TMiMS

Annual Reports 2020

Contents

Message from the Chairperson

Keiji TANAKA

Tokyo is the political, economic and cultural center of Japan. Developing Tokyo into a more healthy welfare state will therefore go a long way 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 and health 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 and 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 instance, many people suffer from rare and intractable diseases that researchers often overlook. TMIMS has been actively working on these important problems, promptly and practically addressing health-related issues with the aim of protecting the health of all Tokyo citizens.

In 2020, the highly contagious COVID-19 disease spread throughout the world causing unprecedented damage at all levels of society. Combatting this disease is a top priority. At TMIMS, we swiftly set up a "Coronavirus Countermeasures Special Team" last year and in cooperation with the Tokyo Metropolitan Government, we have been making every effort to develop effective strategies to eliminate this disease. However, unfortunately, the pandemic is still ongoing and TMIMS will need to continue fundamental research in order to develop effective countermeasures to combat the disease in 2021. Throughout history there has always been an ongoing struggle between humans and infectious 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 allowed the spread of infections at unprecedented speeds. Thus, it is critically important for people in the modern world to have effective strategies for preventing infectious diseases, minimizing their spread, 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.

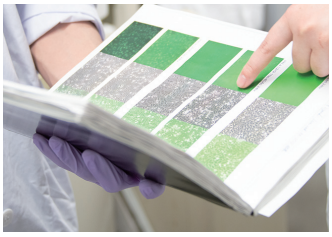
I am of the opinion that scientific research is a symbol of culture. A society cannot be considered cultured if it has no interest and knowledge of science and research. Accordingly, TMIMS aims to be acclaimed both academically and culturally for the knowledge and wisdom of its excellent researchers. 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 fundamental 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.

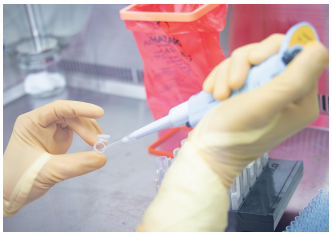
Our medical researchers are energetically pursuing their research to develop preventive medicine and new therapeutic methods to protect citizens' health. During this process, TMIMS also takes on a role in educating young researchers who will continue to develop human knowledge and contribute to social 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.

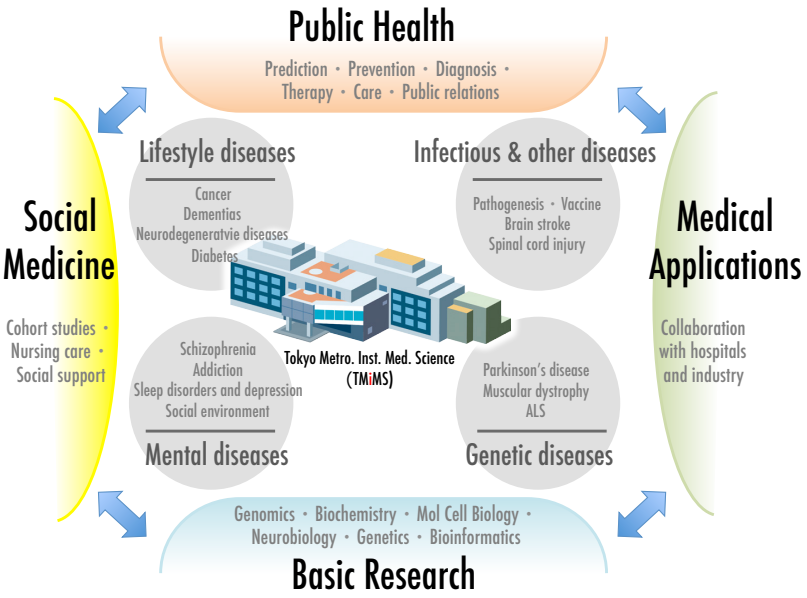
We are working to make TMIMS the world's premiere research institute, and advancing and enriching its research power will create an institute capable of providing wide-ranging services to society. To this end, the entire staff of TMIMS strives to help pursue incomparable fundamental research, and pass 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 2020

Hisao MASAI

2020 marks the 9th anniversary of the founding of the Tokyo Metropolitan Institute of Medical Science (TMIMS) from the merger of three medical institutes that had been operated independently by the Tokyo Metropolitan Government for more than 35 years. This year would have been more celebratory for us, but for the unprecedented and devastating pandemic which has affected all people on earth. 2020 started peacefully with much anticipation in Tokyo for the upcoming Olympics, but ended in a struggle to overcome the pandemic which is still ongoing.

The outbreak of COVID-19 will likely irreversibly change our way of life. We will have to learn to live with this virus and others from now on. What is different now compared to 100 years ago when the Spanish flu infected 600 million and killed 20-40 million people is that we now have better scientific tools with which we can scrutinize viruses, prevent infections, treat infected patients, analyze infection patterns, and predict the future spread.

What can we do to combat COVID-19?

As scientists working in the field of medical science, it is our responsibility to join worldwide efforts to understand the pathological mechanisms of viral spread, elucidate the causes of severe cases, develop drugs to counterattack viral proliferation and treat infection-associated symptoms, and develop effective vaccines. Indeed, we have organized a special project team in our institute to combat COVID-19. This team is composed of three research/ development groups; vaccine development, antibody screening, and interdisciplinary research.

1 Vaccine development: We are developing SARS-CoV-2 vaccines based on vaccinia virus vectors which will induce immunological responses that are longer lasting and more versatile in dealing with ever changing viruses. We are now at the stage of non-clinical testing and will start clinical testing in 2021.

