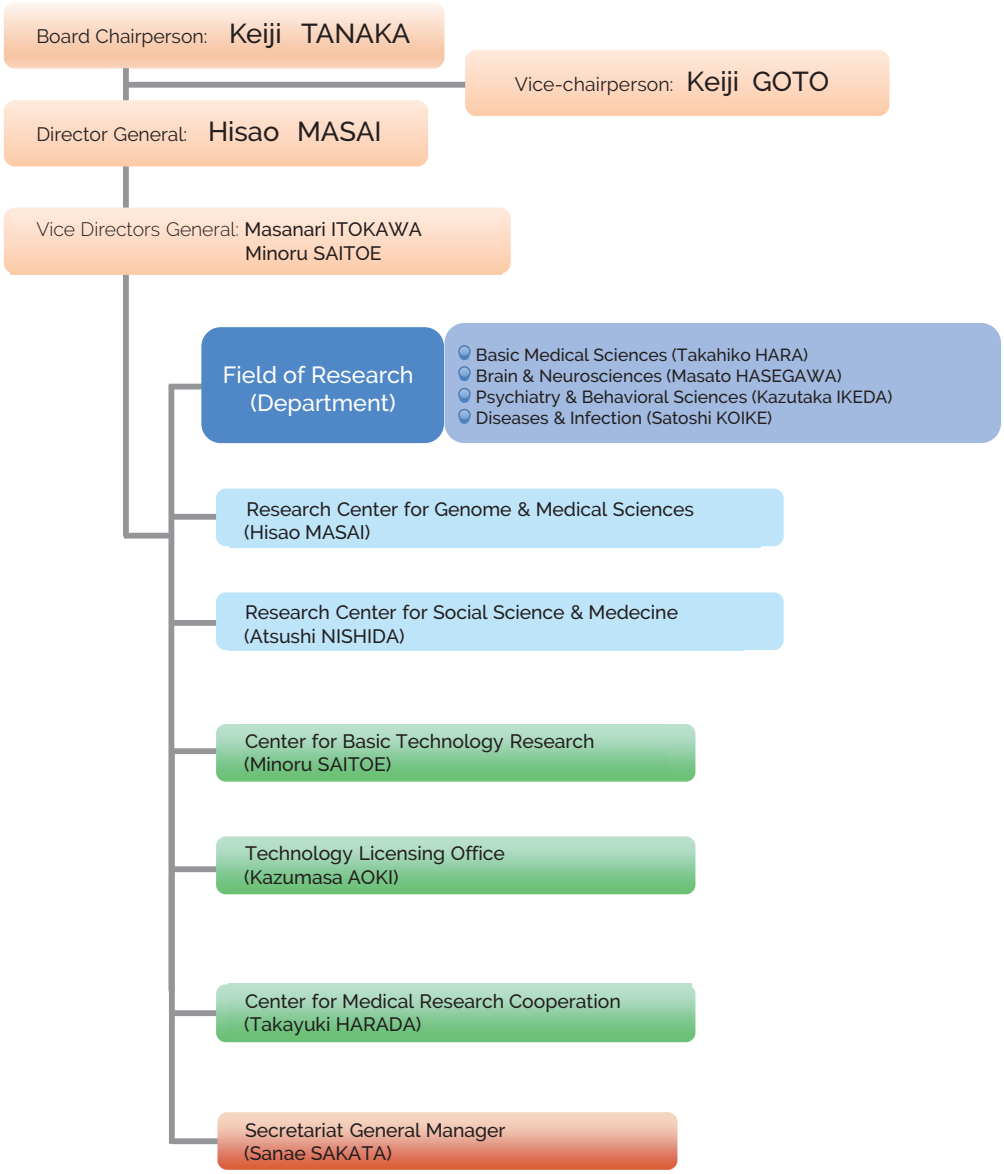
In 2024, we will be in the final year of the 4th term of project research. Each project is expected to complete and summarize its progress. TMiMS, established by the merger of three medical institutions, each specializing in different branches of medical research, is unique in its potential to conduct a wide range of medical research aimed ultimately at developing new treatments for diseases including cancers, neurological disorders, neurodegenerative diseases, infectious diseases, and mental diseases. We have a strong background in basic medical research and aim to elucidate the mechanisms of various cellular operations including protein metabolism, genome maintenance, brain functions, circadian rhythms/aging, memory, and gene editing, at the molecular level. We strive to understand disease mechanisms for neurodegeneration, sleep disorders, addiction and mental diseases, and viral infections. We also use various organisms and develop animal models for studies of disease mechanisms and treatment. We collaborate with hospitals to expand our studies to humans. For an example, we are trying to restore lost neural connections using ANCs (artificial neuronal connections). Furthermore, we study social and economic factors that may affect the health of individuals within a society. The goal of our studies is to develop novel therapies which will benefit humankind and to expand human knowledge. Our results could also aid in policy-making by the Tokyo Metropolitan Government. Each project is expected to make unique and innovative discoveries in their fields and make joint efforts with other researchers in the institute to explore new horizons in medical research.

Wishes for 2024

I proposed "Sharing," "Synergy," and "Internationalization" as keywords at the start of my term as director. Twelve years after our founding, we have made much progress in "Sharing" and "Internationalization". With effective and unique collaborations within the institute as well as with Tokyo Metropolitan hospitals, more "Synergy" will be created, facilitating the development of truly unprecedented medical research. In 2024, with the end of the pandemic, I expect enhanced constructive interactions among the scientists of the institute and hope that our institute will be a place where everyone works in full devotion to research with daily excitement and joy.

The world witnessed many tragedies and atrocities in 2023. At present, there is no sign of a cease-fire in the Ukrainan-Russian or the Israeli-Palestinian conflicts. Many innocent people are dying every day. I can only pray that the brutal wars will come to an end very soon and people suffering will be able to live in a warm, safe, and peaceful places with their loved ones.

Organizational Chart



Our People at a Glance

Position	Number
Researchers	141
Postdoctoral Fellows	55
Students	149
Visiting Scientists	138
Guest Scientists	146
Administrative Staffs	34
Total	663

February 1, 2024

Meet Our Scientists!

Meet Our Scientists!

Our experiences get stored in our brains as memories and these experiences and corresponding mold our personalities to make us who we are. Thus, to understand who we are, we need to understand how memories are formed and retained in the brain. Tomoyuki Miyashita, in the Learning and Memory Project, is working to understand learning and memory using the fruitfly, *Drosophila melanogaster*. He trains *Drosophila* to learn to associate an odor with pain by exposing them to an odor and, at the same time, electrically shocking them. He knows that flies learn this association because they actively run away from the odor after training. Learning and memory of this association occur in a region of the fly brain called the mushroom bodies. While the neuronal pathways and neurotransmitters that transmit odor information to the mushroom bodies are known, the pathways and transmitters that convey electrical shock information have been unclear. Recently, Tomoyuki found that shock information is conveyed to the mushroom bodies through glial cells, instead of neurons, using the transmitter, glutamate. This work was published in Science in an article entitled, "Glia transmit negative valence information during aversive learning in *Drosophila*." We spoke to him about this work.

Tomoyuki Miyashita

What was the rationale behind this work?

In order to understand memory formation, we need to understand how pain information is conveyed to the mushroom bodies. Previously, people proposed that this information is conveyed by dopaminergic neurons, which release dopamine onto mushroom body neurons. But dopamine seems to be a more complex transmitter involved in synaptic and neuronal plasticity instead of simply conveying sensory information. More recent work from our lab indicated that glutamate may convey this information rather than dopamine. I wanted to prove this and also identify the cells that release glutamate onto mushroom body neurons. There were very few glutamatergic neurons known to synapse onto the mushroom bodies, so I started to look for unidentified cells that could release glutamate onto the mushroom bodies. Surprisingly, I found that glial cells, which have traditionally been thought of as support cells for neurons, could release glutamate. I then showed that inhibiting glutamate release from these glial cells prevented transmission of shock information to the mushroom bodies, while artificially inducing glutamate release from glia could mimic the effects of electrical shock during training.

Why was this result so surprising?

Neurons have always been thought of as the cells that rapidly transmit information throughout the nervous system. Glia were either thought of as support cells that provided neurons with energy, or as modulatory cells that allowed neurons to work more efficiently or modified the signaling of neurons by regulating neurotransmitter reuptake. Glia were not thought of as cells that directly or rapidly transmitted information. In fact, it was even

debated whether vesicular release of transmitters occurred from glia. Our work identified a new aspect of glia that wasn't previously known.

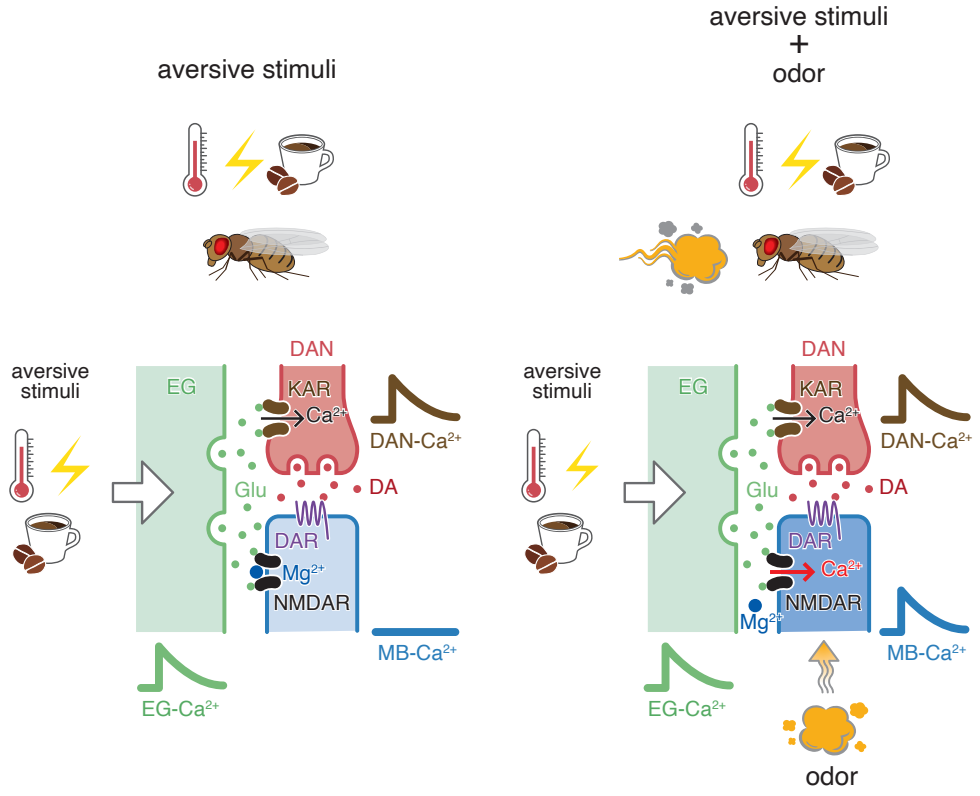
Why do you think shock information might be transmitted by glia instead of neurons?

A traditional neuronal synapse involves release of neurotransmitters from a specific presynaptic neuron to a specific post-synaptic neuron. In other words, these connections are one-to-one. A particular neuron may synapse onto many different neurons by forming many different synapses, but each synapse is one-to-one. However, there are thousands of different mushroom body neurons that respond to many different odors. Pain information needs to be sent to all of these neurons since flies can form associations between different odors and pain depending on what odor is used during training. The type of glia that releases glutamate and conveys shock information is called ensheathing glia. Ensheathing glia surround or ensheath different mushroom body compartments. My data suggest that when flies are shocked, ensheathing glia release glutamate into specific mushroom body compartments. Glutamate diffuses throughout a compartment binding to a type of glutamate receptor called NMDA receptors on all neuronal axons within a compartment. This type of volume release may be more efficient when conveying information to large numbers of neurons than traditional one-to-one synapses.

If glutamate is released onto many different neurons, how can flies learn to run away from one specific odor?

Even though glutamate binds to NMDA receptors throughout a mushroom body compartment, glutamate binding by itself isn't able to activate NMDA receptors. NMDA receptors are called coincidence detectors because they require two different stimuli in order to become active, glutamate binding and post-synaptic depolarization. Post-synaptic depolarization occurs upon odor exposure in specific odor-responsive mushroom body neurons. So, flies learn to run away from an odor if it is paired with electrical shocks. In the brain, odor exposure causes depolarization in specific mushroom body neurons that recognize the odor. If flies are shocked at the same time, NMDA receptors become active specifically in these odor-responsive neurons. This specificity is important for forming odor-specific memories.

Written by Jun Horiuchi



Ensheathing glia transmit aversive information. Aversive stimuli induce vesicular exocytosis from ensheathing glia (EG) and release of glutamate (Glu) onto kainate receptors (KAR) on dopaminergic neurons (DANs) and NMDA receptors (NMDARs) on mushroom body (MB) neurons. When aversive stimuli are unpaired, Mg^{2+} block prevents Ca^{2+} influx (left). When paired with odors, odor-dependent depolarization removes Mg^{2+} block allowing Ca^{2+} influx into appropriate MB neurons (right).

Meet Our Scientists!

We spend roughly one third of our lives asleep. Not only that, we also have to sleep regularly, alternating between sleep and wake cycles every day. Why do we need to sleep? That is the question that drives Akiyo Natsubori in the Sleep Disorders Project. Recently, she found that an excitatory neurotransmitter, serotonin, which is involved in arousal and awakening from sleep, also signals astrocytes, support cells in the brain, to provide fuel to neurons to generate the increased energy used during wakefulness. This work was published in iScience in an article entitled, "Serotonergic neurons control cortical neuronal intracellular energy dynamics by modulating astrocyte-neuron lactate shuttle." We spoke to her about her work.

Akiyo Natsubori

How did you first become interested in research?
I've always been interested in the human brain and consciousness. My curiosity about sleep stemmed naturally from this since sleep is a state when we lose consciousness. As a high school student, I wondered why we have sleep-wake cycles. What happens to the brain when we transit between sleep and wake states? These questions led me to pursue a career as a research scientist.

What was the rationale for your recent iScience paper?
Neurons are more active when we are awake compared to when we are asleep. That means that we use more energy when we are awake. But curiously, when I measured amounts of ATP, which is the principal energy source used in neurons, I found that amounts of ATP were higher in the cortex of awake animals compared to animals that were asleep. That means that there must be a tremendous increase in ATP production when animals awaken, which increases the amount of energy available when animals are awake. I wanted to find the mechanism behind this wake-dependent increase in ATP.

How did you do that?

There are several stimulatory neuronal systems that regulate wakefulness in animals. These systems use neurotransmitters such as noradrenalin, serotonin, histamine, or dopamine. When we activate these systems, they increase arousal in the animal and causes sleeping animals to awaken. I hypothesized that these systems may also regulate ATP production, and I tested this using serotonergic neurons. I first used optogenetics to activate serotonergic neurons in the dorsal raphe nucleus, which form extensive axonal connections to neurons in the cerebral cortex and regulate arousal and wakefulness. And I found that stimulation of these neurons increases amounts of ATP in cortical neurons. We also did the reverse experiment of inhibiting activity of these neurons using chemogenetic methods and found that less ATP was produced when these animals woke up.

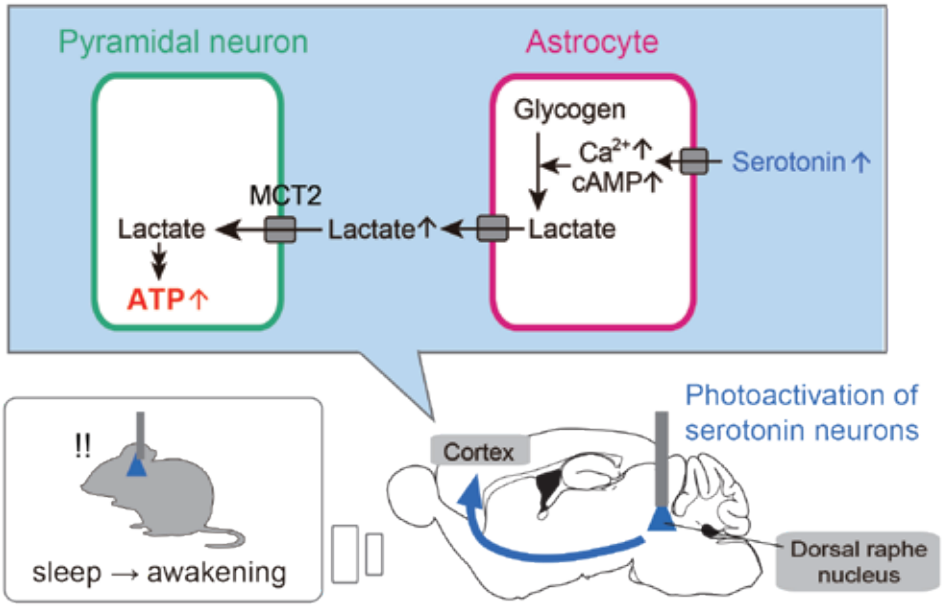
Is the neural pathway that regulates ATP production the same as the pathway that regulates wakefulness?

Serotonin acts on cortical neurons to regulate wakefulness, but it acts on astrocytes, which are cells that support neurons, to regulate ATP production, so they are different pathways. We found that serotonin induces Ca^{2+} and cAMP surges in astrocytes and causes them to produce lactate. Lactate is an energy source that neurons use to produce ATP, and lactate produced in astrocytes is transported to neurons through an astrocyte-neuron lactate shuttle.

What are the implications of this work?

Although serotonin regulates both wakefulness and energy production, it does these through different cellular and molecular pathways. This suggests that there may be different states of wakefulness. For example, you might be awake with lots of energy available, or you might be awake with low energy. We usually think of being awake as an on/off switch. You are either awake or asleep. But our work suggests that multiple different pathways might contribute to the fully awakened state. Interestingly, it's been shown that injecting ATP into the brains of mice models of depression rescues symptoms of depression. So it's intriguing to consider that decreased lactate production in astrocytes might contribute to depression, and increasing activity of the astrocyte-neuron lactate shuttle might improve symptoms of depression. These are the current questions that I find interesting.

Interviewed by Jun Horiuchi



Mechanism of regulation of cerebral energy metabolism by serotonergic neurons.

The activation of serotonergic neurons in the dorsal raphe nucleus immediately awakens animals from sleep. Simultaneously, it increases intracellular ATP levels in excitatory neurons in the cerebral cortex. The mechanism involves serotonin released in the cortex acting on astrocytes, a type of glial cell, which enhances their Ca^{2+} and cAMP activities, promoting lactate supply from astrocytes to neurons (astrocyte-neuron lactate shuttle: ANLS). This leads to rapid intracellular ATP synthesis in cortical neurons. MCT2: A lactate transporter in neurons.

Meet Our Scientists!

Schizophrenia is a mental disorder characterized by recurrent psychoses and alterations in perception, thoughts, and behaviors. While schizophrenia can be treated with antipsychotic medications, its causes are still relatively unknown. Kazuya Toriumi of the Schizophrenia Research Project is interested in identifying the molecular pathways involved in the development of schizophrenia. Previously studies from the Schizophrenia Research Project had shown that advanced glycation end products (AGEs), deleterious products formed by oxidative and carbonyl stresses, are found at high levels in a large subset of patients with schizophrenia. In particular, pentosidine, an AGE consisting of a crosslink between arginine and lysine residues in proteins, is found in high amounts in many patients with schizophrenia. Dr. Toriumi wanted to understand why pentosidine amounts increase in these patients with schizophrenia and identified glucuronic acid as a pentosidine precursor. This work will be helpful in developing more accurate animal and cell models of schizophrenia and may have positive implications in the development of novel therapies. It was published in Redox Biology in an article entitled, "Glucuronic acid is a novel source of pentosidine associated with schizophrenia." We spoke to him about his work and interest in science.

Kazuya Toriumi

How did you first become interested in research and schizophrenia?

I originally wanted to become a high school teacher, but when I pursued undergraduate research in college, I realized that I really enjoy research. Almost 1% of people are diagnosed with schizophrenia during their lifetime. My primary interest is in understanding what causes schizophrenia and helping these people. Furthermore, I am also interested in understanding how the brain works. In particular, I want to know how we sense and understand the world around us, and schizophrenia involves an alteration in the way we understand the world, so, if we can figure out what changes in schizophrenia, we will also gain an understanding of what happens in a "normal" brain.

Why did you focus on pentosidine?

Pentosidine is an advanced glycation end product or AGE, where a sugar is covalently attached to a protein. Previously, we found that high amounts of pentosidine are found in a subset of patients with schizophrenia, and we think that high pentosidine might be a cause of some types of schizophrenia. So, I wanted to know why pentosidine increases in some people. It's commonly thought that high amounts of sugar cause increases in pentosidine and other AGEs, but when we looked at patients with schizophrenia with high pentosidine, we didn't see high levels of sugars or hemoglobin A1c, which is an indicator of excess sugar in the bloodstream. This led me to hypothesize that there must be a different pathway responsible for high pentosidine. If I could find this

pathway, it would help us understand what causes some types of schizophrenia. It would also allow us to make more accurate cell and animal models of schizophrenia.

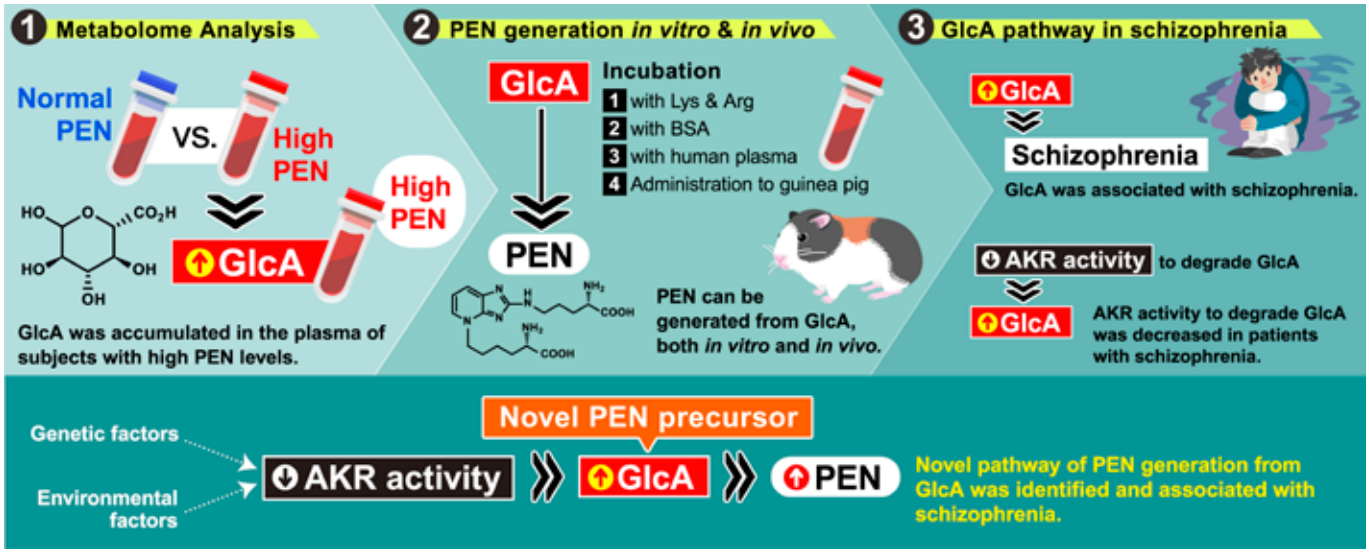
How did you identify glucuronic acid as a precursor for pentosidine?

We did metabolome analyses on patients with schizophrenia with high pentosidine and healthy controls and looked for differences in metabolites. We found that in patients with high pentosidine, there was a high amount of glucuronic acid. Pentosidine consists of a sugar bridge between lysine and arginine amino acids, so we next mixed lysine, arginine, and glucuronic acid, and we found that pentosidine is produced over time. Mixing glucuronic acid with proteins or plasma also produced pentosidine. Finally, we showed that injecting glucuronic acid into guinea pigs caused pentosidine to increase. When we looked at the correlation between high pentosidine and schizophrenia, we found that an increase of pentosidine by one standard deviation roughly doubles the chances that a person has schizophrenia. An enzyme, aldo-keto reductase or AKR breaks down glucuronic acid and we found that AKR enzymatic activity is reduced in patients with schizophrenia. So, we think that reduced AKR increases glucuronic acid, which increases pentosidine, and increases the chances of someone becoming schizophrenic.

Fascinating! What are your plans for the future?

We're planning to use this information to make more accurate cell and animal models of schizophrenia. For example, we can knock out AKR in animals and determine whether these animals display schizophrenia-like phenotypes. I don't think increasing glucuronic acid on its own is sufficient to cause schizophrenia, but I think it could be an important step. In addition, we are excited to be pursuing large-scale cohort studies with Dr. Nishida at the institute. In these studies, we start with large cohorts of Tokyo residents starting at 10 years of age and examine them every two years. Some of the people in these studies will develop schizophrenia or other neurological diseases as they age. By looking at cohort data, we will be able to determine whether high amounts of AGEs or pentosidine at early ages are associated with development of schizophrenia at later ages.

Interviewed by Jun Horiuchi

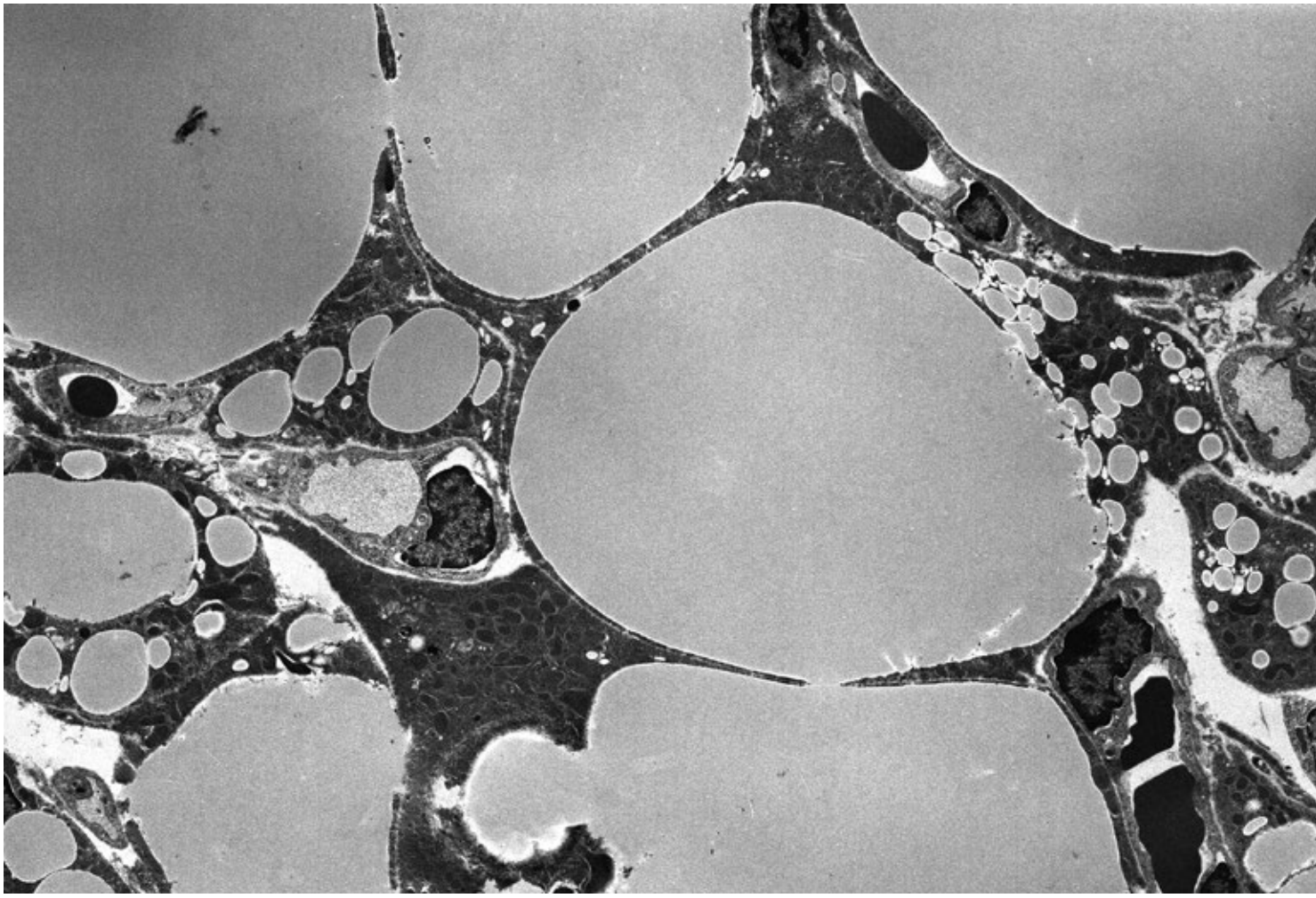


Overview of our findings.
Abbreviations: Pentosidine (PEN), glucuronic acid (GlcA), bovine serum albumin (BSA), aldo-keto reductase (AKR).


Our Goal

Our goal is to be a leading and role model institute for the life/medical science by conducting cutting-edge basic, clinical and social medical researches, that will help prediction, prevention, diagnosis, and treatment of various diseases and improve the care of patients, leading to longer healthy life.

Research Activities



White adipocytes are filled with a large lipid droplet that occupies most of the cytoplasm, whereas beige adipocytes contain multilocular lipid droplets with a high density of mitochondria.

Basic Medical Sciences

Project Leader
Hisao MASAI

Hisao Masai, the director-generalof the institute since 2018, has led the Genome Dynamics Project since 2009. After graduating from the University of Tokyo in 1981, he worked on mechanisms of DNA replication as a graduate student under the supervision of Dr. Ken-ichi Arai at DNAX Research Institute in Palo Alto, California, USA. He received his Ph.D. in 1987 from the University of Tokyo, Graduate School of Science and has spent his career studying how genetic information is duplicated and inherited. His current interests include understanding the prototypical modes of DNA replication, how biological stresses contribute to tumorigenesis, and how unusual nucleic acid structures regulate DNA replication and genome stability.

Genome Dynamics

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

Staff

Senior Researcher
Hiroyuki SASANUMA

Researchers
Zhiying YOU
Taku TANAKA
Yutaka KANOH
Tomohiro IGUCHI
Youichi TAJIMA
Sayuri ITO
Chi-Chun YANG
Kenji MORIYAMA

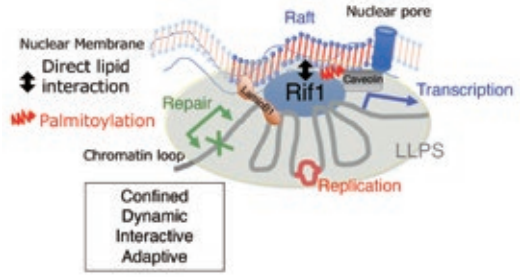
Research Assistants
Naoko KAKUSHO
Rino FUKATSU
Akiko MINAGAWA

Students
Tomoko SAGI
Hao-Wen HSIAO
Trinh Thi To NGO
Manaho SASHIDA
Zheng WANXIN
Ayaka ONUKI
Kosuke YAMAZAKI
Bingyi LI
Lanxin ZHENG
Tatsuki FUKUMOTO

Research Summary

Our goal is to understand the molecular mechanisms responsible for faithful inheritance of genetic materials and stable maintenance of the genome. In particular, we focus on elucidating regulatory mechanisms for DNA replication in E. coli, fission yeast, and mammalian cells as well as roles of homologous recombination in DNA damage repair. Understanding how chromosomes are replicated, repaired, and inherited will allow us to determine how defects in these processes cause diseases, such as cancers, or lead to cellular senescence. We aim to identify novel target proteins for cancer treatments and amelioration of age-associated phenotypes. Specific questions we are addressing:

1) How are the timing and location of DNA replication determined, and how are these coordinated with other chromosomal processes?
2) How do G-quadruplex structures regulate DNA replication and chromosome architecture?
3) How do various biological stresses induce replication stress and how does this affect genome stability and potentially cause cancers?
4) What are the roles of replication and checkpoint factors in developmental processes?
5) How have replication systems evolved and diversified in response to changing environments?
6) How do defects in homologous recombination factors, BRCA1/2, lead to breast cancer?
7) How are endogenous double-stranded breaks in DNA generated by topoisomerases?
8) How can we develop effective cancer therapies by targeting replication/checkpoint factors?



A model for chromatin compartmentalization generated by Rif1 near nuclear periphery. Rif1 protein binds to G4 structures in chromatin and promotes chromatin loop formation through oligomerization. Rif1 also binds to nuclear membranes directly and through lipid modification, tethering chromatin fibers to the nuclear periphery. It can also induce compartmentalization through liquid-liquid phase separation to generate confined, but dynamic and interactive chromatin compartments.

Selected Publications

Tajima Y. et al. (2024) "Cell fusion upregulates PD-L1 expression for evasion from immunosurveillance" ***Cancer Gene Ther***. 31(1) :158-173.

Kanoh Y, et al. (2023) "Aberrant association of chromatin with nuclear periphery induced by Rif1 leads to mitotic defect" ***Life Science Alliance*** 6(4) : e202201603.

Yoshizawa-Sugata N, et al. (2021) "Loss of full-length DNA replication regulator Rif1 in two-cell embryos is associated with zygotic transcriptional activation." ***J Biol Chem***, 297: 101367.

Yang C-C, et al. (2019) "Cdc7 activates replication checkpoint by phosphorylating the Chk1 binding domain of Claspin in human cells." ***E-life***, 8. pii: e50796

Sasanuma H, et al. (2018) "BRCA 1 ensures genome integrity by eliminating estrogen-induced pathological Topoisomerase II-DNA complexes." ***Proc. Natl. Acad. Sci. USA***, 115 (45) : E10642-E10651

You Z and Masai H (2017) "Potent DNA strand annealing activity associated with mouse Mcm2-7 heterohexamer complex." ***Nucleic Acids Res***. 45: 6495-6506.

Yang C-C, et al. (2016) "Claspin recruits Cdc7 kinase for initiation of DNA replication in human cells." ***Nature Communications*** 7: 12135.

Hoa, N.N. et al. (2016) "Mrel 1 is Essential for the Removal of Lethal Topoisomerase 2 Covalent Cleavage Complexes." ***Molecular Cell***, 64: 580-592.

Kanoh Y, et al. (2015) "Rif1 binds to G-quadruplexes and suppresses replication over long distances." ***Nature Struct. Mol. Biol***. 22: 889-897.

Project Leader
Yoshiaki KIKKAWA

Yoshiaki Kikkawa has been leading the Deafness Project since 2020. Dr. Kikkawa completed his Ph.D. on animal genetics and evolution in 1998 from the Tokyo University of Agriculture. He then worked in mouse genetics and genomics under the supervision of Dr. Hiromichi Yonekawa at TMIMS where he identified key genes involved in several diseases by positional cloning. In particular, he focused on using mouse models to elucidate the molecular basis for genetic deafness, and identified *Sans*, one of the few genes identified to date that are associated with human deafness. Subsequently he conducted research on protein-protein interactions associated with deafness with Prof. Steve Brown at the MRC, Harwell, UK, where he discovered protein complexes associated with stereocilia elongation in hair cells in the inner ear.

Deafness

Laboratory HP: https://www.igakuken.or.jp/mammal/english/index.html

Staff

Researchers
Shumpei YASUDA
Yuta SEKI
Ornjira PRAKHONGCHEEP

Research Assistants
Ai TAKAHASHI
Ting MAO
Kayoko TAHARA

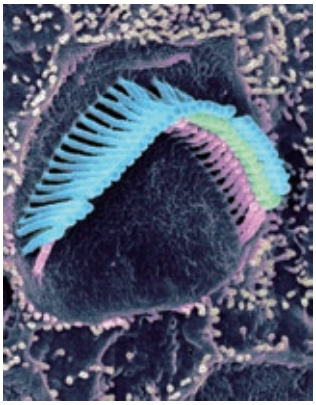
Students
Xuehan HOU
Hiroko BEPPU

Research Summary

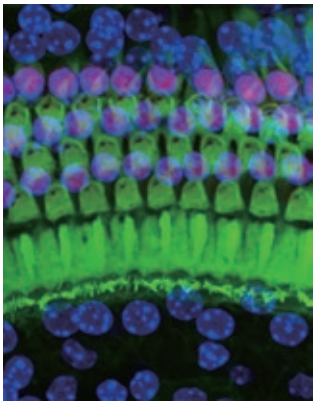
Hearing loss is a very common sensory disorder that severely affects human quality of life. In order to develop effective therapeutic strategies for deafness, it is critical to understand the mechanisms regulating its onset. Our aim is to discover novel genes associated with deafness. In particular, we are focused on identifying genes responsible for age-related hearing loss (ARHL). While genes responsible for congenital hearing loss have been identified, genes associated with ARHL, which affects a far greater number of people, have not.

Many types of hearing loss are associated with loss of outer hair cells (OHCs), which are responsible for the amplification of sound. Thus, we study the development and maintenance of OHCs. OHCs form a characteristic V-shaped stereocilia architecture. However, the genetic and molecular mechanisms involved in OHC development and death are poorly understood. To better understand OHCs and ARHL, we are:

1) Identifying genes causing and modifying ARHL in mouse models using forward genetics approaches.
2) Functionally analyzing proteins involved in the development of the OHC V-shaped stereocilia architecture.
3) Investigating the molecular mechanisms involved in OHC deaths using an OHC-specific depletion system.



The V-shaped stereocilia architecture of OHCs in 1-month-old mice. Stereocilia bundles are arranged in rows (blue, green, and magenta) of increasing height and form a staircase-shaped configuration.



OHC-specific expression of oncomodulin. Ocomodulin signals (red) were specifically labeled in the nuclei of OHCs. Green and blue signals indicate phalloidin and DAPI staining.

Selected Publications

Hou et al. (2023) "Impacts of an age-related hearing loss allele of cadherin 23 on severity of hearing loss in ICR and NOD/Shi mice." ***Biochem. Biophys. Res. Commun.*** 674:147-153.

Yasuda SP et al. (2022) "Two loci contribute to age-related hearing loss resistance in the Japanese wild-derived inbred MSM/Ms mice" ***Biomedicines*** 10: 2221

Seki et al. (2021) "Myosin VI haploinsufficiency reduced hearing ability in mice." ***Neuroscience.*** 478:100-111.

Yasuda SP et al. (2020) "c.753A>G genome editing of a *Cdh23*^{ahl} allele delays age-related hearing loss and degeneration of cochlear hair cells in C57BL/6J mice." ***Hear. Res.*** 389: 107926.

Matsuoka K et al. (2019) "OHC-TRECK: A novel system using a mouse model for investigation of the molecular mechanisms associated with outer hair cell death in the inner ear." ***Sci. Rep.*** 9:5285.

Seki Y, et al. (2017) "A novel splice site mutation of myosin VI in mice leads to stereociliary fusion caused by disruption of actin networks in the apical region of inner ear hair cells." ***PLoS One*** 12, e0183477.

Miyasaka Y, et al. (2016) "Heterozygous mutation of *Ush1g/Sans* in mice causes early-onset progressive hearing loss, which is recovered by reconstituting the strain-specific mutation in *Cdh23*." ***Hum. Mol. Genet.*** 25: 2045-2059.

Project Leader
Yasuko ONO

Calpain

Laboratory HP: https://www.igakuken.or.jp/calpain/indexEnglish.html

Yasuko Ono has been the leader of the Calpain Project since 2018. As a graduate student she studied the roles of calpains, a family of intracellular cysteine proteases, in muscle functions, and received her Ph.D in 1999 from the University of Tokyo, Graduate School of Science. She then studied mechanisms of sarcomere assembly as a postdoctoral fellow at the University of Arizona. Her current research includes studying the physiological impact of calpain-mediated proteolysis on cellular functions and understanding mechanisms of calpain regulation.

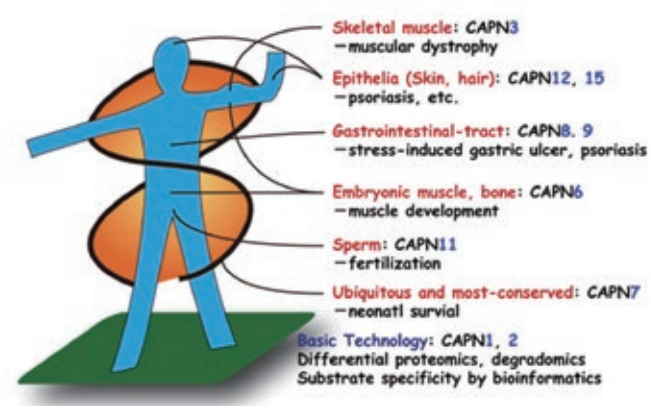
Staff

Researchers
Shoji HATA
Atsushi IRIE
Chihiro HISATSUNE
Fumiko SHINKAI-OUCHI
Aya NOGUCHI

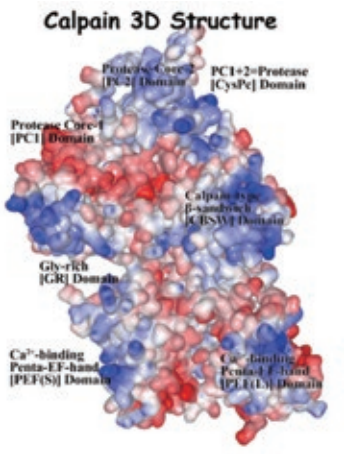
Research Assistants
Naoko DOI

Research Summary

Proteins are chains of amino acids, and their functions change when they are cut or partially cut. Calpains are proteolytic enzymes that perform such cuts or limited proteolytic processing in cooperation with calcium. Humans have 15 calpain species. Defects of these species cause various deficiencies, such as muscular dystrophy, stomach ulcers, and embryonic lethality.



In this project, we aim to understand the biology of calpains, and translate this knowledge into improvements in health.



Selected Publications

Ono Y, et al. (2022) "Cryptic splicing events result in unexpected protein products from calpain-10 (CAPN10) cDNA." ***Biochim. Biophys. Acta Mol. Cell Res***. 1869(3): 119188.

Shinkai-Ouchi F, et al. (2020) "Calpain-2 participates in the process of calpain-1 inactivation." ***Biosci. Rep***., 40: BSR20200552.

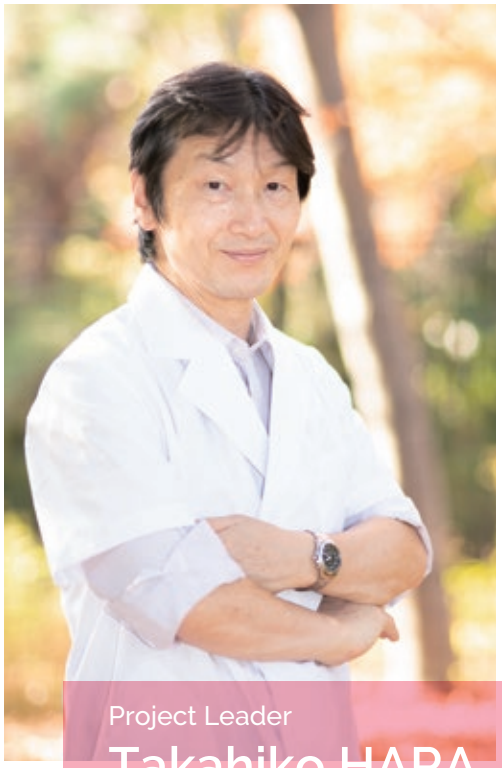
Hata S, et al. (2020) "A muscle-specific calpain, CAPN3, forms a homotrimer." ***Biochim. Biophys. Acta, Proteins Proteomics***, 7: 140411.

Hata S, et al. (2016) "A gastrointestinal calpain complex, G-calpain, is a heterodimer of Capn8 and Capn9 calpain isoforms, which play catalytic and regulatory roles, respectively." ***J. Biol. Chem***., 291: 27313-27322.

Ono Y, et al. (2016) "Calpain research for drug discovery: challenges and potential." ***Nature Reviews: Drug Discovery***,15: 854-876.

Shinkai-Ouchi F, et al. (2016) "Predictions of cleavability of calpain proteolysis by quantitative structure-activity relationship analysis using newly determined cleavage sites and catalytic efficiencies of an oligopeptide array." ***Mol. Cell. Proteomics***, 15: 1262-1280.

Ono Y, et al. (2014) "The N- and C-terminal autolytic fragments of CAPN3/p94/calpain-3 restore proteolytic activity by intermolecular complementation." ***Proc. Natl. Acad. Sci. USA***, 111: E5527-5536.



Project Leader
Takahiko HARA

Takahiko Hara, the department chief of the Institute since April of 2018, has been the leader of the Stem Cell Project since 2005. After receiving Ph.D from the Graduate School of Science, Univ. of Tokyo in 1990, he conducted researches at DNAX Research Institute in Palo Alto, California, USA, as a postdoctoral fellow under the supervision of Dr. Atsushi Miyajima. He molecularly cloned a cDNA encoding mouse IL-3 receptor alpha subunit. Next, he developed *ex vivo* culture system of hematopoietic stem cells (HSCs) in the aorta-gonad-mesonephros region of mouse embryo. Since then, molecular mechanism of HSC development has been his major research interest. In the mean while, he started to investigated regulators of spermatogonial stem cells and muscle regeneration factors. Subsequently, he focused on a RNA helicase DDX1 and a CXC-type chemokine CXCL14, as they are involved in tumorigenesis and anti-tumor immunity, respectively.

Stem Cell

Laboratory HP: https://www.igakuken.or.jp/english/project/detail/stem-cell.html

Staff

Researchers
Kenji KITAJIMA
Kosuke TANEGASHIMA
Teruhiko SUZUKI
Masatoshi MURAOKA

Research Assistants
Tsuruyo TANIGUCHI
Mana YAMAKAWA

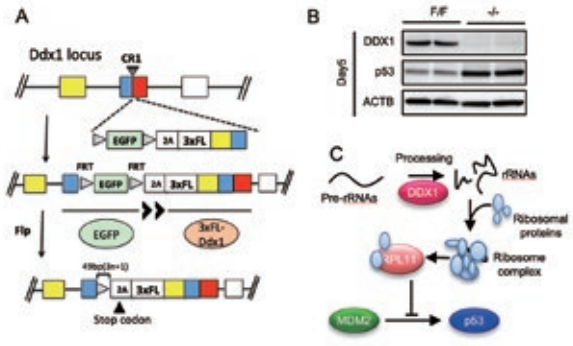
Students
Satoko TAKAGI
Shota HOYANO
Fumiya SEKI
Hikaru ANDO
Riku TAKAHASHI
Yuka EGAWA
Manaka HASEBE
Junta FUNADA

Research Summary

Dr. Yamanaka's inducible pluripotent stem cell (iPSC) technology has opened a new avenue to overcome incurable diseases by cell transplantation. In 2011, we discovered that overexpression of Lhx2 (transcription factor) in hemogenic mesodermal cells resulted in ex *vivo* expansion of transplantable HSCs from mouse embryonic stem cells (ESCs) and iPSCs. Since then, we have been making efforts for applying this method to human iPSCs. We believe that comparison of the *in vitro* differentiation capacity of hematopoietic cells between mouse and human iPSCs will uncover novel and fundamental aspects of human HSC development.

We discovered that CXCL14 is one of the causative factors for obesity-associated diabetes. In contrast, CXCL14 is known to possess tumor-suppressive activity against lung and oral carcinomas. In 2017, we found that CXCL14 carries CpG DNA into dendritic cells. This causes activation of the TLR9 signaling pathway, which is effective in immune-suppression of cancers. In addition, we discovered that CXCL14 plays a critical role in protecting skin from over-proliferation of S. aureus. We are vigorously investigating physiological roles of CXCL14 and its action mechanisms.

The presence of cancer stem cells has been proposed in various types of human cancer. Presumably, both tissue and cancer stem cells commonly express critical transcriptional regulators and signal transducers. We have identified DDX1 (RNA helicase) and PTPN23 (tyrosine phosphatase) as essential molecules for the onset of testicular tumors. In 2020, we discovered that DDX1 is essential for ribosome RNA metabolism in ESCs and cancer cells. In the absence of DDX1, these cells stop proliferation and undergo apoptosis by p53 activation (Figure).



Conditional knockout system of ES cells uncovered a novel role of DDX1 in ribosome RNA processing which is linked to p53-mediated cell growth control.

Selected Publications

Kitajima, K., et al. (2022) "An interferon-/FLT3 axis positively regulates hemopoietic progenitor cell expansion from human pluripotent stem cells." ***Stem Cells***, 40: 906-918.

Tsujihana, K., Tanegashima, K. et al. (2022)"Circadian protection against bacterial skin infection by epidermal CXCL14-mediated innate immunity." ***Proc. Natl. Acad. Sci. U.S.A.***, 119: e2116027119.

Iwase, R. et al. (2021)"Identification of functional domains of CXCL14 involved in high-affinity binding and intracellular transport of CpG DNA." ***J. Immunol.***, 207: 459.

Suzuki, T. et al. (2021) "A novel all-in-one conditional knockout system uncovered an essential role of DDX1 in ribosomal RNA processing." ***Nucl. Acid Res.***, 49: e40.

Sato K, et al. (2020) "Nitric oxide and a conditioned medium affect the hematopoietic development in a microfluidic mouse embryonic stem cell/OP9 co-cultivation system." ***Micromachines,*** 11: 305.

Kitajima K, et al. (2018) "Domain-specific biological functions of the transcription factor Gata2 on hematopoietic differentiation of mouse embryonic stem cells." ***Genes Cells*** 23: 753-766.

Tanegashima K, et al. (2017) "CXCL14 acts as a specific carrier of CpG DNA into dendritic cells and activates Toll-like receptor 9-mediated adaptive immunity." ***EBioMed.*** 24: 247-256.

Project Leader
Hikari YOSHITANE

Circadian Clock

Laboratory HP: https://www.igakuken.or.jp/project/detail/circadian.html

Hikari Yoshitane has been the leader of the Circadian Clock Laboratory since 2021. He started studying the circadian clock under the supervision of Prof. Yoshitaka Fukada in the Department of Biophysics and Biochemistry, Graduate School of Science, at the University of Tokyo. He received his Ph.D in 2009 and continued his research as an Assistant Professor in the Fukada laboratory from 2009 to 2021. His main research interest is to understand the molecular mechanisms of how the circadian clock oscillates autonomously with a period of 24 hours. He is interested in cellular input signals into the circadian clock and physiological outputs from the clock. This research should help develop novel medical treatment strategies for many circadian clock- related diseases including aging.

Staff

Researchers
Nobuhiro KURABAYASHI
Tomoko TANAKA
Yuki KATO
Kyohei UEMOTO

Research Assistants
Arisa KURABAYASHI

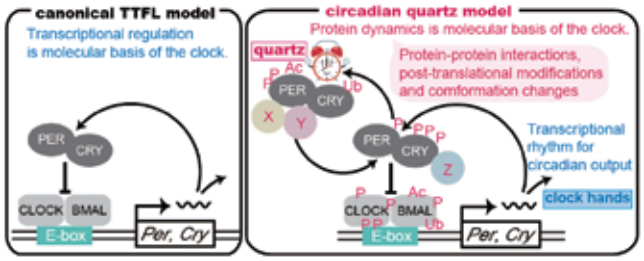
Visiting Scientist
Yoshitaka FUKADA
Miho YOSHIMURA

Students
Yuta OTOBE
Satoshi KAWAKAMI
Etsuko MITSUYOSHI
Taiki MORIMURA
Anna UCHIDA

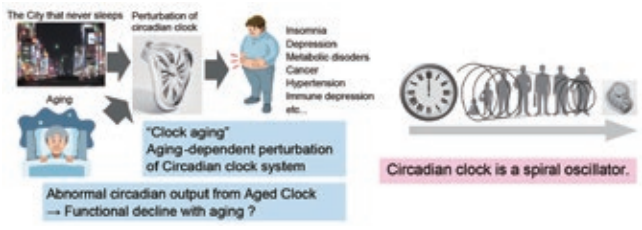
Research Summary

<background>
Many organisms exhibit circadian rhythms, which are governed by the circadian clock. Clock genes and their encoded proteins form transcriptional/ translational feedback loops (TTFLs) that drive gene expression rhythms. Disruption of the circadian clock increases the risk of developing many diseases including insomnia, hypertension, metabolic disorders, and cancers.

<objective 1. circadian quartz>
How does the circadian clock autonomously oscillate with a period of about 24 hours? While the canonical TTFL model shown below is an essential component of the clock that regulates expression of downstream circadian genes, we believe that the critical timekeeping aspect of the clock is maintained by protein dynamics, where protein modifications and protein conformational changes regulate protein-protein interactions in an oscillatory manner. Thus, TTFL is required for clock read-out and is akin to the hands of the clock, while protein dynamics may be more similar to the quartz timekeeper in the clock. Currently we are studying TTFL-independent protein-based clock components to identify the quartz timing mechanism.



<objective 2. clock aging>
Disruption of the circadian clock causes dysregulation of gene expression rhythms. This leads to functional declines including aging-associated declines, which we refer to as “clock aging”. We are studying the molecular mechanisms of how aging disrupts the functional rhythms of the circadian clock and how clock perturbations cause aging-associated symptoms.



Selected Publications

Abe et al., (2022) Rhythmic transcription of Bmal1 stabilizes the circadian timekeeping system in mammals. ***Nature Communications***, 13 (1): 4652.

Yoshitane et al., (2022) mTOR-AKT signaling in cellular clock resetting triggered by osmotic stress. ***Antioxidants & Redox Signaling***, 37(10):631.

Hiroki et al., (2022) Molecular encoding and synaptic decoding of context during salt chemotaxis in C. elegans. ***Nature Communications,*** 13(1): 2928.

Masuda et al., (2020) “Mutation of a PER2 phosphodegron perturbs the circadian phosphoswitch.” ***Proc. Natl. Acad. Sci. USA,*** 117(20): 10888-10896.

Yoshitane et al., (2019) “Functional D-box sequences reset the circadian clock and drive mRNA rhythms.” ***Communications Biology,*** 2: 300.

Imamura et al., (2018) “ASK family kinases mediate cellular stress and redox signaling to circadian clock.” ***Proc. Natl. Acad. Sci. USA,*** 115(14): 3646-3651.

Terajima et al., (2017) “ADARB1 catalyzes circadian A-to-I editing and regulates RNA rhythm.” ***Nature Genetics,*** 49(1): 146-151.

Laboratory Head
Yukiko YOSHIDA

Protein Metabolism

Laboratory HP: https://www.igakuken.or.jp/pro-meta/

Yukiko Yoshida is the head of the Laboratory of Protein Metabolism. She received her Ph.D in 1994 from the Graduate School of Agricultural and Life Sciences at the University of Tokyo, and then worked as a postdoctoral fellow studying glycobiology at RIKEN (Wako). She has been working at the Tokyo Metropolitan Institute of Medical Science since 1997. In 1999 she identified a novel glycoprotein-specific ubiquitin ligase using chemical biology probes. Her research focus has been to understand the physiological functions of the ubiquitin system.

Staff

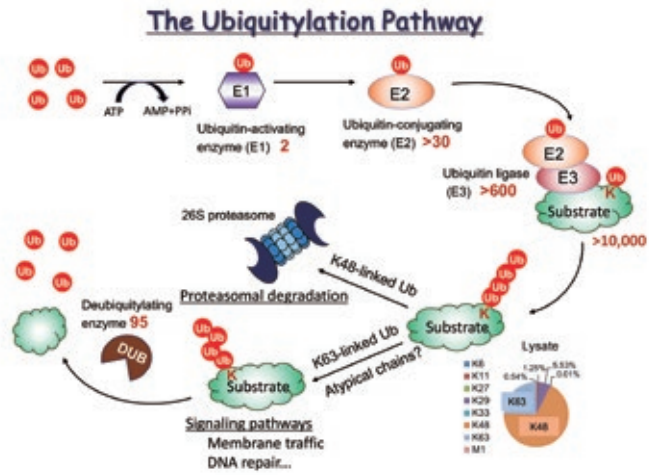
Researchers
Akinori ENDO
Hikaru TSUCHIYA
Hiromichi YONEKAWA

Research Assistants
Naoko ARAI
Chikara ANDO
Meari OKADA
Chikage TAKAHASHI
Kyoko UEDA

Research Summary

Protein recycling is essential for our health. All proteins in our bodies have distinct lifespans after which they are recycled. Old or defective proteins are identified and tagged with K48-linked chains by the ubiquitin system (see figure). K48-linked polyubiquitin chains target proteins for proteasomal degradation. Defects in this ubiquitin-proteasome system (UPS) are implicated in the pathogenesis of various diseases including cancers, neurodegenerative diseases, infectious diseases and immune responses, and genetic disorders. Our laboratory studies mechanisms of ubiquitin signaling and proteasomal degradation to understand cellular proteostasis and to understand the pathogenesis of these diseases.

To obtain a comprehensive understanding of the ubiquitylation system, we have developed methods to identify ubiquitylated substrates (PNAS, 2015) and types of ubiquitin chains (Mol Cell, 2017). We have also studied glycoprotein-specific ubiquitin ligases in the cytosol, where glycoproteins are normally absent, and found that ubiquitylation of glycoproteins is involved in the detection and recycling of damaged organelles (PNAS, 2017). Moreover, we found that a disease associated with reduced deglycosylation activity in the cytosol causes accumulation of ubiquitylated glycoproteins and proteasomal dysfunction (PNAS, 2021). Further, we have found that a deubiquitylating enzyme protects cells from organelle stress (JCB, 2024). Thus, our goal of understanding cellular proteostasis and the ubiquitinproteasome system is important for understanding the pathogenesis of many diseases affecting our health.



Ubiquitination is catalyzed by three enzymes, E1, E3, and E3, with E3 providing target selectivity. This reaction can be repeated to form polyubiquitin chains on substrates. Different types of ubiquination modification target proteins to different fates. In the figure, numbers in red indicate the numbers of identified proteins of each type.

Selected Publications

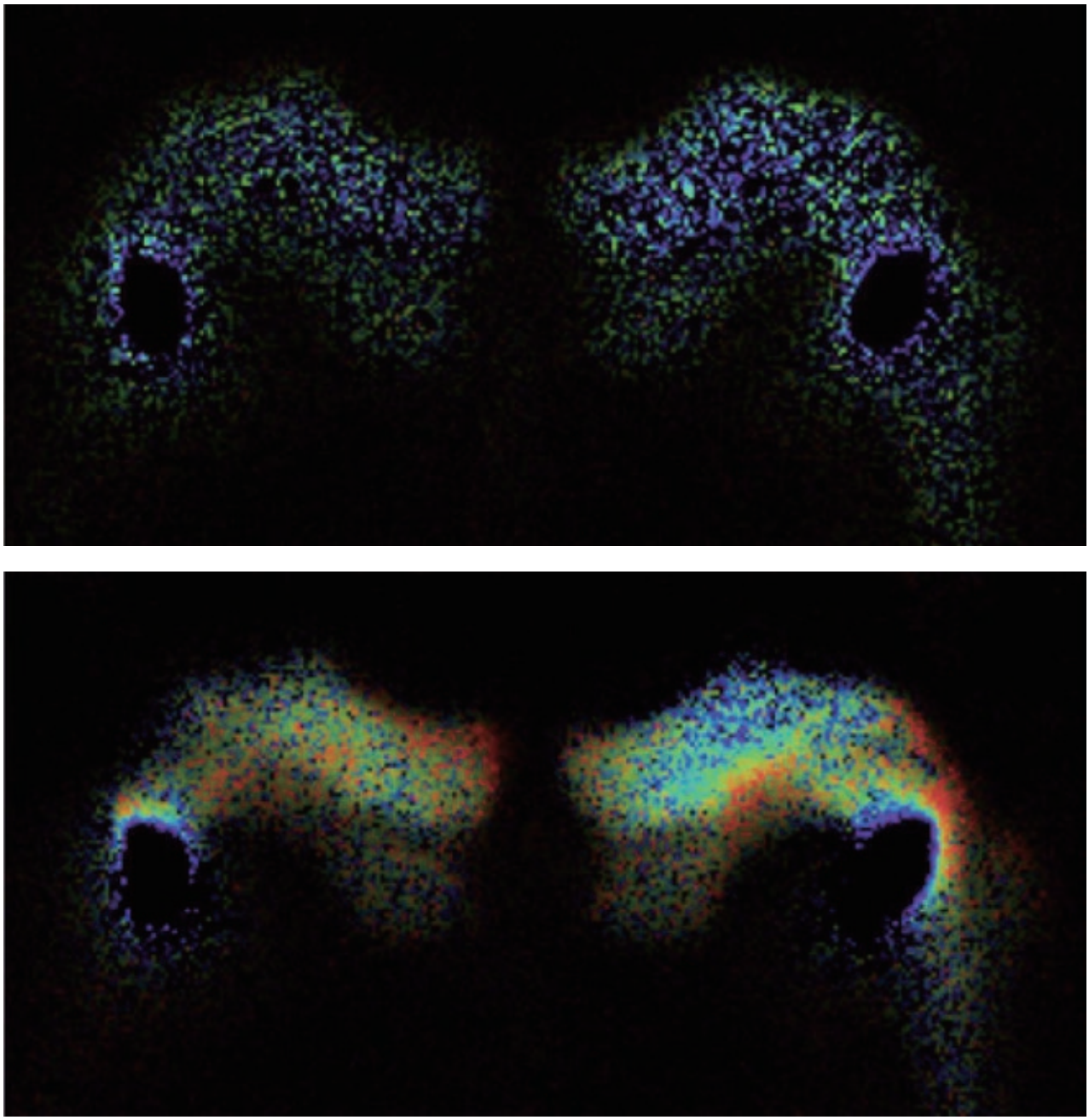
Endo A, et al. (2023) "USP8 prevents aberrant NF-kB and Nrf2 activation by counteraciting ubiquitin signals from endosomes." ***J. Cell Biol.*** 223:e202306913.

Yoshida Y, et al. (2021) "Loss of peptide:N-glycanase causes proteasome dysfunction mediated by sugar-recognizing ubiquitin ligase." ***Proc Natl Acad Sci USA.*** 118: e2102902118.

Tsuchiya H, et al. (2017) "In vivo ubiquitin-type analysis reveals that the Cdc48-Rad23/Dsk2 axis contributes to K48-linked chain specificity of the preoteasome." ***Mol Cell*** 66:488-502.

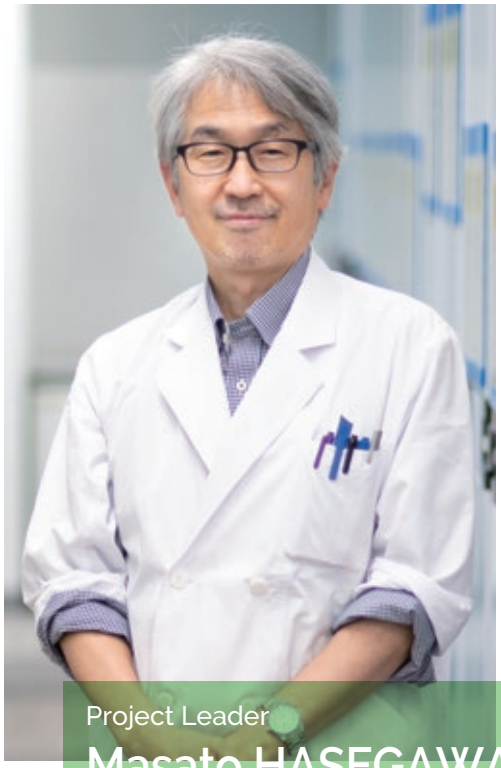
Yoshida Y, et al. (2017) "Ubiquitination of exposed glycoproteins by SCFFBXO27 directs damaged lysosomes for autophagy." ***Proc Natl Acad Sci USA.*** 114: 8574-8579.

Yoshida Y, et al. (2015) "A comprehensive method for detecting ubiquitinated substrates using TR-TUBE." ***Proc Natl Acad Sci USA.*** 112: 4630-4635.



Extracellular glutamate imaging in the mushroom body, the memory center of Drosophila. The extracellular glutamate sensor, iGlusnFR, was expressed in the mushroom bodies. When a naïve fruit fly (top panel) is given an electric shock, glutamate is released from glial cells surrounding the mushroom body (bottom panel).

Brain & Neurosciences



Project Leader
Masato HASEGAWA

Masato Hasegawa, the Head of Department of Brain and Neurosciences, studies the molecular pathogenesis and progression of neurodegenerative diseases. He started working on Alzheimer's disease at Yasuo Ihara's lab in 1988 where he identified phosphorylation and ubiquitination sites in tau. In 1995, he joined Michel Goedert's lab at MRC LMB where he and others demonstrated that alpha-synuclein is the major component of filamentous inclusions in Parkinson's disease and dementia with Lewy bodies. He next joined Takeshi Iwatsubo's group in 1999 where he identified phosphorylation and ubiquitination of alpha-synuclein. In 2006, while at the Tokyo Metropolitan Institute of Psychiatry, he collaborated with Tetsuaki Arai and found that phosphorylated TDP-43 accumulates in frontotemporal dementias and amyotrophic lateral sclerosis. More recently, he has been studying the prion-like spread of neurodegenerative disease-associated proteins.

Dementia Research

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

Staff

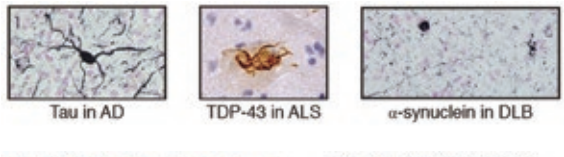
Researchers
Takashi NONAKA
Genjiro SUZUKI
Yoshiki TAKAMATSU
Masami SUZUKAKE
Fuyuki KAMETANI
Ito KAWAKAMI

Research Assistants
Reiko OOTANI
Marina TAHIRA

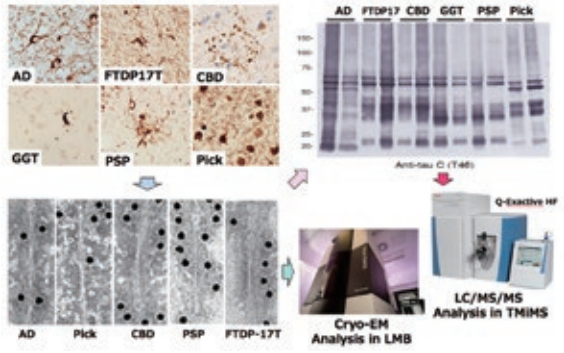
Students
Mina TAKASE
Shohei TAKAKI
Yuta SATO
Syunsuke KANNO

Research Summary

Many neurodegenerative diseases are associated with intracellular amyloid-like protein pathologies, such as tau in Alzheimer's disease (AD), α-synuclein in dementia with Lewy bodies (DLB) and TDP-43 in amyotrophic lateral sclerosis (ALS) and frontotemporal dementias (FTD). Importantly, the distribution and spread of these proteins closely correlates with clinical presentation and disease progression.



We have been investigating these intracellular pathological proteins prepared in these diseases, immuno-histochemically, ultrastructurally, and biochemically using liquid chromatography with tandem mass spectrometry (LC/MS/MS).



In collaboration with Michel Goedert and Sjors Scheres in LMB and the Japan brain bank network (JBBN), we determined the structures of pathological tau and alpha-synuclein filaments from brains of patients with corticobasal degeneration (CBD) and multiple system atrophy. We further identified numerous post-translational modifications in these filamentous assemblies. We demonstrated that injection of aggregate recombinant tau filaments into wild-type mice seeded the aggregation of endogenous murine tau, leading to the spread of aggregates into distinct brain areas. In addition, we generated two different types of alpha--synuclein fibrils from identical wild-type alpha--synuclein monomers under different conditions and showed that these fibrils have different prion-like ablilities to convert endogenous soluble alpha--synuclein monomers into amyloid-like fibrils.

Selected Publications

Yang Y, et al. (2022) "Structures of α-synuclein filaments from human brains with Lewy pathology". ***Nature***. 610(7933):791-795.

Schweighauser M, et al. (2022) "Age-dependent formation of TMEM106B amyloid filaments in human brains". ***Nature***. 605(7909):310-3148.

Arseni D, Hasegawa M, et al. (2022) "Structures of TDP-43 filaments from amyotrophic 1 lateral sclerosis with frontotemporal lobar degeneration". ***Nature*** 601(7891):139-143.

Tarutani A, et al. (2022) Ultrastructural and biochemical classification of pathogenic tau, α-synuclein and TDP-43. ***Acta Neuropathol***. 143(6):613-640.

Tarutani A, et al. (2021) "Human tauopathy-derived tau strains determine the substrates recruited for templated amplification." ***Brain.*** Sep 4;144(8):2333-2348.

Hosokawa M, et al. (2021) "Development of a novel tau propagation mouse model endogenously expressing 3 and 4 repeat tau isoforms." ***Brain.*** Sep 13:awab289.

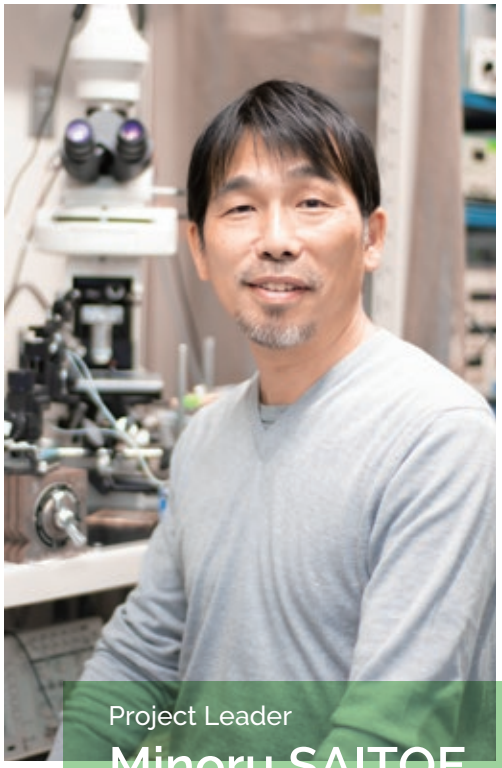
Shi Y, et al. (2021) "Structure-based classification of tauopathies." ***Nature.*** Sep 29. Online ahead of print. (Oct 14)

Zhang W, et al. (2020) "Novel tau filament fold in corticobasal degeneration." ***Nature*** Apr;580(7802):283-287.

Masuda-Suzukake M, et al. (2020) "Dextran sulphate-induced tau assemblies cause endogenous tau aggregation and propagation in wild-type mice." ***Brain Communications*** Jul 8;2(2):fcaa091.

Suzuki G, et al. (2020) "α-Synuclein strains that cause distinct pathologies differentially inhibit proteasome." ***eLife.*** Jul 22;9:e56825.

Schweighauser M, et al. (2020) "Structures of α-synuclein filaments from multiple system atrophy." ***Nature*** Sep; 585(7825):464-469 .



Project Leader
Minoru SAITOE

Minoru Saitoe is the vice-director of TMIMS, the head of the Learning and Memory Project, the director of the Center for Basic Technology Research, and a visiting professor at Tokyo Metropolitan University. Dr. Saitoe received his B.A. in Organic Chemistry from Osaka University, his M.S. in Biochemistry from the Tokyo Institute of Technology, and his Ph.D. from the University of Tokyo for studying physiological functions of gap junctions during Ascidian neural development. Currently, his research focus is to elucidate mechanisms involved in Drosophila learning and memory and synaptic plasticity. He is especially interested in glial-neuron networks, functional diversity of the monoamine system, and age-related memory impairments. Other interests include the molecular and neural bases of psychological phenomenon such as empathy and causality.

Learning and Memory

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

Staff

Researchers
Kohei UENO
Tomoyuki MIYASHITA
Motomi MATSUNO
Shintaro NAGANOS
Takahiro ISHIKAWA

Postdoctoral fellows
Hiroshi KUROMI

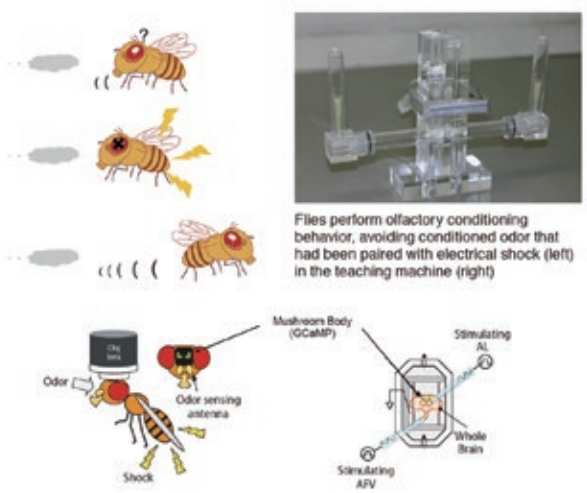
Research Assistants
Saki KOMIYA
Takae HASEGAWA
Tomoko TAKAMISAWA
Kayoko GOTO
Yayoi ONODERA

Students
Maximiliano Martinez-Cordera
Hinako MURATANI

Research Summary

Memories define us and mold our personalities. Using genetic tools, we have identified genes and neural substrates required for memory-associated behaviors in Drosophila. We investigate when, where and how memory-associated gene products function to produce memory-based behaviors and how memory mechanisms are affected by physiological changes such as aging.

In addition to behavioral and genetic approaches, we use *in vivo* and *ex vivo* imaging techniques to characterize physiological properties of memory-associated neural networks. Our goal is to understand how the brain forms associations between specific sensory signals and positive and negative preferences, how these associations are stored in the brain in neural memory networks, and how they are later recalled at appropriate times. We further aim to understand how memory-associated genes and neuromodulatory systems regulate function of these networks.



Lower left, schematic diagram of our *in vivo* imaging set-up. A living fly is fixed under a microscope and can be exposed to both odors and electrical shocks. Neuronal activity can be observed during formation, storage, and retrieval of odor-shock associative memories. Lower right, in our *ex vivo* imaging set-up, we can make artificial memories in cultured brains by stimulating odor and shock sensory pathways.

Selected Publications

Miyashita et al. (2023). "Glia transmit negative valence information during aversive learning in Drosophila" ***Science*** 382: eadf7429.

Ueno K et al. (2020). "Carbon monoxide, a retrograde messenger generated in post synaptic mushroom body neurons evokes non-canonical dopamine release." ***J Neurosci.*** 40, 3533-3548.

Ueno K, et al. (2017) "Coincident postsynaptic activity gates presynaptic dopamine release to induce plasticity in Drosophila mushroom bodies." ***eLife,*** 6: e21076.

Hirano Y, et al. (2016) "Shifting transcriptional machinery is required for long-term memory maintenance and modification in Drosophila mushroom bodies." ***Nat. Commun.***7: 13471.

Matsuno M, et al. (2015) "Long-term memory formation in Drosophila requires training-dependent glial transcription." ***J. Neurosci.*** 35: 5557-5565.

Yamazaki D, et al. (2014) "Glial dysfunction causes age-related memory impairment in Drosophila." ***Neuron*** 84: 753-763.

Hirano Y, et al. (2013) "Fasting Launches CRTC to Facilitate Long-term Memory Formation in Drosophila." ***Science*** 339: 443-446.

Miyashita T, et al. (2012) "Mg2+ block of Drosophila NMDA receptors is required for long-term memory formation and CREB-dependent gene expression." ***Neuron*** 74: 887-898.

Project Leader
Yukio NISHIMURA

Neural Prosthetics

Laboratory HP: https://www.igakuken.or.jp/english/project/detail/neuroprosth1.html
https://neural-prosthetics.jp/

Dr. Yukio Nishimura has led the Neural Prosthetics Project since 2017. He received a PhD from Chiba University Medical School in 2003. He was a postdoctoral fellow at the National Institute for Physiological Science in Japan from 2003 and at the University of Washington in the US from 2007. He started working at the National Institute for Physiological Science in 2011, and then joined the faculty of Kyoto University as an Associate Professor in 2016. His overall research is in neural control of limb movements in humans and non-human primates. His current research focuses on neural mechanisms of functional recovery after neural damage and restoration of lost functions using brain computer interfaces.

Staff

Researchers
Yoshihisa NAKAYAMA
Toshiki TAZOE
Sho K. SUGAWARA
Kyuengbo MIN
Osamu YOKOYAMA
Michiaki SUZUKI

Postdoctoral fellows
Noboru USUDA
Kei OBARA
Hironori TSUJI

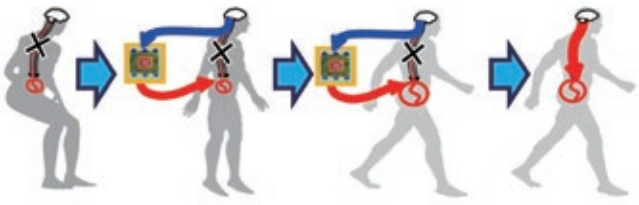
Research Assistants
Naoko YOSHIDA
Shoko HANGUI
Yukie AIZAWA
Sachiko SHIMAKAWA
Sumiko URA
Nao MOTOYANAGI
Tsuta UCHIDA

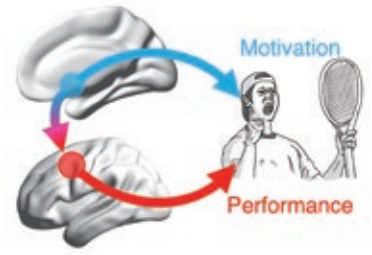
Students
Kouichi URAMARU
Kokoro KAWAMURA
Norihiro IWAMOTO

Research Summary

Our goal is to conceive of innovative ideas for neuro-rehabilitation of lost function after nervous system damage, and to translate these ideas into clinical applications capable of improving the quality of life for individuals with neural damage.
Specifically, we are developing a neural interface known as an "Artificial Neuronal Connection (ANC)". This ANC bridges spinal lesions by connecting supraspinal systems with spinal networks distal to the lesion to restore lost function. We are conducting clinical trials to assess the efficacy of ANCs in restoring motor function in paralyzed patients. We are also investigating the neural changes that occur during recovery.

Depression impedes, and motivation enhances functional recovery after neuronal damage. Although higher motivation seems to boost motor performance and recovery, neural substrates underlying this psychological effect remain unknown. We are identifying these neuronal substrates using humans and animal models.





Selected Publications

Kaneshige et al., Tuning of motor outputs produced by spinal stimulation during voluntary control of torque directions in monkeys. ***Elife***. 2022, 11:e78346.

Umeda et al., Temporal dynamics of the sensorimotor convergence underlying voluntary limb movement. ***PNAS***. 2022, 119(48):e2208353119.

Kato K, et al. (2019) "Bypassing stroke-damaged neural pathways via a neural interface induces targeted cortical adaptation." ***Nature Communications***. 10(1):4699.

Umeda, et al., (2019) "The somatosensory cortex receives information about motor output." ***Science Advances***., 5(7):eaaw5388.

Sawada M, et al. (2015) "Function of the nucleus accumbens in motor control during recovery after spinal cord injury." ***Science*** 350(6256):98-101.

Nishimura Y, et al. (2013) "Spike-timing-dependent plasticity in primate corticospinal connections induced during free behavior." ***Neuron*** 80(5):1301-1309.

Project Leader
Hiroshi SAKUMA

Hiroshi Sakuma has been the leader of the Child Brain Project since 2015. He graduated and obtained his MD (1993) and PhD (2005) degrees at Tokyo Medical and Dental University and pursued training in pediatric neurology at the National Center of Neurology and Psychiatry. He started his research activities on neuroimmunology in National Institute of Neuroscience under the supervision of Prof. Sachiko Miyake in 2010, and also was involved in the Health Labour Sciences Research on virus-associated acute encephalopathy since 2010. He has been working at Tokyo Metropolitan Institute of Medical Science since 2012. His current research interests include 1) pathomechanisms of virus-associated acute encephalopathies including febrile infection-related epilepsy syndrome, 2) biomarkers for pediatric immune-mediated neurological diseases, and 3) making international consensus on pediatric autoimmune neurological diseases.

Child Brain

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

Staff

Researchers
Tadayuki SHIMADA
Kuniko KOHYAMA

Visiting scientists
Hiroko TADA
Ai HOSHINO
Tomonori SUZUKI
Naoyuki TANUMA
Masaharu HAYASHI

Research Assistants
Mariko OZAKI

Students
Asako HORINO
Hiroya NISHIDA
Kengo MORIYAMA
Motoshi FUJITA
Rie NAKAI
Takayuki MORI

Research Summary

Our research focuses on autoimmune and inflammatory neurological diseases (AINDs) in childhood. They are significant social burden because of poor prognosis and high mortality. We have established a sustainable platform (a multicenter registry of patients and sample repository) for a prospective cohort studies on AINDs based on nationwide collaborative study. We perform multi-omics analysis of biomarkers including inflammatory mediators, microRNAs, and metabolites. This multifaceted approach using high-throughput methods enables us to explore novel molecular targets associated with AINDs.
Recent studies have highlighted the importance of glial cells in the pathogenesis of AINDs. Our transgenic animal models are expected to shed new light on how gilal cells contribute to the pathomechanisms of AINDs by regulating brain metabolism and inflammation, and also provide a rationale for a novel therapeutic strategy.

Our main research areas include:
1. Pathomechanisms of virus-associated acute encephalopathies
2. The role of inflammation in febrile infection-related epilepsy syndrome
3. Autoimmune encephalitis and acquired demyelinating syndromes
4. Autoantibodies associated with neurological diseases
5. New biomarkers for pediatric immune-mediated neurological diseases

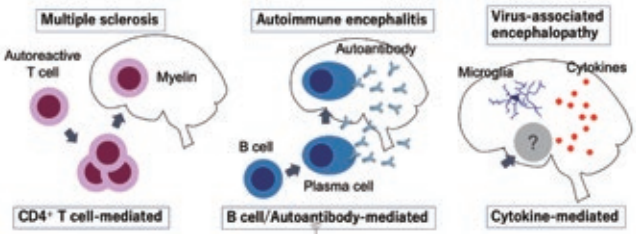


Figure Pathomechanisms of inflammatory and autoimmune neurological diseases
Multiple sclerosis has been regarded as CD4 T-cell mediated disease, in which autoreactive T cells are activated, proliferate, migrate into brain, and cause myelin damage. Autoimmune encephalitis is caused by autoantibodies against neuronal surface antigens, produced by plasma cells in both periphery and central nervous system. Although the pathogenesis of virus-associated encephalopathy has not been fully elucidated, pro-inflammatory cytokines and chemokines are highly increased in biofluids, suggesting cytokine-mediated mechanisms.

Selected Publications

Nosadini M et al. (2021) "Use and safety of immunotherapeutic management of N-methyl-d-aspartate receptor antibody encephalitis: a meta-analysis." ***JAMA Neurol.*** 78:1333-1344.

Nosadini M et al. (2021) International consensus recommendations for the treatment of pediatric NMDAR antibody encephalitis. ***Neurol Neuroimmunol Neuroinflamm.*** 8:e1052.

Nishida H et al. (2021) "Evaluation of the diagnostic criteria for anti-NMDA receptor encephalitis in Japanese children." ***Neurology.*** 50:e2070-e2077.

Horino A, et al. (2021) "Intrathecal dexamethasone therapy for febrile infection-related epilepsy syndrome." ***Ann. Clin. Transl. Neurol.*** 8:645-655.

Suzuki T, et al. (2020) "Extracellular ADP augments microglial inflammasome and NF-κB activation via the P2Y12 receptor." ***Eur. J. Immunol.*** 50:205-219.

Sakuma H, et al. (2015) "Intrathecal overproduction of proinflammatory cytokines and chemokines in febrile infection-related refractory status epilepticus." ***J. Neurol. Neurosurg. Psychiatr.*** 86:820-822

Project Leader
Chiaki OHTAKA-MARUYAMA

Chiaki Ohtaka-Maruyama graduated with a Ph.D. from the University of Tokyo with a diploma in Biology. After postdoctoral training at NEI, NIH (Bethesda, MD, USA) and RIKEN(Wako), she became Research Scientist in 2006 at the Tokyo Metropolitan Institute for Neuroscience (the predecessor of Tokyo Metropolitan Institute of Medical Science). She started her research in the neural development field. She has been the project leader since April 2019. Her research focuses on understanding the molecular and cellular mechanisms of cortical development and evolution. In particular, she is interested in how mammalian six-layer structure was developed during evolution. Using time-lapse imaging and functional analyses of subplate neurons, she found this cell population's novel function in regulating radial neuronal migration.

Developmental Neuroscience

Laboratory HP: https://www.igakuken.or.jp/stroke-renaiss/

Staff

Researchers
Keisuke KAMIMURA
Takuma KUMAMOTO
Yumiko HATANAKA
Keiko MORIYA-ITO
Yasuhiro MATSUMURA
Katsuko TAKASAWA

Research Assistants
Kumiko HIRAI
Aiko ODAJIMA
Yoshiko TAKAHASHI
Ayako MORITA
Yukiko MAKINO

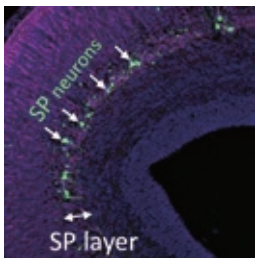
Students
Hitomi ACHIWA
Ayumu MORIOKA
Kyosuke WADA
Haruka NOMURA
Yusuke SUGITA
Ryoka KATAYAMA
Xianghe SONG
Yurika NOGUCHI
Shouma ISHIZUKA

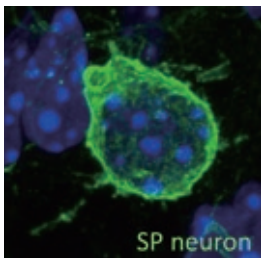
Research Summary

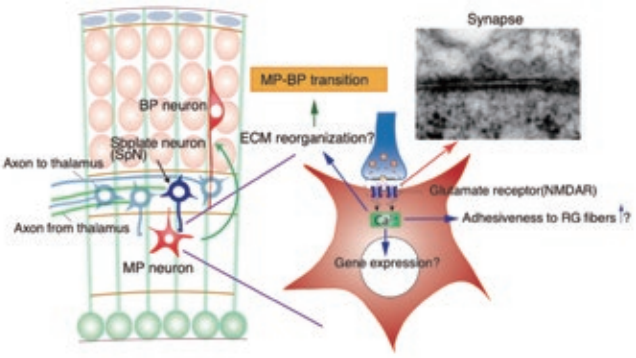
Mechanisms of Neural Network ormation: Neocortical development and synapse formation

How does the mammalian neocortex acquire the unique six-layered structure considered to be the structural basis for the remarkable evolution of complex neural circuits? We focus on subplate (SP) neurons that develop and mature too early during cortical development but disappear postnatally to approach this question. Recently, we found that SP neurons play an essential role in radial neuronal migration via direct interaction with young migrating neurons. Moreover, the SP layer is surrounded by a rich extracellular matrix (ECM), suggesting that it may be an important signaling center for mammalian corticogenesis. Functional elucidation of the SP layer should lead to a better understanding of brain development during evolution.

"We are interested in transient neural circuits that involve SpN and form during development. The proper balance of the spontaneous activity of the SpN and the activity elicited from sensory input is essential for brain development, and we want to elucidate the mechanisms involved."







Selected Publications

Kumamoto T and Ohtaka-Maruyama C (2022) "Visualizing Cortical Development and Evolution: A Toolkit Update" ***Front Neurosci.,*** 16,876406

Miyatake S, et al. (2021) "Polymicrogyria: a novel ATP1A3-related phenotype." ***Science Advances,*** 7(13): eabd2368.

Ohtaka-Maruyama C (2020) "Subplate neurons as an organizer of mammalian neocortical development. "***Front. Neuroanat***. 14, 8.

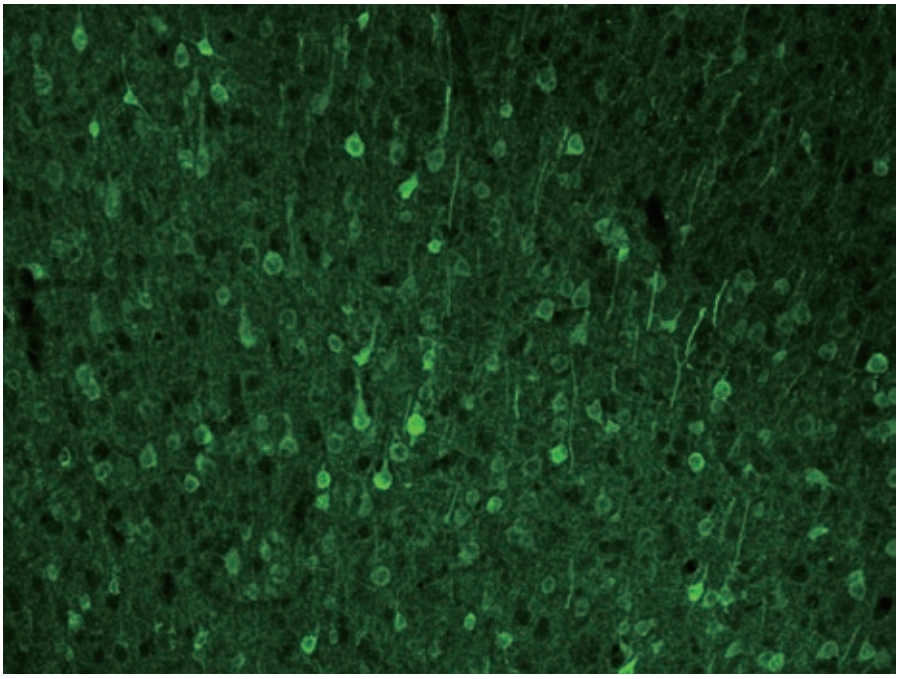
Nomura T, et al. (2020) "Changes in Wnt-dependent neuronal morphology underlie the anatomical diversification of neocortical homologs in amniotes." ***Cell Reports, 31***,107592.

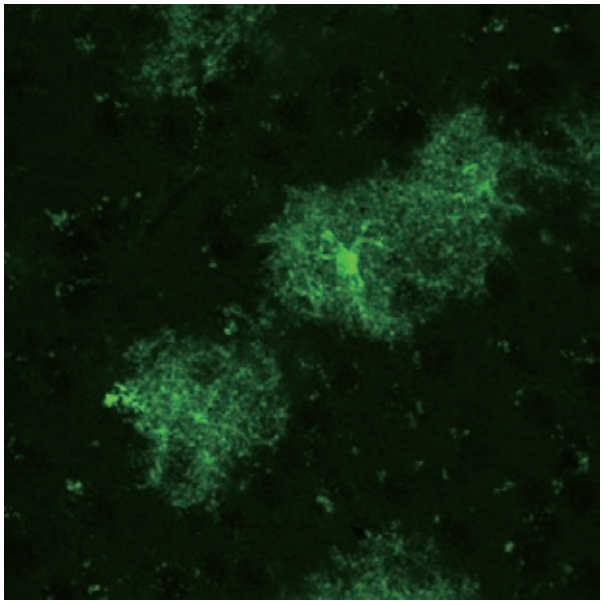
Kamimura K et al. (2019) "The HSPG Glypican Regulates Experience-Dependent Synaptic and Behavioral Plasticity by Modulating the Non-Canonical BMP Pathway." ***Cell Reports, 28***, 3144-3156.

Ohtaka-Maruyama C, et al. (2018) "Synaptic transmission from subplate neurons controls radial migration of neocortical neurons." ***Science*** 360, 313-317

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

Kamimura, K, et al. (2013) "Perlecan regulates bidirectional Wnt signaling at the Drosophila neuromuscular junction." ***J Cell Biol***. 200, 219-233.





Cortical pyramidal neurons expressing a fluorescent probe for monitoring intracellular ATP concentration (ATeam; top), and cortical astrocytes expressing a fluorescent probe for cytoplasmic calcium ions (Yellow Cameleon-Nano50; bottom)

Psychiatry & Behavioral Sciences

Project Leader
Makoto ARAI

Makoto Arai has been the leader of the schizophrenia research project since April 2015. After obtaining his master's degree from the Department of Biological Science and Technology at Tokyo University of Science, he obtained his Ph.D. in engineering from Tokyo University of Science in 2002. He then shifted his research focus to molecular mechanisms causing schizophrenia as a postdoctoral fellow under the supervision of Dr. Masanari Itokawa 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
Masanari ITOKAWA
Kazuya TORIUMI
Hiroaki ISHIDA

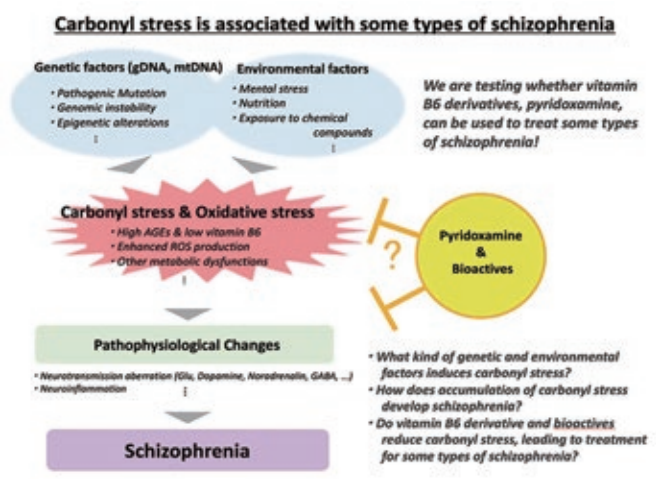
Research Assistants
Eriko MAKIYAMA
Koichi TABATA
Hidetoshi TAKAGI
Tomoko INOUE

Students
Yasuhiro MIYANO
Mai ASAKURA
Tianran WANG
Kyoka IINO
Mayuko MASADA
Azuna OZAWA
Yasufumi TOMITA
Amika YASUMURA

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

Toriumi, K. et al. (2023) Glucuronic acid is a novel source of pentosidine, associated with schizophrenia. ***Redox biology***, 67, 102876.

Tomita, Y. et al. (2023). Urinary exosomal microRNAs as predictive biomarkers for persistent psychotic-like experiences. ***Schizophrenia***, 9(1), 14.

Tabata, K. et al. (2022). Hair zinc levels and psychosis risk among adolescents. ***Schizophrenia***, 8(1), 107.

Suzuki K, et al. (2022) "Role of advanced glycation end products in the longitudinal association between muscular strength and psychotic symptoms among adolescents." ***Schizophrenia*** (Heidelb). 8(1):44.

Toriumi K, et al. (2022) "Role of glyoxalase 1 in methylglyoxal detoxification-the broad player of psychiatric disorders." ***Redox Biol***. 49:102222.

Iino K, et al. (2021) "AKR1A1 Variant Associated With Schizophrenia Causes Exon Skipping, Leading to Loss of Enzymatic Activity." ***Front Genet***. 12:762999.

Miyashita M, et al. (2021) "Fingertip advanced glycation end products and psychotic symptoms among adolescents." ***NPJ Schizophr***. 7:37.

Toriumi K, et al. (2021) "Combined glyoxalase 1 dysfunction and vitamin B6 deficiency in a schizophrenia model system causes mitochondrial dysfunction in the prefrontal cortex."***Redox Biology*** 45: 102057.

Toriumi K, et al. (2021) "Vitamin B6 deficiency hyperactivates the noradrenergic system, leading to social deficits and cognitive impairment." ***Transl Psychiatry***. 11: 262.

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
Yoshiki MATSUDA
Tohru KODAMA

Research Assistants
Takashi KOJIMA
Yasuko SEKI
Yoshiko HONDA
Hiroko SHIMBO
Nobuyuki OZAWA
Takiko SHINOZAKI

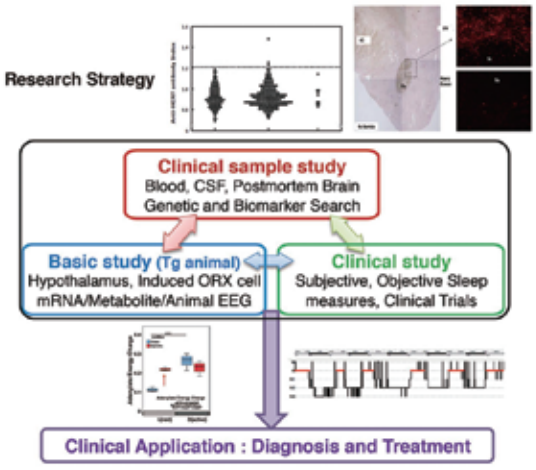
Visiting Scientist
Mihoko SHIMADA

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

Yoshida-Tanaka K, et al (2023) Narcolepsy type I-associated DNA methylation and gene expression changes in the human leukocyte antigen region. ***Sci Rep***. 2023 Jun 28;13(1):10464 .doi: 10.1038/s41598-023-37511-4.

Natsubori A et al. (2022) Serotonergic neurons control cortical neuronal intracellular energy dynamics by modulating astrocyte-neuron lactate shuttle ***iScience*** 26, 105830, 2023 doi: 10.1016/j.isci.2022.105830.

Miyagawa T, et al (2022) A rare genetic variant in the cleavage site of prepro-orexin gene is associated with idiopathic hypersomnia. ***npj Genomic Medicine*** 7:29 [2022/4/12]

Honda M, et al (2022) Low carnitine palmitoyltransferase 1 activity is a risk factor for narcolepsy type 1 and other hypersomnia. ***Sleep*** 45:zsac160

Miyagawa T, et al (2022) A variant in orexin receptor-2 is associated with self-reported daytime sleepiness in the Japanese population. ***J Hum Genetics*** 67:377-380

Honda M, et al (2021) Evaluation of pathological sleepiness by Multiple Sleep Latency Test and 24-hour polysomnography in patients suspected of idiopathic hypersomnia. ***Psychiatry Clin Neurosci*** 75:149-151

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) Epigenome-wide association study of narcolepsy-affected lateral hypothalamic brain and overlapping DNA methylation profiles between narcolepsy and multiple sclerosis. ***Sleep*** 43:zsz198

Shimada M, et al (2020) Metabolome analysis using cerebrospinal fluid from narcolepsy type 1 patients. ***Sleep.*** 43:zsaa095.

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
Soichiro IDE
Daisuke NISHIZAWA
Masayo FUJITA
Seii OHKA
Hiroko KOTAJIMA
Yuki MORIYA

Research Assistants
Yoko HAGINO
Junko HASEGAWA
Yuiko IKEKUBO
Yuki SERITA
Yuko EBATA
Kyoko NAKAYAMA

Students
Aimi YAMAGISHI
Yasuharu YAMAGUCHI
Masato OKITSU
Joei ZOU
Ryunosuke MARUYAMA
Jun ARAIDA
Yuna KANG
Futaba UMEMURA
Mayuko HAYASHI
Rina AIDA
Rina OKOUCHI

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.

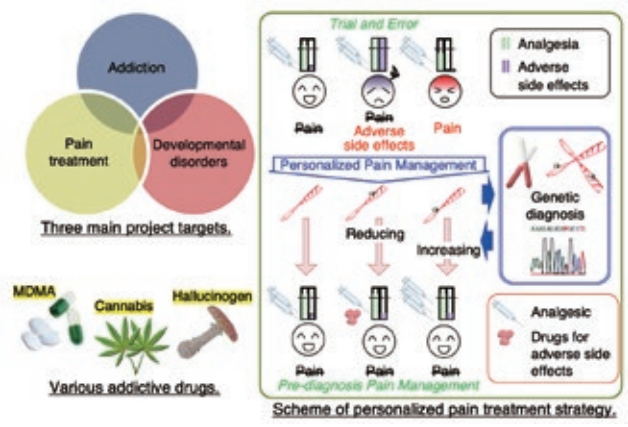
Some addictive drugs are also widely used as analgesics and for the treatment of developmental disorders. Some molecules that are involved in the actions of addictive drugs may be shared between analgesia and developmental disorders. The goals of our project are the following:

(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.



Selected Publications

Nishizawa D, et al. (2023) "Genome-Wide Association Study Identifies Novel Candidate Variants Associated with Postoperative Nausea and Vomiting." ***Cancers (Basel)*** 15:4729.

Kashii H, et al. (2023) "Tsc2 mutation rather than Tsc1 mutation dominantly causes a social deficit in a mouse model of tuberous sclerosis complex." ***Hum Genomics*** 17:4.

Kotajima-Murakami H, et al (2022). "Exposure to GABAA receptor antagonist picrotox in inpregnant mice causes autism-like behaviors and aberrant gene expression in offspring. "***Front Psychiatry*** 13:821354

Ide S, et al. (2021) "Caenorhabditis elegans exhibits morphine addiction-like behavior via the opioid-like receptor NPR-17." ***Front Pharmacol***, 12:802701

Ohka S, et al. (2021) "Heparan sulfate 3-O-sulfotransferase 4 is genetically associated with herpes zoster and enhances varicella-zoster virus-mediated fusogenic activity." ***Mol Pain*** 17:17448069211052171.

Kasai S, et al. (2021) "Short tandem repeat variation in the CNR1 gene associated with analgesic requirements of opioids in postoperative pain management." ***Front Genet*** 13:815089.

Frontier Research Laboratory

Laboratory HP: https://www.igakuken.or.jp/frontier01/

Head researcher,
independent research group
Shinobu HIRAI

Staff

Shinobu HIRAI
Jonghyuk PARK
Shoko TAMURA
Hiroko SHIMBO
Kyoko OFUSA
Yayoi ONODERA
Kayoko HIROKADO
Sena UCHIDA
Nobuyuki ARUGA

Research Summary

Sugars are critical to brain function since they are the energy source required for neurons and glial cells. Our goals are to elucidate the dynamics of sugar movement in the brain and to examine how alterations in sugar dynamics affect physiological brain activity to cause or aggravated brain diseases (Figure 1).

Using a mouse model, we recently determined that excess sugar consumption during adolescence is a potential contributing factor to psychological disease (Science Advances, doi: 10.1126/sciadv.abl6077). In these mice, brain capillary angiopathy and impairment of glucose transport from blood vessels to the brain parenchyma were observed along with psychiatric-like symptoms. In addition, the connection between sugar metabolism and Alzheimer's disease is so strong that Alzheimer's disease has been described as a third type of diabetes. These evidences indicate that breakdowns in metabolic pathways and sugar homeostasis are almost certain to contribute to the development and severity of psychological and neurological diseases. Our work will contribute to the development of new drugs to improve metabolism and novel treatments for psychological and neurological diseases.

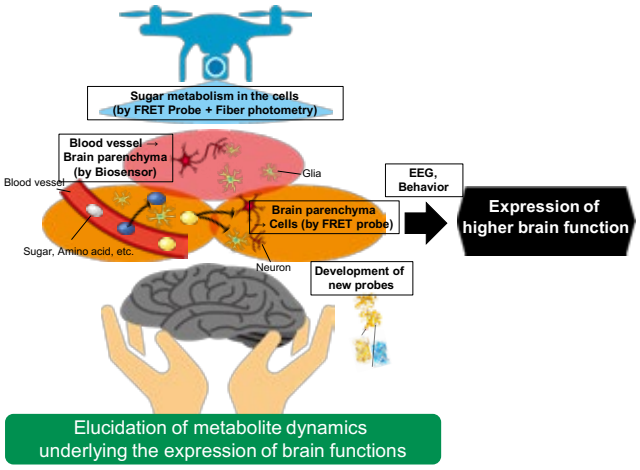


Figure 1. Conceptual diagram of our research. To understand the effects sugar dynamics have on higher brain functions by identification of cells contributing to sugar transport to the brain (construction and behavioral analyses of conditional knock-out mice) and analyses of intra- and extracellular sugar metabolism (using fiber photometry, FRET probes and biosensors).

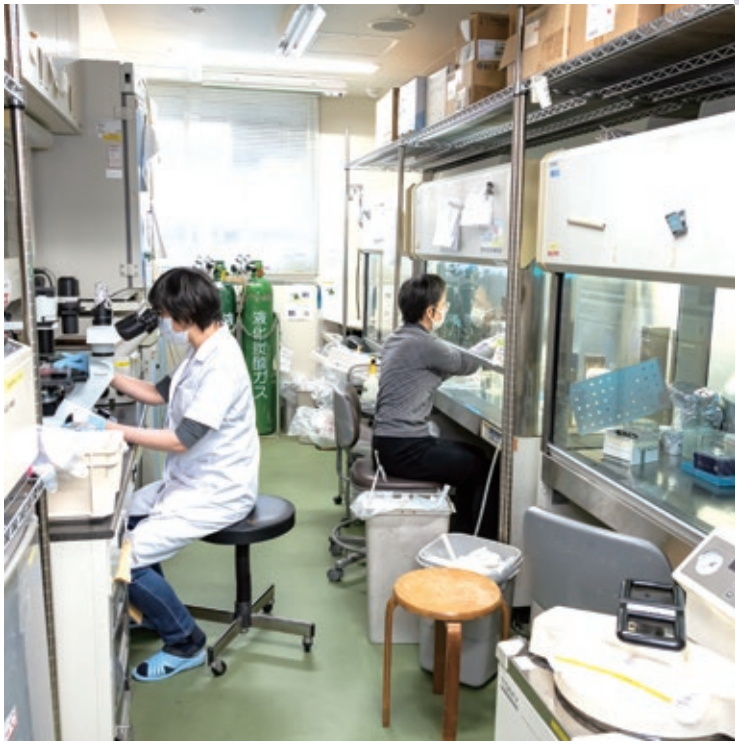
Selected Publications

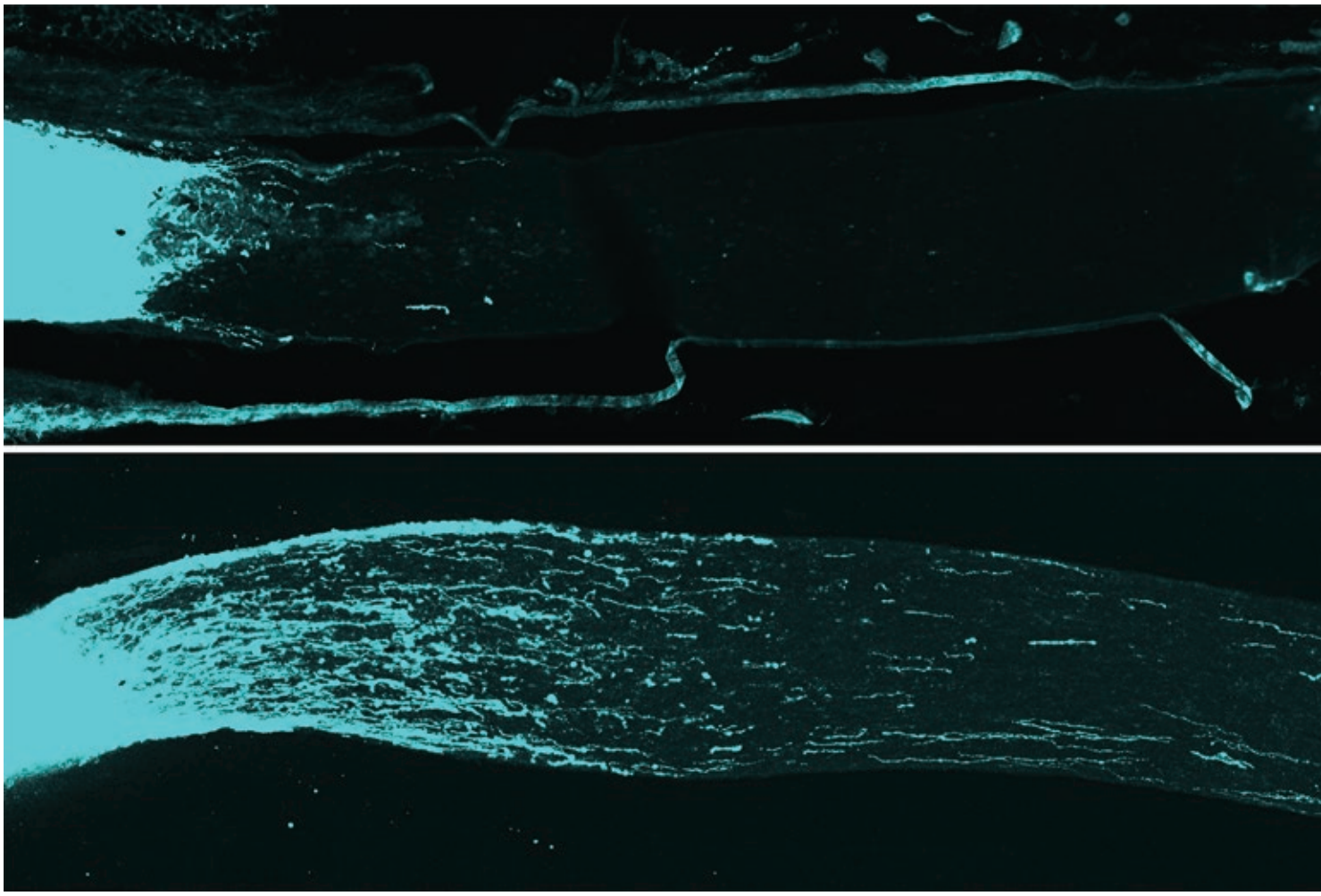
Hirai S.*, Sakuma A, Kunii Y, Shimbo H, Hino M, Izumi R, Nagaoka A, Yabe H, Kojima R, Seki E, Arai N, Komori T, Okado H* (2023). Disease specific brain capillary angiopathy in schizophrenia, bipolar disorder, and Alzheimer's disease. ***J Psychiatr Res***, 163 74-79.

Hirai S. et al. (2023) "The mouse model of intellectual disability by ZBTB18/RP58 haploinsufficiency shows cognitive dysfunction with synaptic impairment." ***Molecular Psychiatry*** doi: 10.1038/s41380-023-01941-3.

Hirai S. et al. (2021) "High Sucrose Diets Contribute to Brain Angiopathy with Impaired Glucose Uptake, and Psychosis-related Higher Brain Dysfunctions in Mice" ***Science Advances*** 7: eabl6077.

Hirai S. et al. (2017) "AMPA glutamate receptors are essential for sensory-organ formation and morphogenesis in the basal chordate" ***PNAS*** 114: 3939-3944.


炭酸ガス



Regenerating axons in mouse optic nerve after injury. Intraocular injection of DOCK3 activator induced axon regeneration (bottom) compared to control (top).

Diseases & Infection

Project Leader
Fumihiko YASUI

Viral Infection Control

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

Fumihiko Yasui has been the leader of the Viral Infection Control Project since 2017. He received Ph.D in 2004 from Graduate School of Engineering, University of Yamanashi. He joined The Tokyo Metropolitan Institute of Medical Science as a postdoctoral fellow in 2004 and started to work on mechanisms of pathogenesis of viral infections. He is interested in how immunity controls viral infection, and how viruses escape from host defense.

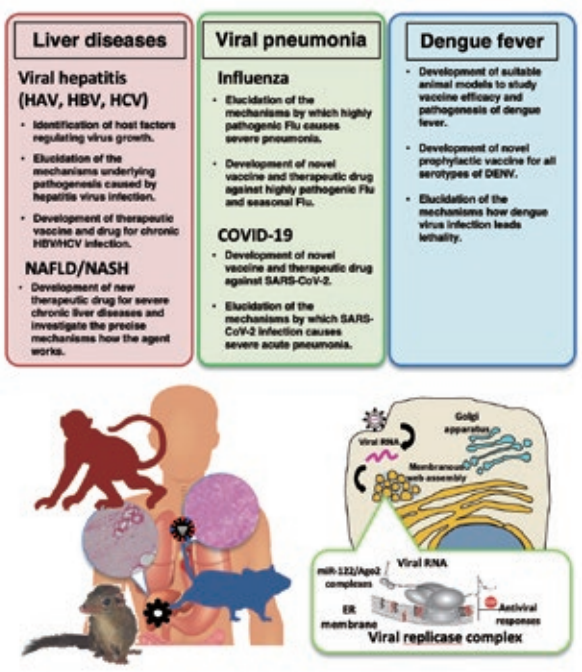
Staff

Researchers
Michinori KOHARA
Tsubasa MUNAKATA
Daisuke YAMANE
Kenzaburo YAMAJI
Naoki YAMAMOTO
Takahiro SANADA
Tomoko HONDA

Research Assistants
Asako TAKAGI
Risa KONO
Sakiko TOYAMA

Research Summary

Our project studies the virology, immunology, vaccinology and therapy of incurable viral diseases. We currently focus on liver diseases, viral acute pneumonia and dengue fever. However, the lack of suitable infection models in vitro and in vivo has hampered the clarification of viral pathogenesis. To overcome this problem, we have been developing various animal models including transgenic mice, humanized mice with human liver cells, monkeys and tree shrews. We also investigate the precise mechanisms by which host factors regulate viral growth.



Selected Publications

Yamaji K, et al. (2023) "HYPERLINK "https://pubmed.ncbi.nlm.nih.gov/37647690/ "Molecular insights of a CBP/-catenin-signaling inhibitor on nonalcoholic steatohepatitis-induced liver fibrosis and disorder." ***Biomed Pharmacother***. 166:115379.

Toyama S, et al. (2023) "HYPERLINK "https://pubmed.ncbi.nlm.nih.gov/37545501/"Application of spatial transcriptomics analysis using the Visium system for the mouse nasal cavity after intranasal vaccination." ***Front Immunol***. 14:1209945.

Matsumoto M, et al. (2023) "HYPERLINK "https://pubmed.ncbi.nlm.nih.gov/37094077/"CSNK2B modulates IRF1 binding to functional DNA elements and promotes basal and agonist-induced antiviral signaling." ***Nucleic Acids Res***. 51(9):4451-4466.

Sanada T, et al.(2023)"Antibody response to third and fourth BNT162b2 mRNA booster vaccinations in healthcare workers in Tokyo, Japan." ***J Infect Chemother***.29(3):339-346.

Ishigaki H, et al. (2022) "An attenuated vaccinia vaccine encoding the SARS-CoV-2 spike protein elicits broad and durable immune responses, and protects cynomolgus macaques and human ACE2 transgenic mice from SARS-CoV-2 and its variants." ***Front Microbiol***. 13:967019.

Yasui, F, et al. (2022) "Infection with the SARS-CoV-2 B.1.351 variant is lethal in aged BALB/c mice." ***Sci Rep***. 12: 4150.

Sanada T, et al. (2022) "Serologic survey of IgG against SARS-CoV-2 among hospital visitors without a history of SARS-CoV-2 infection in Tokyo, 2020-2021." ***Journalof Epidemiology***. 32(2):105-111.

Project Leader
Satoshi KOIKE

Satoshi KOIKE has been the leader of Neurovirology Project since 2005. He received Ph.D in 1987 from the Graduate School of Medicine, the University of Tokyo. He started his work on poliovirus, a neurotropic enterovirus, at Tokyo Metropolitan Institute of Medical Science in 1987 with Dr. Akio Nomoto. After he stayed several years at Institute Pasteur in Paris and National Institute for Basic Biology in Okazaki, he began to study on enterovirus 71 (EV71) and other related enteroviruses at Tokyo Metropolitan Institute of Neuroscience in 1998. His group identified Scavenger receptor B2 as the receptor for EV71 and generated a transgenic mouse model susceptible to EV71. His current interest is molecular mechanism of infection and pathogenesis of enteroviruses.

Neurovirology

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

Staff

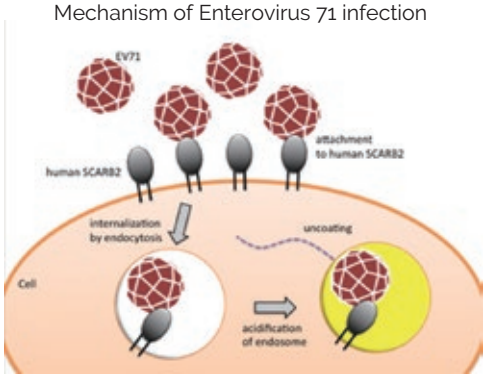
Researchers
Kyousuke KOBAYASHI

Research Assistants
Masako UKAJI
Namiko NOMURA
Tomoha NISHIZAWA
Sayaka ESAKI
Noriko KITAMURA

Research Summary

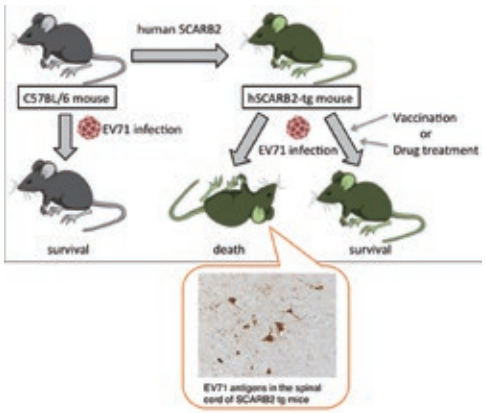
Enterovirus 71 (EV71), a human enterovirus species A of the genus Enterovirus within the Picornaviridae family, is known to be one of the causative agents of hand-foot-and-mouth disease (HFMD). HFMD is generally a mild and self-limiting disease. However, in some infants and young children, HFMD caused predominantly by EV71 can be complicated by neurological manifestations. Thus, EV71 infection is a serious public health concern. Unfortunately, there is still very little information concerning EV71 pathogenesis, and vaccines or anti-EV71 drugs have yet to be developed.

Research Topics
Mechanism of Enterovirus 71 infection



We recently found that Scavenger receptor B2 (SCARB2) is a receptor for EV71. SCARB2 plays a central role in early stages of EV71 infection. SCARB2 is able to mediate binding of the virus at the cell surface, internalization of the virus and initiation of uncoating.

Development of an animal model for Enterovirus 71 infection



Transgenic mice expressing human SCARB2 are susceptible to EV71, and are a useful model for the study of EV71 pathogenesis and vaccine efficacy.

Selected Publications

Miwatashi W, et al. (2022)"Mouse Scarb2 Modulates EV-A71 Pathogenicity in Neonatal Mice." ***J. Virol.***,96:(15)e0056122

Tamura K, et al. (2022) "TAK - 021, an inactivated Enterovirus 71 vaccine candidate, provides cross-protection against heterologous sub-genogroups in human scavenger receptor B2 transgenic mice." ***Vaccine,***40:(24)3330-7

Kobayashi K, et al. (2021) "Virulence of Enterovirus A71 Fluctuates Depending on the Phylogenetic Clade Formed in the Epidemic Year and Epidemic Region." ***J. Virol.,***95:(23) e0151521

Kobayashi K, et al. (2020) "Heparan sulfate attachment receptor is a major selection factor for attenuated enterovirus 71 mutants during cell culture adaptation." ***PLoS Pathog.,*** 18:16(3)e1008428

Imura A, et al. (2020) "Development of an Enterovirus 71 Vaccine Efficacy Test Using Human Scavenger Receptor B2 Transgenic Mice." ***J. Virol.,*** 94:(6)e01921-19

Kobayashi K, et al. (2018) "Amino Acid Variation at VP1-145 of Enterovirus 71 Determines Attachment Receptor Usage and Neurovirulence in Human Scavenger Receptor B2 Transgenic Mice." ***J. Virol.,*** 92:(15)e00681-18

Project Leader
Takayuki HARADA

Takayuki Harada has been the head of the Visual Research Project since 2011 and a visiting professor in the Department of Ophthalmology at Tokushima University since 2013. He obtained his MD from Hokkaido University School of Medicine in 1992 and worked as a long-term fellow of the Human Frontier Foundation at the University of Texas Southwestern Medical Center in 2001, and as a molecular neuroscientist at the Medical Research Institute of Tokyo Medical and Dental University in 2002, before becoming the director of the Molecular Neurobiology Research Division of the Tokyo Metropolitan Institute of Neuroscience in 2004.

Visual Research

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

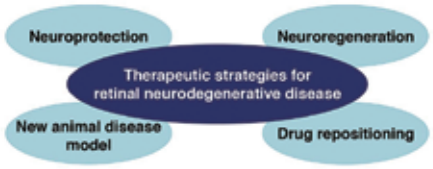
Staff

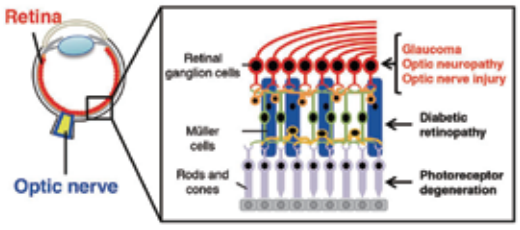
Researchers
Kazuhiko NAMEKATA
Youichi SHINOZAKI
Xiaoli GUO
Chikako HARADA
Takahiko NORO
Euido NISHIJIMA
Yuta KITAMURA
Naoki KIYOTA
Akiko SOTOZONO

Research Assistants
Mayumi KUNITOMO
Tomoko HARA

Research Summary

More than 1.6 million people in Japan are visually impaired and the number of patients with conditions such as glaucoma and diabetic retinopathy is increasing. We seek to elucidate mechanisms involved in the onset of visual impairments such as optic neuritis, develop a neuroprotective retinal therapy using animal disease models, and establish methods to promote regeneration of the optic nerve.





Apoptosis signal related kinase 1 (ASK1) is a mitogen-activated protein kinase kinase kinase that has been shown to cause neuroinflammation, but its mechanism of action has been unclear. We generated conditional knockout mice that lack ASK1 in immune cells or glial cells to assess the cell-type-specific roles of ASK1 in experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis (MS). We found that ASK1 is required in microglia and astrocytes to cause and maintain neuroinflammation by a proinflammatory feedback loop between these two cell types. Disruption of this feedback loop by suppression of glial ASK1 may be a novel and effective approach for reducing neuroinflammation.

We have also been examining the role of DOCK-D family proteins in neuroinflammation. DOCK proteins are atypical guanine nucleotide exchange factors, and we found that deficiencies in DOCK10 reduced neuroinflammation in EAE. Thus, inhibition of DOCK10 may be useful for treatment of diseases such as MS and optic neuritis.

The Rho-ROCK pathway regulates actin cytoskeleton and dynamics, and we have recently reported that application of the Rho-ROCK inhibitor ripasudil eyedrops promoted optic nerve regeneration and neuroprotection by suppressing phosphorylation of CRMP2 and cofilin, two proteins involved in the Rho-ROCK pathway.

Selected Publications

Shinozaki Y, Namekata K, Guo X, Harada T (2024) "Glial cells as a promising therapeutic target of glaucoma: beyond the IOP." ***Frontiers in Ophthalmology*** 3, 1310226.

Namekata K, Tsuji N, Guo X, Nishijima E, Honda S, Kitamura Y, Yamasaki A, Kishida M, Takeyama J, Ishikawa H, Shinozaki Y, Kimura A, Harada C, Harada T (2023) "Neuroprotection and axon regeneration by novel low-molecular-weight compounds through the modification of DOCK3 conformation." ***Cell Death Discovery*** 9, 166.

Kiyota N, Namekata K, Nishijima E, Guo X, Kimura A, Harada C, Nakazawa T, Harada T (2023) "Effects of constitutively active K-Ras on axon regeneration after optic nerve injury." ***Neuroscience Letters*** 799, 137124.

Nishijima E, Honda S, Kitamura Y, Namekata K, Kimura A, Guo X, Azuchi Y, Harada C, Murakami A, Matsuda A, Nakano T, Parada LF, Harada T (2023) "Vision protection and robust axon regeneration in glaucoma models by membrane-associated Trk receptors." ***Molecular Therapy*** 31(3), 810-824.

Inoue-Yanagimachi M, Himori N, Uchida K, Tawarayama H, Sato K, Yamamoto M, Namekata K, Harada T, Nakazawa T (2023) "Changes in glial cells and neurotrophic factors due to rotenone-induced oxidative stress in Nrf2 knockout mice." ***Experimental Eye Research*** 226, 109314.

Shinozaki Y, Leung A, Namekata K, Saitoh S, Nguyen HB, Takeda A, Danjo Y, Morizawa Y, Shigetomi E, Sano F, Yoshioka N, Takebayashi H, Ohno N, Segawa T, Miyake K, Kashiwagi K, Harada T, Ohnuma S, Koizumi S (2022) "Astrocytic dysfunction induced by ABCA1 deficiency causes optic neuropathy." ***Science Advances*** 8(44), eabq1081.

Guo X, Kimura A, Namekata K, Harada C, Arai N, Takeda K, Ichijo H, Harada T (2022) "ASK1 signaling regulates phase-specific glial interactions during neuroinflammation." ***PNAS*** 119(6), e2103812119.

Brahma MM, Takahashi K, Namekata K, Harada T, Goshima Y, Ohshima T (2022) "Genetic inhibition of collapsin response mediator protein-2 phosphorylation ameliorates retinal ganglion cell death in normal-tension glaucoma models." ***Genes to Cells*** 27(8), 526-536.

Project Leader
Kazunori SANGO

After graduation from Yokohama City University School of Medicine in 1988, Kazunori Sango worked at Yokohama City University Hospital as a physician and saw many patients suffering from diabetic neuropathy and other complications. Inspired by that experience, he started to study the pathogenesis of diabetic neuropathy at Department of Physiology, Yokohama City University as a graduate student. He received Ph.D in 1992, and continued to work on pathogenic mechanisms of diabetic neuropathy and other neurodegenerative disorders at National Institutes of Health, USA (1993-1996), National Institute of Health and Nutrition, Japan (1996-1999), Tokyo Metropolitan Institute of Neuroscience (1999-2011), and Tokyo Metropolitan Institute of Medical Science (2011-). He has been the leader of the Diabetic Neuropathy Project since 2015, and his current interest is therapeutic approaches focusing on the cross-talks among the pathogenic factors of diabetic neuropathy, in particular, collateral glycolysis pathways, glycation and oxidative stress.

Diabetic Neuropathy

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

Staff

Researchers
Mari SUZUKI
Hideji YAKO
Naoko NIIMI
Shizuka TAKAKU

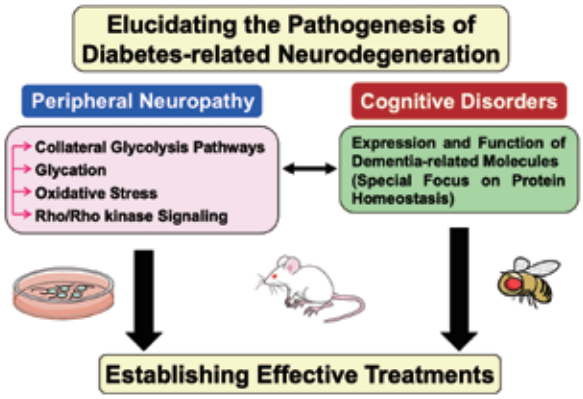
Research Assistants
Kumi SUMIDA

Visiting Scientists
Koichi KATO
Tatsufumi MURAKAMI
Junji YAMAUCHI
Hitoshi KAWANO
Ken MURAMATSU
Keiichiro MATOBA
Ryosuke SHINOUCHI

Research Summary

One of the most common complications of Diabetes Mellitus, and its symptoms such as pain and numbness can be the cause of insomnia and depression. When allowed to progress to more advanced disease stages, peripheral neuropathy can result in serious consequences such as lower limb amputation and lethal arrhythmia. In addition, recent studies have indicated that diabetes is a major risk factor for cognitive disorders such as Alzheimer's disease.

The goals of our project are as follows:
1. Establishing effective pathogenesis-based treatments for diabetic peripheral neuropathy.
2. Elucidating mechanistic links between metabolic dysfunction and neurodegenerative diseases.



Project1:
Therapeutic Approaches to Diabetic Peripheral Neuropathy

Using diabetic model animals and culture systems of adult rodent dorsal root ganglion (DRG) neurons and immortalized Schwann cells, we seek to establish effective pathogenesis-based treatments for peripheral neuropathy.

Project2:
Mechanistic link between Metabolic dysfunction and Neurodegenerative Diseases

By using a Drosophila model, we aim to understand the molecular mechanism by which metabolic conditions influence misfolding protein-induced neurodegeneration.

Selected Publications

Suzuki M, et al. (2023) A Drosophila model of diabetic neuropathy reveals a role of proteasome activity in the glia. ***iScience*** 26:106997.

Muramatsu K, et al. (2023) Motor skills training-induced activation of descending pathways mediating cortical command to hindlimb motoneurons in experimental diabetic rats. ***Exp Neurol*** 363:114357.

Osonoi S, et al. (2022) RAGE activation in macrophages and development of experimental diabetic polyneuropathy. ***JCI Insight*** 7:e160555.

Nagai Y, et al. (2022) Rho-associated, coiled-coil-containing protein kinase 1 regulates development of diabetic kidney disease via modulation of fatty acid metabolism. ***Kidney Int.*** 102:536-545.

Yako H, et al. (2021) Role of pyruvate in maintaining cell viability and energy production under high-glucose conditions. ***Sci. Rep.*** 11:18910.

Takaku S, et al. (2021) Exendin-4 promotes Schwann cell survival/migration and myelination in vitro. ***Int. J. Mol. Sci.*** 22:2971.

Mizukami H, et al. (2020) Role of glucosamine in development of diabetic neuropathy independent of aldose reductase pathway. ***Brain Commun.*** 2:fcaa168.

Lee JS, et al. (2019) Arylsulfatase A, a genetic modifier of Parkinson's disease, is an α -synuclein chaperone. ***Brain*** 142:2845-2859.

*Nakamura S, *Oba M, et al. (2019) Suppression of autophagic activity by Rubicon is a signature of aging. ***Nat. Commun.*** 10:847. (*co-first authors)

Project Leader
Yuichiro MIYAOKA

Yuichiro Miyaoka has been the leader of the Regenerative Medicine Project since 2016.
He received his Ph.D. from the Institute of Molecular and Cellular Biosciences, the University of Tokyo under the supervision of Dr. Atsushi Miyajima in 2009. After receiving his Ph.D., he worked as a staff scientist in the Dr. Atsushi Miyajima's lab from 2009 to 2011. Then, he did his postdoctoral training in the Bruce Conklin's lab at Gladstone Institutes, USA from 2011 to 2015, where he developed the first digital PCR-based method to detect genome editing outcomes. He applied this method to isolate genome-edited cells without antibiotic selection. His current interest is to apply genome editing in human iPS (induced pluripotent stem) cells to cure genetic disorders by disease modeling, cell transplantation therapy, and direct genetic manipulation in patients' cells. For these therapeutic applications, genome editing should be precise. Therefore, he also aims to improve the accuracy and predictability of genome editing.

Regenerative Medicine

Laboratory HP: https://www.igakuken-regmed.com/home

Staff

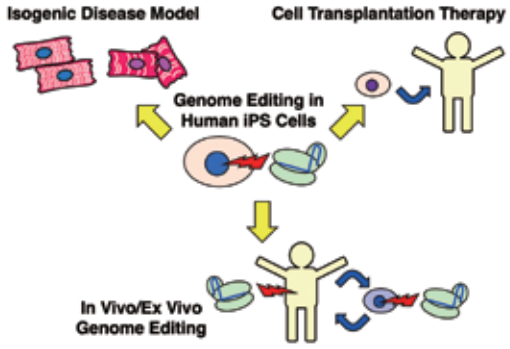
Researchers
Tomoko KATO-INUI
Gou TAKAHASHI

Students
Ittetsu NAKAJIMA
Anri SAITOH
Minato MAEDA
Lanyu HUANG
Kayoko SHINOZAKI
Kanata IMAMURA
Yuga YASUDA

Research Summary

Genome editing technology allows us to rewrite the genetic information in virtually any species and any cell type including human cells. Our focus is on human iPS cells, a type of pluripotent stem cell that can be generated from patients' cells by introduction of specific transcription factors, and differentiated into other cell types. Our goal is to use genome editing in iPS cells to both model human diseases, and develop new therapies. To achieve this goal, we are addressing the following challenges.

1) To establish isogenic disease models for cardiomyopathy, hepatic disease, and neuronal disease to study their pathogenesis.
2) To develop therapeutic strategies by transplantation of genetically engineered iPS cells to cure genetic disorders.
3) To establish a way to directly manipulate genetic information in patients' cells.
4) To improve the accuracy and predictability of genome editing.



Our goal and approaches: By introducing or correcting pathogenic mutations in iPS cells, we can establish isogenic disease models to study molecular pathogenic mechanisms. We are modeling cardiomyopathy, hepatic disease, and neuronal disease. Genetically engineered iPS cells can also be used for transplantation therapies. We can potentially correct mutations in iPS cells derived from patients, or even engineer the cells to express therapeutic molecules. We are targeting metabolic diseases by cell transplantation therapies. Because human iPS cells maintain the normal human genomic information, genome editing in human iPS cells can be used as a model to develop a way to directly manipulate genetic information in patients' cells. We are also trying to improve the accuracy and predictability of genome editing technology.

Selected Publications

Nakajima I, et al. (2023) "In Vivo Delivery of Therapeutic Molecules by Transplantation of Genome-Edited Induced Pluripotent Stem Cells." ***Cell Transplant***. 32:9636897231173734.

Takahashi G, et al. (2022) "Genome editing is induced in a binary manner in single human cells." ***iScience***. 25:105619.

*Song D, *Takahashi G, et al. (2022) "Retinoids rescue ceruloplasmin secretion and alleviate oxidative stress in Wilson's disease-specific hepatocytes." ***Hum. Mol. Genet***. 31:3652-3671.

*Fenix AM, *Miyaoka Y, et al. (2021) "Gain-of-function cardiomyopathic mutations in RBM20 rewire splicing regulation and re-distribute ribonucleoprotein granules within processing bodies." ***Nat Commun***. 12:6324.

Kato-Inui T, et al. (2018) "Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 with improved proof-reading enhances homology-directed repair." ***Nucleic Acids Res.*** 46: 4677-4688.

Miyaoka Y, et al. (2018) "Detection and Quantification of HDR and NHEJ Induced by Genome Editing at Endogenous Gene Loci Using Droplet Digital PCR." ***Methods Mol. Biol.*** 1768: 349-362.

Miyaoka Y, et al. (2016) "Systematic quantification of HDR and NHEJ reveals effects of locus, nuclease, and cell type on genome-editing." ***Sci. Rep.*** 6: 23549.

Miyaoka Y, et al. (2014) "Isolation of single-base genome-edited human iPS cells without antibiotic selection." ***Nat. Methods*** 11: 291-293.

Project Leader
Hidetaka TANNO

Cancer Immunology

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

Hidetaka Tanno has been the leader of the Cancer Immunology Project since 2021. He obtained his Ph.D. in 2013 from the Tokyo Institute of Technology where he studied ubiquitin-dependent protein degradation under the supervision of Prof. Masayuki Komada. After graduating, he worked as a postdoctoral fellow and focused on the development of new technologies in immunology under the supervision of Prof. George Georgiou at The University of Texas at Austin. During this time, he developed a facile single-cell sequencing technology that can determine T cell receptor (TCR) and antibody sequences at the repertoire level. At TMIMS, he is using this technology to 1) elucidate TCR repertoires in cancer patients and 2) develop new cancer therapeutics.

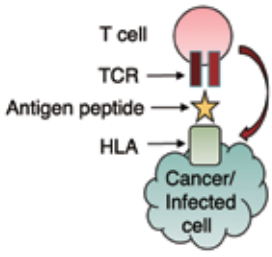
Staff

Researchers
Mayumi SAEKI
Rikio YABE
Kazuhisa AOKI

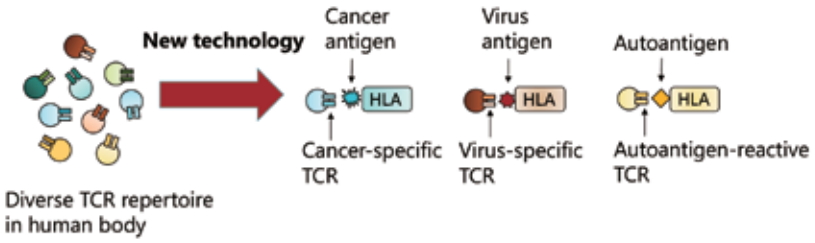
Research Assistants
Sayaka ONO
Yuri TANNO

Research Summary

T cells play a critical role in adaptive immunity. They express an enormous repertoire of TCRs on their surfaces. Using these TCRs, T cells recognize antigen-HLA complexes presented by pathogenic cells and eliminate them. Therefore, elucidating the interactions between TCRs and antigen-HLA complexes will be useful for developing new therapeutics and preventive vaccines. For example, cancer-specific TCRs have shown promising results in recent clinical trials. However, it is still difficult to find useful antigen-specific TCRs. In our project, we are developing new technology that can identify TCR-antigen-HLA interactions in a high-throughput manner. By employing this technology, we are comprehensively analyzing cancer patients' TCR-antigen-HLA repertoires to discover cancer-specific TCRs that can be used for T cell therapies. We will also apply this technology to elucidate the mechanisms of virus infections and autoimmune diseases.



T cells recognize antigen-HLA complexes presented by pathogenic cells using TCRs.



There are diverse TCRs in human bodies including cancer-specific TCRs and virus-specific TCRs. Characterizing antigen-specificities of TCRs is necessary for engineered T cell therapy as well as vaccine development. However, it has been difficult to determine the antigen-specificities of TCRs. We are developing new technologies to identify TCR and antigen-HLA interactions at the repertoire level.

Selected Publications

K Lee et al. (2023) "Peripheral T cell activation, not thymic selection, expands the T follicular helper repertoire in a lupus-prone murine model" ***PNAS.*** 120(48):e2309780120

M Kuraoka et al. (2022) "Infant Antibody Repertoires during the First Two Years of Influenza Vaccination" ***mBio.*** 13(6):e0254622.

J Li et al. (2021) "Molecular Level Characterization of Circulating Aquaporin-4 Antibodies in Neuromyelitis Optica Spectrum Disorder" ***Neurology Neuroimmunology&Neuroinflammation.*** 8(5):e1034.

H Tanno et al. (2020) "A Facile Technology for the High Throughput Sequencing of the Paired VH:VL and TCRβ:TCRα Repertoires." ***Science Advances.*** 6(17):eaay9093

H Tanno et al. (2020) "Determinants governing T cell receptor α/β-chain pairing in repertoire formation of identical twins" ***PNAS.*** 117(1):532-540.

CH Lee et al. (2017) "IgG Fc domains that bind C1q but not effector Fcγ receptors delineate the importance of complement-mediated effector functions." ***Nature Immunology.*** 18(8):889-898

JR McDaniel et al. (2016) "Ultra-high-throughput sequencing of the immune receptor repertoire from millions of lymphocytes." ***Nature protocols.*** 11(3):429-42.

B Wang et al. (2016) "Discovery of high affinity anti-ricin antibodies by B cell receptor sequencing and by yeast display of combinatorial VH: VL libraries from immunized animals." ***mAbs.*** 8(6):1035-44.


T100 Thermal Cycler

Research Centers

Vice Director
Hideya KAWAJI

Hideya Kawaji has been the vice director of Center for Genome & Medical Sciences since 2020. He received Ph.D from the Graduate School of Engineering Science, Osaka University in 2003. He started his research in information science, development of a method to explore conserved sequence domain in uncharacterized amino acid sequences. He then moved to RIKEN to study transcriptome and its regulation through transcription starting site (TSS) profiles at base-pair levels, with development of computational and experimental methodologies. After working as researcher, unit leader, coordinator at RIKEN and visiting associate professor at Yokohama City University, he moved to the current position. His current interest is the logic of gene regulation encoded in the human genome sequences, impacting our health and diseases.

Genome & Medical Sciences

https://www.igakuken.or.jp/genome-center/

Staff

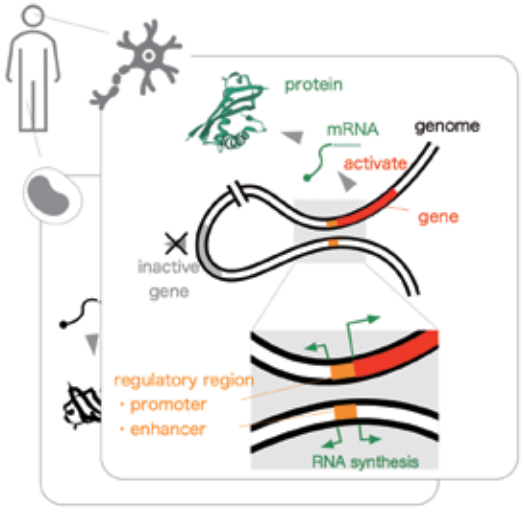
Director
Hisao MASAI
Senior Researcher
Keisuke OBOKI

Researcher
Nobumasa WATANABE
Naoko YOSHIZAWA
Toyoaki NATSUME
Yuichiro HARA
Saki SAITO
Research Assistant
Ryoko WADA
Naomi IDA

Research Summary

Our body consists of around thirty-seven trillion cells, each of them carries almost identical genetic information composed of three billion base-pairs. Meanwhile, individual cells express a unique subset of genes, not all, and the expressed ones comprise the molecular basis within (or outside sometimes) the cells. Our genomes carry the structural information specifying both expressed molecules (genes), and the regulatory signals orchestrating molecules to be present in the cells (regulatory elements).

Given that such protein coding sequences occupy only 1 ~ 2% of the genome, identification of functional regions within the remaining 98 ~ 99% is crucial in understanding human biology as well as in interpretation of human diseases. Through a unique RNA profiling technology, called CAGE (Cap Analysis Of Gene Expression), that determines frequency of transcription initiation at the base-pair resolution across the genome, we discovered a series of regulatory regions, called promoters and enhancers, 10-fold or more than the protein coding genes. It indicates presence of still uncovered regulatory regions, and raises a challenge to assess their contribution to the expression of genes. We are going to tackle these challenges by combining high-throughput genome-wide experiments with large-scale computing. We will also seek the opportunities of collaborations with other research groups in TMIMS to accelerate medical science in individual fields, and with hospitals to understand diseases and to develop new diagnostics and therapeutic tools.



Selected Publications

Ueno Y, et al. (2023) "Use of clinical variables for preoperative prediction of lymph node metastasis in endometrial cancer". ***Jpn J Clin Oncol.*** hyad135.

Jayakumar V, et al. (2021) "Chromosomal-scale de novo genome assemblies of Cynomolgus Macaque and Common Marmoset." ***Sci Data.*** 8(1):159.

Abugessaisa I, et al. (2021) "FANTOM enters 20th year: expansion of transcriptomic atlases and functional annotation of non-coding RNAs." ***Nucleic Acids Res.*** 49(D1):D892-D898.

Ito Y, et al. (2021) "Nanopore sequencing reveals TACC2 locus complexity and diversity of isoforms transcribed from an intronic promoter." ***Sci Rep.*** 11(1):9355.

Hirabayashi S, et al. (2019) "NET-CAGE characterizes the dynamics and topology of human transcribed cis-regulatory elements." ***Nat Genet.*** 51(9):1369-1379.

Yoshida, E., et al. (2017) "Promoter-level transcriptome in primary esions of endometrial cancer identified biomarkers associated with ymph node metastasis." ***Sci. Rep.*** 7(1):14160

Takamochi,K., et al. (2016) "Novel biomarkers that assist in accurate discrimination of squamous cell carcinoma from adenocarcinoma of the ung."***BMC Cancer*** 16(1): 760.

Kawaji, H., et al. (2014) "Comparison of CAGE and RNA-seq ranscriptome profiling using clonally amplified and single-molecule ext-generation sequencing."***Genome Res.*** 24(4):708–717.

Forrest, A.R.R., Kawaji,H., et al. (2014) "A promoter-level mammalianÞxpression atlas." ***Nature,*** 507(7493):462–70.

Director Unit Leader
Atsushi NISHIDA

Atsushi Nishida has been the leader of the Unit for Mental Health Promotion and the director of the Research Center for Social Science and Medicine since 2020. Previously he worked as a research scientist from 2008 to 2010 at the Tokyo Institute of Psychiatry, and from 2010 to 2014 at the Tokyo Metropolitan Institute of Medical Science. He was a visiting scientist at University College of London MRC Unit in Lifelong Health & Aging from 2012 to 2014, and the project leader for the Mental Health Promotion Project at the Tokyo Metropolitan Institute of Medical Science from 2015 to 2020.

Mental Health Promotion

https://www.igakuken.or.jp/english/r-center_en/rc-social_e/unit-mhp.html

Staff

Researchers

Syudo YAMASAKI
Mitsuhiro MIYASHITA
Kaori BABA
Junko NIIMURA
Satoshi YAMAGUCHI

Research Summary

Mental health is important for one's quality of life (QOL). During adolescence, healthy physical and mental development lays the foundations for a better QOL and is also an integral part of a flourishing society. On the other end of the spectrum, since we live in a hyper-aging society where it is not uncommon for people to live to 100, more and more old people are experience dementia. It is therefore necessary to create a social system that allows people with dementia to live happy healthy lives.
The Unit for Mental Health Promotion examines mental health issues that have a direct impact on the health and livelihoods of Tokyo residents, from childhood mental health issues to dementias affecting the elderly. We use research methods from both social and clinical epidemiology, including cohort studies and randomized controlled trials, to better understand the societal and environmental conditions which will enrich people's mental well-being from birth to old age. In this way, we aim to contribute towards building a society which promotes the mental health needs of the people of Tokyo and elsewhere.

Teen Cohort is a project that scientifically examines how to support young people as they face the future and grow into adults.

We are promoting the participation of people with mental illnesses in creating a platform for them to participate in research and service planning.

We have developed a care program to support people with dementia, and are verifying the effectiveness of the program and promoting it to all municipalities in Tokyo.

Selected Publications

DeVylder J, Yamaguchi S, Hosozawa M, Yamasaki S, Ando S, Miyashita M, Endo K, Stanyon D, Usami S, Kanata S, Tanaka R, Minami R, Hiraiwa-Hasegawa M, Kasai K, Nishida A (2023) Adolescent Psychotic Experiences before and during the COVID-19 Pandemic: a Prospective Cohort Study. ***Journal of Child Psychology and Psychiatry***, 2023 Nov 13. Online ahead of print.

Narita Z, DeVylder J, Yamasaki S, Ando S, Endo K, Miyashita M, Yamaguchi S, Usami S, Stanyon D, Knowles G, Hiraiwa-Hasegawa M, Furukawa TA, Kasai K, Nishida A (2023) Uncovering associations between gender nonconformity, psychosocial factors, and mental health in adolescents: a prospective birth cohort study. ***Psychological Medicine***, 1-10.

Hosozawa M, Ando S, Yamaguchi S, Yamasaki S, DeVylder J, Miyashita M, Endo K, Stanyon D, Knowles G, Nakanishi M, Usami S, Iso H, Furukawa TA, Hiraiwa-Hasegawa M, Kasai K, Nishida A (2023) Sex difference in adolescent depression trajectory before and into the second year of COVID-19 pandemic. ***Journal of the American Academy of Child & Adolescent Psychiatry***, 2023 Oct 4:S0890-8567(23)02127-5. Online ahead of print.

Yamaguchi S, Ando S, Miyashita M, Usami S, Yamasaki S, Endo K, DeVylder J, Stanyon D, Baba K, Nakajima N, Niimura J, Nakanishi M, Hiraiwa-Hasegawa M, Kasai K, Nishida A (2023) Longitudinal relationships between help-seeking intentions and depressive symptoms in adolescents. ***Journal of Adolescent Health***, 73(2023)1061-1067.

Okada Y, Yamasaki S, Nishida A, Shibasaki R, Nishiura H (2023) Night-time population consistently explains the transmission dynamics of coronavirus disease 2019 in three megacities in Japan. ***Frontiers in Public Health***, 2023 11, 1163698.

Unit Leader
Yuki NAKAYAMA

Yuki Nakayama received her Ph.D. from Tokyo University of Health and Science in 2006 after working as a nurse. She joined the Tokyo Metropolitan Institute of Medical Science in 2007.
She has been a project leader for intractable disease care nursing since 2015.
Her specialty is the nursing research for intractable diseases, and she has carried out research on the support of the social participation of ventilator users and research activities contributing to respiratory management and improvement of QOL.

Intractable Disease Nursing Care

https://nambyocare.jp/
https://www.igakuken.or.jp/english/r-center_en/rc-social_e/unit-idnc.html

Staff

Researchers
Michiko HARAGUCHI
Chiharu MATSUDA
Akiko OGURA
Yumi ITAGAKI

Research Assistants
Saori KAWAMURA
Sachiko KOBAYASHI
Kaoru MORISHITA
Kayoko SHIMIZU
Kazuyo SHIMIZU
Yoshie SANO
Chizu MAEDA

Research Summary

Since the establishment of our laboratory, we have pursued methods for alleviating sufferings related to human dignity such as difficulty in breathing, inability to swallow food, and inability to communicate, as well as support systems for living a safe and secure life for recuperation in familiar areas, targeting ALS (amyotrophic lateral sclerosis) patients who are said to have the most severe medical and disability needs. This unit aims to contribute to the improvement of the quality of life of people living with incurable diseases by presenting a home care support model in Japan, which is facing a super-aging society, while inheriting this tradition.
Our Research Objectives are,

To promote the practical application of new communications support technologies and create a support system that can be used when needed

To improve nursing care that will lead to the dignity and life maintenance of patients with ALS and other severe disabilities

To promote the enhancement of a safe care environment and support system through the promotion of home care safety and health activities for patients with intractable diseases

Selected Publications

Shimizu T , Nakayama Y, Hayashi K, et al.(2023) Somatosensory pathway dysfunction in patients with amyotrophic lateral sclerosis in a completely locked-in state. ***Clinical Neurophysiology*** 156,253-261,

Matsuda C, Shimizu T, Nakayama Y, et al.(2023) Clinical relevance of macroglossia to disease progression in ventilation dependent patients with advanced ALS. ***Neurol Sci***. 44(6):2025-2031

Nakayama Y, Shimizu T*, Matsuda C ,Haraguch M et al. (2022) "Body Weight Gain is Associated with the Disease Stage in Advanced Amyotrophic Lateral Sclerosis with Tracheostomy and Invasive Ventilation, Metabolites." ***Metabolites 2022,*** Volume 12, Issue 2, 191

CazzolliPA, BrooksRB, Nakayama Y et al.(2020) "The Oral Secretion Scale and Prognostic Factors for Survival in Subjects. With Amyotrophic Lateral Sclerosis." ***Respiratory Care***. 65(8)1063-107

Nakayama Y, Shimizu T, Matsuda C, Haraguchi M, et al. (2019) "Body weight variation predicts disease progression after invasive ventilation in amyotrophic lateral sclerosis." ***Scientific Reports*** volume 9, s41598-019-48831-9

Shimizu T, Nakayama Y, Matsuda C, Haraguchi M, et al. (2019) "Prognostic significance of body weight variation after diagnosis in ALS: a single-centre prospective cohort study." ***Journal of Neurology*** .266(6), 1412–1420

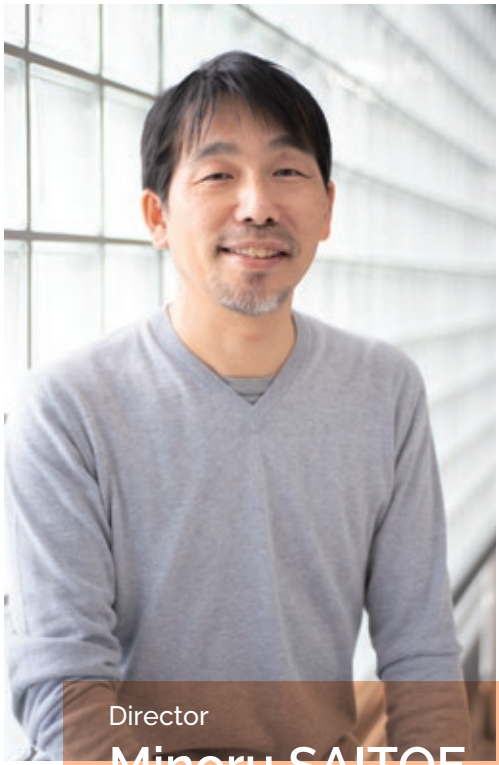
Matsuda C, Shimizu T, Nakayama Y, Haraguchi M. (2019) "Cough peak flow decline rate predicts survival in patients with amyotorophic lateral sclerosis" ***Muscle & Nerve***. 59(2) 168-173.

Shimizu T, Nakayama Y, et al. (2018) "Sensory cortex hyperexcitability predicts short survival in amyotrophic lateral sclerosis." ***Neurology*** 1 ;90(18): e1578-e1587.

Nakayama Y, Shimizu T,Matsuda C, et al. (2018) "Non-Motor Manifestations in ALS Patients with Tracheostomy and invasive ventilation." ***Muscle and Nerve***. 57(5):735-741.

Nakayama Y, Shimizu T, Matsuda C, et al. (2016) "Predictors of impaired communication in amyotrophic lateral sclerosis patients with tracheostomy invasive ventilation." ***Amyotroph Lateral Scler Frontotemporal Degener***. 17(1-2):38-46

Research Supports



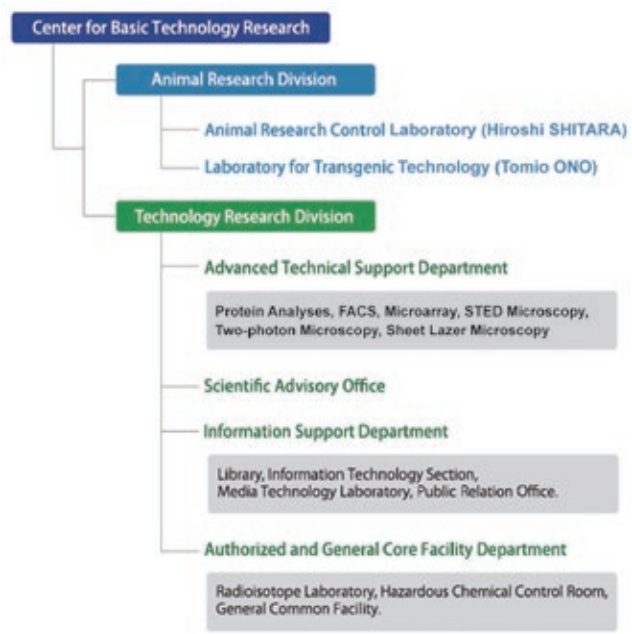
Basic Technology Research

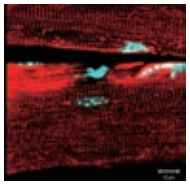
Laboratory HP: https://www.igakuken.or.jp/english/center/basic/basictech.html

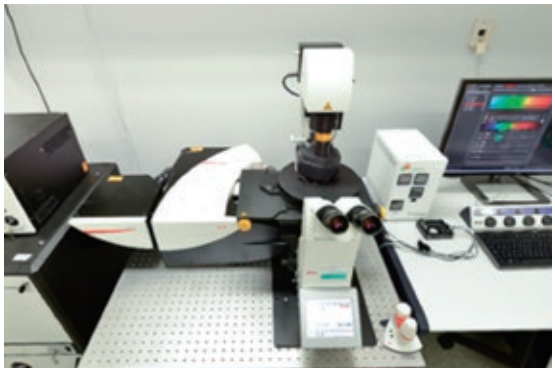
Director
Minoru SAITOE

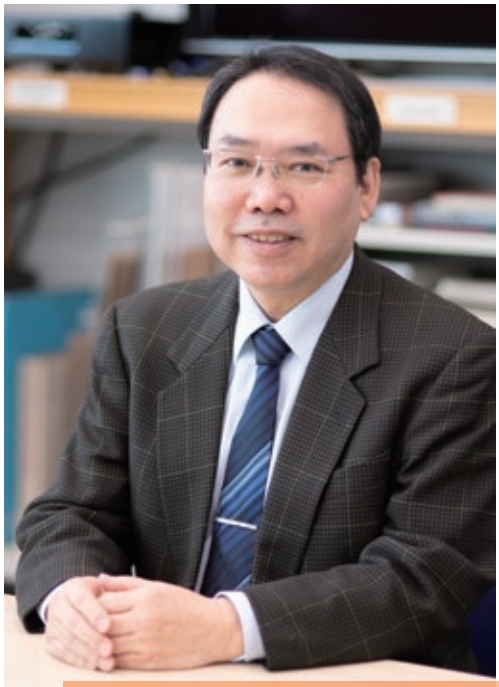
The Basic Technology Research Center provides resources to assist scientists to conduct their research efficiently. We provide state-of-the-art technologies required for biomedical and life science research and maintain various facilities used by researchers.

1. The Animal Research Division maintains our animal facilities and provides care and welfare for the animals used in research. This division assists researchers in generating transgenic and knock-out animals and maintains sperm and eggs of various mutant animal lines.
2. The Advanced Technical Support Department provides state-of-the-art technology for our scientists including facilities for protein analyses, FACS, microarrays, confocal and electron microscopy, histology and other technologies.
3. The Information Support Department consists of the library, the information technology section, the media technology laboratory, and the public relations office. It assists researchers in searching for references and information, deals with the media and public relations, and provides support for our computer systems.
4. The Authorized and General Core Facility Department consists of the radioisotope laboratory, the hazardous chemical control room, and the general common facility. It provides researchers with various special and common facilities and maintains safety standards for accident-free daily operation of the institute.









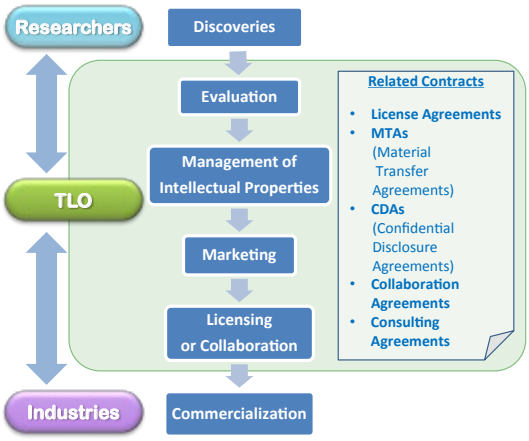
Technology Licensing Office

TLO HP: https://www.igakuken.or.jp/english/center/tlo/tlo.html

General Manager
Kazumasa AOKI

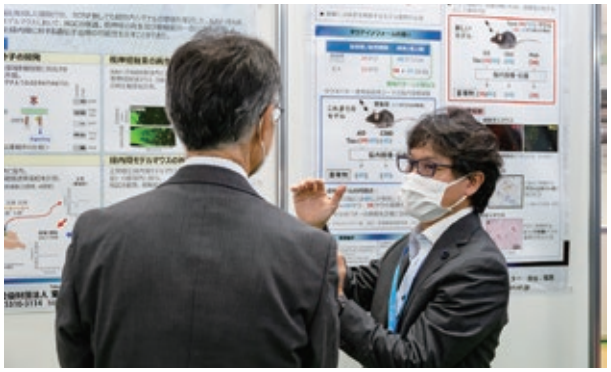
Who we are

- The Technology Licensing Office (TLO) facilitates the conversion of scientific discoveries to innovative technologies with the ultimate goal of improving public health and welfare.
- We evaluate basic research findings (seeds) as intellectual property assets, and license promising candidates to industries for development as medicines, diagnostics, medical devices, foods, cosmetics and research tools.



What we do

- We manage intellectual properties from our institute including patents, copyrights and materials in order to develop them for commercialization.
- To promote technology transfer, we introduce seeds and intellectual properties with potential commercial value to pharmaceutical, medical device, and startup companies.
- We attend business meetings such as the BIO international convention in the US, BIO-EUROPE, and BioJapan, to develop Public Private Partnership opportunities between industries and our institute.
- We support collaborative research projects with industries by arranging Joint Research Agreements, Material Transfer Agreements (MTA), and other contracts to protect and develop a wide range of research discoveries.



Director
Takayuki HARADA

Medical Research Cooperation

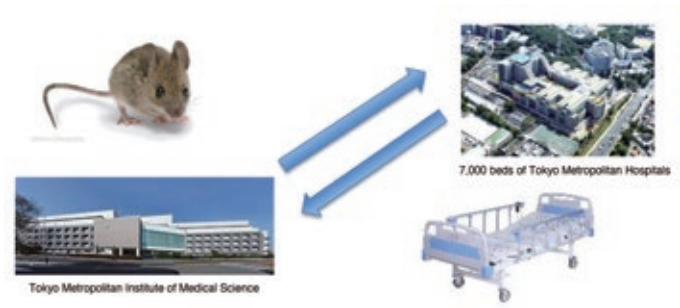
Laboratory HP: https://www.igakuken.or.jp/english/center/tr/tr.html

Staff

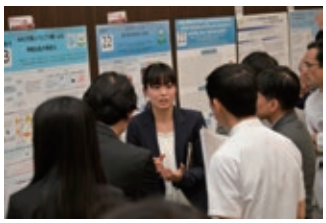
Kimi UEDA
Chikako ISHIDA
Hiroko KOUSAKA
Junya MAEDA

Strengthening Medical Research by Bringing Research Institutes and Hospitals Together - From bench to bed and back again -

We facilitate collaboration between basic scientists at research institutes and medical doctors at hospitals. We have a supporting budget of 500,000 yen for collaborative clinical studies with medical doctors at Tokyo Metropolitan Hospitals. We manage ethical issues related to human specimens and we provide specialized support for bringing knowledge and findings from basic scientific research to development of new therapy in humans.

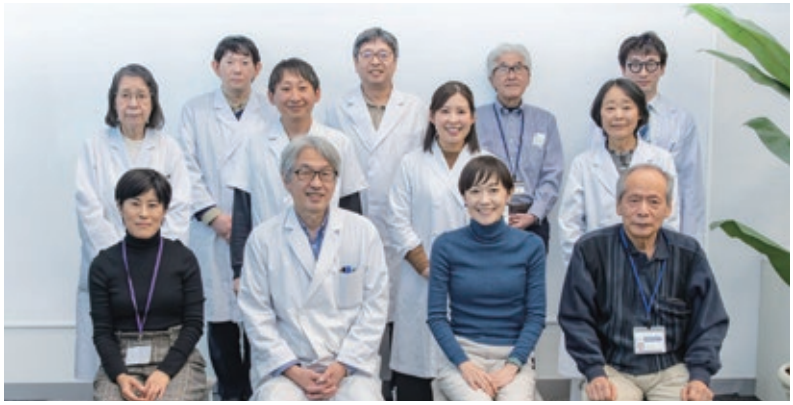


Conference with researchers and medical doctors



A young scientist discussing with medical Conference with researchers and medical doctors in conference

Molecular Pathology and Histology



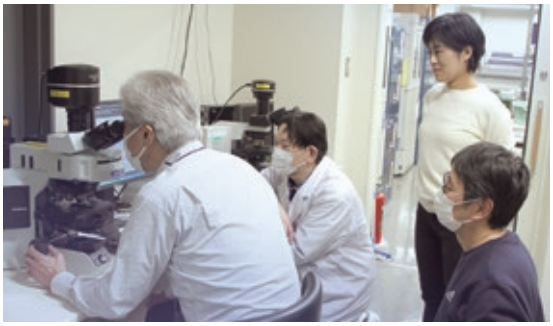
Laboratory HP: https://www.igakuken.or.jp/hist_kaiseki/

Translational Research using human materials and Management of Database for Essential Brain Anatomy & Neuropathology

Staff

Researchers
Masato HASEGAWA
Ito KAWAKAMI
Technicians
Erika SEKI
Kentaro ENDO
Kazunari SEKIYAMA
Rika KOJIMA
Kyohei MIKAMI
Yoshinobu IGUCHI
Emiko KAWAKAMI
Hiromi KONDO
Students
Araki KIMURA
Akito NAGAKURA

We mainly study the pathology of neurodegenerative diseases at the molecular level and aim to elucidate the pathogenesis of mechanisms. In addition to the further promoting neuropathological research, we aim to enhance the support for each project research and the collaborative research of metropolitan hospitals, by technicians specializing in neuropathology. Our laboratory features research use of over 5,000 human neuropathology specimens and samples, one of the largest in the world.



Public Relations and Other Activities

TMIMS Programs

Public Lectures

Each year we present 8 public lectures to inform the public of our research progress and enlighten people on various medical issues pertinent to their health and welfare. In 2023, we conducted 9 hybrid lectures.
Lecture topics included diabetes, oxitocine, Calpine, Parkinson's diseases, addiction, hearing loss, dementia, and cancer therapies..

Better understanding of type 1 diabetes
What is type 1 diabetes?
..... Rimei NISHIMURA (Jikei University School of Medicine)

Oxytocin known as the 'Love Hormone' is effective also for curing inflammation
..... Yasuhiko YAMAMOTO
(Kanazawa University Graduate School of Medical Sciences)

Regulation of calpain in neurodegenerative disease associated with gene mutations
Understanding molecular mechanism of Lissencephaly, a disorder with a brain that does not have wrinkles.
..... Masami YAMADA (University of Fukui)

Functions and relevance to disease of calpains
..... Yasuko ONO (TMIMS)

Parkinson's disease: basic medical scientist's point of view
..... Atsushi NAMBU (NIPS)

iPS cells stories: behind the discovery of iPS cells
iPS cells
..... Kazutoshi TAKAHASHI (Kyoto University)
Impact of the birth of iPS cells
..... Yuichiro MIYAOKA (TMIMS)

Addiction in the modern era
How to deal with the internet game addiction: facts and treatment
..... Ichiro SORA (Kobe University Graduate school of Medicine
Addiction: It could be your own problem!
..... Soichiro IDE (TMIMS)

Healthy Hearing and Future Society
..... Hiroshi HIBINO (Osaka University)

Preventing Dementia in the Era of 100-Year Life
..... Masahito YAMADA (Kudanzaka Hospital)




TMIMS Seminar Series on "Aging and Health"

In 2022, we had initiated a special TMiMS seminar series, "Aging and Health", where we have invited prominent scientists in the field, to have lectures of the forefront research on aging as well as of how to promote healthy life. In 2023, we initiated the second round of the series "Aging and Health 2", due to the favorite responses from the viewers. We had 8 lectures for the first round of the series, and 3 for the second round.

Aging and Heakth I and II (11 lectures for each series)
What should we do now to lead healthy, long life?
What should we eat, and how should we excercise, sleep, and care our health?

I-IV. Smart aging
..... Ryuta KAWASHIMA
(Tohoku University)

I-V. Sleep and life rhythm: Good sleep brings a happy life
..... Hideki TANAKA
(Hiroshima International University)

I-VI. What and how to eat: Nutritional science and health
..... Teiji NAKAMURA
(Kanagawa University of Human Services)

I-VII. Training your vision
..... Takayuki HARADA (TMIMS)

I-VIII. Healthy brain from healthy guts
..... Nobuyuki SUDO (Kyushu University)

I-IX. Training your memory
..... Minoru SAITOE (TMIMS)

I-X. Brain fitness: joyful light exercise for heathy and happy life
..... Hideaki SOYA (Tsukuba University)

I-XI. How does motivation improve your mind and acts?
..... Yukio NISHIMURA (TMIMS)

II-I. How will you survive the stressful society?
..... Fuyuki ISHIKAWA (Kyoto University)

II-II. How to control your blood sugar level for healthy life?
..... Kazunori SANGO (TMIMS)

II-III. How will you prepare for the era of 100 year life?
..... Akira IKEGAMI (The University of Tokyo)

Science café

In the past twelve years we have had 44 special science presentations geared toward the general public. These "science cafes" provide people of all ages with the opportunities to learn, experience, and enjoy science first hand in a casual setting. In 2023, we had one online science café on mind and brain, and two face-to-face science cafes one of which features pigments that can be isolated from microorganisms. The participants enjoyed real experiences of laboratory experiments.

Is your mind controlled by your brain?
..... Masanari ITOKAWA (TMIMS)

How to make rainbow with things in your refrigerator
..... Yuuka EGAWA, Manaka HASEBE, Junta FUNADA,
Koji KASAHARA (TMIMS)

Phycocyanin and Chlorophylls: fluorescent pigments from microorganisms
..... Manaka HASEBE , Yuuka EGAWA,
Junta FUNADA, Koji KASAHARA (TMIMS)



Institutional seminars (Igakuken Seminars)

We have institutional seminars on a regular basis. In 2023, coronavirus pandemic has finally subdued, and we had 29 seminars, (17 in face to face,and 12 on hybrid format) by both domestic and foreign scientists (seven scientists based outside the country) including those from Harvard University and Queen's University in UK. We were particularly delighted to have many seminars in a face-to-face manner this year.

Why do animals need to sleep? Studies on vertebrates and invertebrates
.....Yu HAYASHI (The University of Tokyo)

Clonal evolution in the tumor microenvironment.
.....Yosuke TOGASHI (Okayama University)

A novel angiogenesis mechanism deciphered by motility analysis of endothelial cells
.....Kazuo TONAMI (The University of Tokyo)

Developmental mechanisms that contributed to the evolution of mammalian anatomical features
.....Tadashi NOMURA
(Kyoto Prefectural University of Medicine)

The art of silence: Replication forks, histone chaperones and gene silencing in S. cerevisiae
.....Krassimir Joseph YANKULOV (University of Guelph)

Sequence-specific LINE: its strategy for survival and mechanisms of transposition
.....Haruhiko FUJIWARA (The University of Tokyo)

Mechanisms of hibernation in mammals: chipmunk as a model
.....Nobuhiko TAKAMATSU (Kitasato University)

Interactions between monoamines and glutamate in the antidepressant response: from the laboratory to the clinic
.....Pierre BLIER (University of Ottawa)

Mitochondrial aconitase 1 regulates age-related memory impairment via autophagy/mitophagy-mediated neural plasticity in middle-aged flies
.....Joong-Jean PARK (Korea University)

Toward understanding the significance and mechanisms of astrocyte heterogeneity across brain regions
.....Yuuichi HIRAOKA (Tokyo Medical and Dental University)

Neural mechanisms underlying stress-induced augmentation of cocaine cravings and behavioral addictions
.....Katsuyuki KANEDA (Kanazawa University)

Calpain-3 structure and its role in limb-girdle muscular dystrophy R1
.....Peter L. DAVIES (Queen's University)

Understanding the triplex DNA structure embedded in the genome.
.....Shintaro YAMADA (Kyoto University)

The neural cell populations that renew your memory
How is the old memory renewed and updated?
.....Akinobu SUZUKI (Toyama University / TMIMS)

Hypothalamic supramammillary region in motivated behavior and nicotine
.....Satoshi IKEMOTO (National Institute on Drug Abuse)

Evolutionary psychology of homocides
.....Mariko HASEGAWA (Japan Arts Council)

Multimodal Optical Interrogation of Neural Circuits Regulating Social Interactions
.....Masatoshi INOUE (Stanford University)

Neural basis underlying behavioral changes across the estrous cycle in females
.....Sayaka INOUE (Stanford University)

Dynamic instability of the brain shaped by aging
.....Masashi TABUCHI (Case Western Reserve University)

Cancer treatment and future prospects: Ongoing activities at the Komagome Hospital
.....Masakazu TOI (Tokyo Metropolitan Cancer and
Infectious Diseases Center Komagome Hospital)

From fMRI of the Brain to Spinal Cord at 7 Tesla
.....Robert BARRY (Massachusetts General Hospital)

Neurodegenerative diseases and chaperone-mediated autophagy
.....Takahiro SEKI (Himeji Dokkyo University)

Domestic Violence by Husbands against Wives and Children, and its Prevention
.....Daijyu ABE (Psychiatrist)

Generation and implementation of designer cells and animals using chromosome engineering techniques.
.....Yasuhiro KAZUKI (Tottori University)

Elucidating neural stem cell fates from fly to mouse
.....Tzumin LEE (University of Michigan)

What is start-up business?~ What you need to know as a scientist.
.....Megumi TAKATA (Kyushu University)

Construction of an evaluation system for the development of vaccines and treatments for dengue virus and analysis of the disease mechanism
.....Meng Ling MOI (The University of Tokyo)

Phenotypic analysis of dystonia musculorum mice with involuntary movement
.....Hirohide TAKEBAYASHI (Niigata University)

Overview of 35 years of research on systematic review, meta-analyses, and randamized controlled trial: How to publish papers in high profile journals such as BMJ, Lancet, JCO and JAMA?
.....Toshiaki FURUKAWA (Kyoto University)

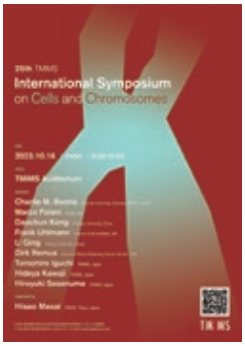
TMIMS International Symposium

In 2023, we were able to have two TMIMS International Symposia, as shown below. We invited three (24th) and six (25th) foreign scientists, and had a very exciting face-to-face presentations and heated discussion.
24th TMIMS International Symposium
"Early Detection and Social Intervention for Psychosis and Suicide" organized by Dr. Atsushi Nishida, and 25th TMIMS International Symposium "Cells and Chromosomes" organized by Dr. Hisao Masai.

We give lectures to high-school and university students who visit our institute and we also send staffs to visit schools and deliver lectures. This year, we gave face-to-face lectures at Toyama high school delivered by Yoshiaki Kikkawa.

Joint programs with universities

Many scientists at TMIMS have joint appointments as visiting professors or lecturers at various universities.
In 2023, for the first time in the last four years. We held our annual "open institute" events for prospective graduate students face to face. More than 50 students came to the event, and joined the lectures and visited laboratories. We currently have 149 students from affiliated universities and other schools, who conduct their research at our institute.



Support for students and young scientists

Research Associate Fellowships

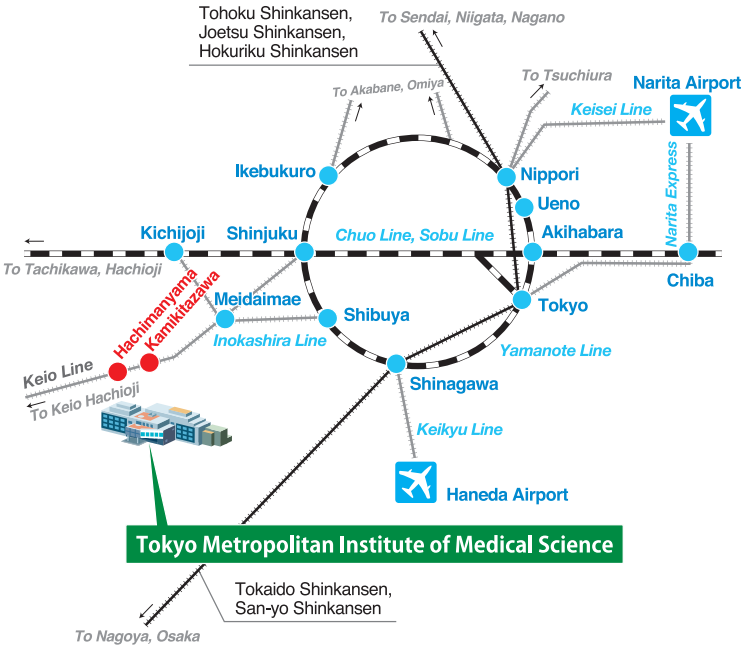
We provide graduate students who conduct their masters/Ph.D. research at TMIMS with research associate fellowships that provide them with financial support, and allow them to concentrate on their studies and research.

Travel support for young scientists attending international meetings

We provide students and young scientists at TMIMS with travel fellowships to attend international meetings where they can present their results and meet other students and scientists in their fields.

Access Map

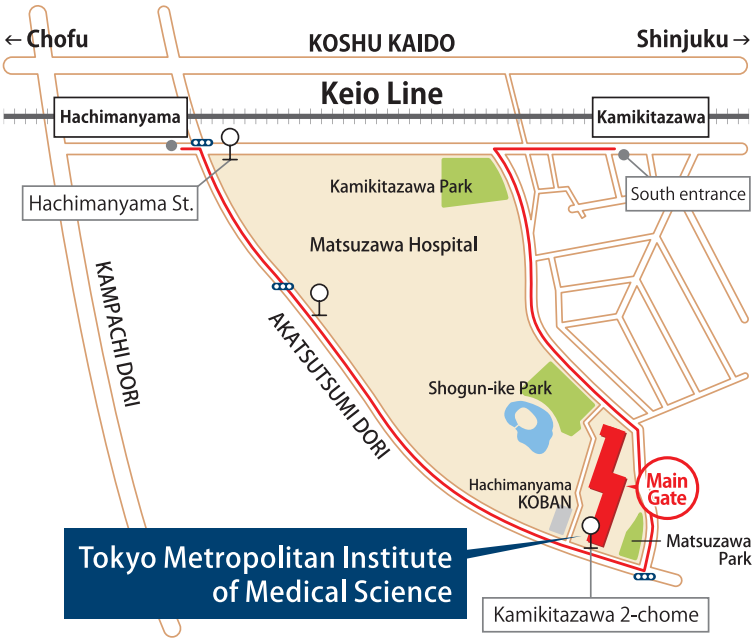
Tokyo Metropolitan Institute of Medical Science	
Address	2-1-6 Kamikitazawa, Setagaya-ku, Tokyo, 156-8506, Japan
Tel	+81-3-5316-3100
Fax	+81-3-5316-3150



AIRPORT to INSTITUTE

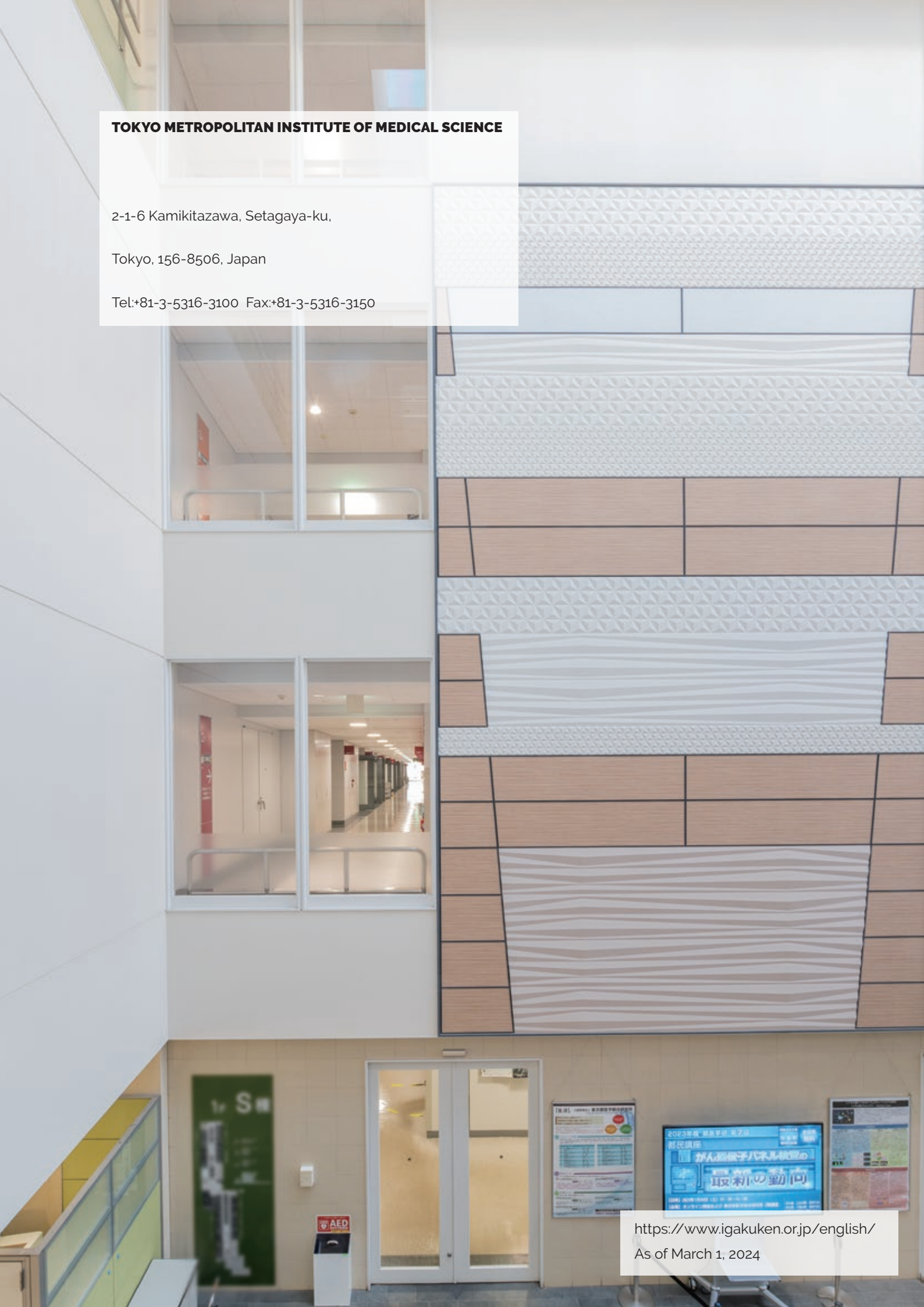
From Narita Airport to Kamikitazawa Station / Hachimanyama Station	
Narita Airport - Shinjuku Station	JR Narita Express
Shinjuku Station - Kamikitazawa Station / Hachimanyama Station	Keio Line

From Haneda Airport to Kamikitazawa Station / Hachimanyama Station	
Haneda Airport - Shinagawa Station	Keikyu Line
Shinagawa Station - Shinjuku Station	JR Yamanote Line
Shinjuku Station - Kamikitazawa Station / Hachimanyama Station	Keio Line



- **From Kamikitazawa Station to Institute**
  Walk (approx. 10 min From South entrance of Station).
- **From Hachimanyama Station to Institute**

Hachimanyama Station - Kamikitazawa 2-chome	Keio bus / Odakyu bus
Kamikitazawa 2-chome - Institute	Walk



TOKYO METROPOLITAN INSTITUTE OF MEDICAL SCIENCE

2-1-6 Kamikitazawa, Setagaya-ku,

Tokyo, 156-8506, Japan

Tel:+81-3-5316-3100 Fax:+81-3-5316-3150

https://www.igakuken.or.jp/english/

As of March 1, 2024