2 Antibody screening: In collaboration with 14 hospitals in the Tokyo Metropolitan district, we have been monitoring SARS-CoV-2 antibodies in the general populace to track and monitor infections. We initiated this project in June and have accumulated data for more than 20,000 people in the Tokyo Metropolitan area. Data are reported to the Tokyo Metropolitan Government in order to design and develop effective policies for preventing the spread of infections.

3 Interdisciplinary research: Interdisciplinary research includes analyses of interactions between cellular glycolipids and the viral Spike protein, development of novel anti-virus drugs targeting the RNA genome, searches for genetic factors that contribute to serious cases, development of vaccine adjuvants that boost vaccine efficacy, and proteomic analyses of host responses to virus infection.

The team also includes various support groups as well as a

public relations group which reports important up-to-date scientific news regarding COVID-19 on our homepage to enlighten the general public.

In addition to these efforts, we are helping the newly established Tokyo iCDC (Centers for Disease Control and Prevention) by providing board members with expertise in viral infections, vaccine development, and statistical analyses of infectious spread.

Despite several hundred papers published every day, SARS-CoV-2 is still far from being completely understood. Why does SARS-CoV-2 cause only mild effects in children? Why are elderly people more prone to serious cases? Are antibodies against SARS-CoV-2 short-lived? Why can some people be reinfected by the virus? What are the host factors that contribute to severe infections? How do viral mutations affect transmissibility? We are currently examining these questions in order to help combat this disease and bring back the life we enjoyed pre-COVID-19.

The start of a new project term

Research at TMIMS is organized into projects with 5-year goals. The 3rd project term ended in March 2020 and the 4th term started this year. We currently have 21 projects and 6 laboratories organized in four departments: Basic Medical Sciences, Brain & Neurosciences, Psychiatry & Behavioral Sciences, and Diseases & Infections. We also established the Research Center for Genome & Medical Sciences in 2020. This center will focus on informatics analyses of genomes for both basic research and for collaborative research with hospitals aimed at developing novel diagnostic and therapeutic tools. The Research Center for Social Science & Medicine was also launched in 2020 to improve our research in social medicine using long-term cohort studies. The establishment of these centers will enable us to conduct projects that require support for longer terms and allow us to deal with problems in a more flexible manner.

Our recent findings

During the 3rd project term, Chiaki Maruyama discovered a novel role of subplate neurons in development of the six-layered structure of the cerebral cortex. She discovered that these neurons form temporary synaptic connections with recently born neurons to control their migration. This work was published in Science. Yukio Nishimura and colleagues discovered that the primary somatosensory cortex receives information about motor output even before the arrival or sensory feedback signals, suggesting that this cortex receives anticipatory information with which it can process somatosensory signals. Keisuke Kamimura found that Glypican, a heparin sulfate peptide glycan, is required for experience-dependent synaptic and behavioral plasticity. This work demonstrates the importance of extracellular matrix proteins in behaviors. Tomoyuki Miyashita and Minoru Saitoe identified cellular mechanisms by which repeated trainings establish long-term memory engram cells, an important breakthrough in understanding how memories are formed and stored in the brain. Hikaru Tsuchiya analyzed different types of ubiquitin linkages and found that the Cdc48-Rad23/Dsk2 axis is responsible for directing certain types of ubiquitin-linked substrates to proteasome-dependent protein degradation. Yukiko Yoshida uncovered a novel mechanism by which damaged lysosomes are recycled in cells. These damaged lysosomes release glycosylated polypeptides which are then ubiquitinated and target lysosomes for autophagic degradation. Yutaka Kanoh analyzed G-quadruplex structures on genomes and discovered that they are important elements for generating higher-order nuclear architecture and for regulating DNA replication timing by binding to the Rif1 DNA binding protein.

Achievements in 2020

In the 4th research term we have continued making important findings. Yasushi Saeki and colleagues continued their work on protein ubiquitination and proteasome-dependent protein degradation and found that under stressful conditions, where cells have to increase protein degradation, proteasomes and ubiquitinated substrates form liquid droplets where protein degradation occurs. This concentration of protein degradation to specific nuclei likely enhances efficiency of degradation (featured in "Meet our scientists!"). Masato Hasegawa, in collaboration with the MRC Laboratory of Molecular Biology in Cambridge, UK, reported the structures of α-synuclein filaments from different human neurodegenerative diseases. This work shows how non-genetic changes in one protein can cause distinct diseases with different symptoms. The results from the Saeki and Hasegawa projects were both published in Nature. Akihiro Yamano discovered that the optineurin-ATG9 axis is important in degradation of damaged mitochondria, shedding new light on cellular pathways by which old or non-functional organelles are recycled in cells (featured in "Meet our scientists!"). Syudo Yamazaki and Atsushi Nishida in collaboration with a group from London University, UK, analyzed the results of a 60 year cohort study and found that adolescents who actively pursued their aspirations, curiosity and interests expressed greater life satisfaction at early old ages. Akiyo Natsubori and Makoto Honda discovered that intracellular ATP levels oscillate during sleep-wake states in mouse cortical excitatory neurons. They found that ATP levels significantly decrease during REM sleep cycle, suggesting that energy consumption increases during this period of sleep.

Despite the COVID-19 pandemic, we have also continued our outreach activities, conducting five public lectures and three science café educational programs online. With the uncertain outlook for the coming year, we will continue to expand and improve our online lectures to educate the public on the importance and excitement of science and research.

Outlook for 2021

Cutting-edge basic medical research will continue to be the key to the understanding various diseases, developing preventive and therapeutic measures, and improving physical and mental health. The strength of our institute is the presence of experts in wide areas of life sciences and medical sciences who enjoy research and work together to discover previously unknown biological phenomena for the benefit of all people. In 2021, we will continue to strive for new discovery that will contribute to the health and welfare of the public.

Team Director, Special Team for COVID-19 Countermeasures

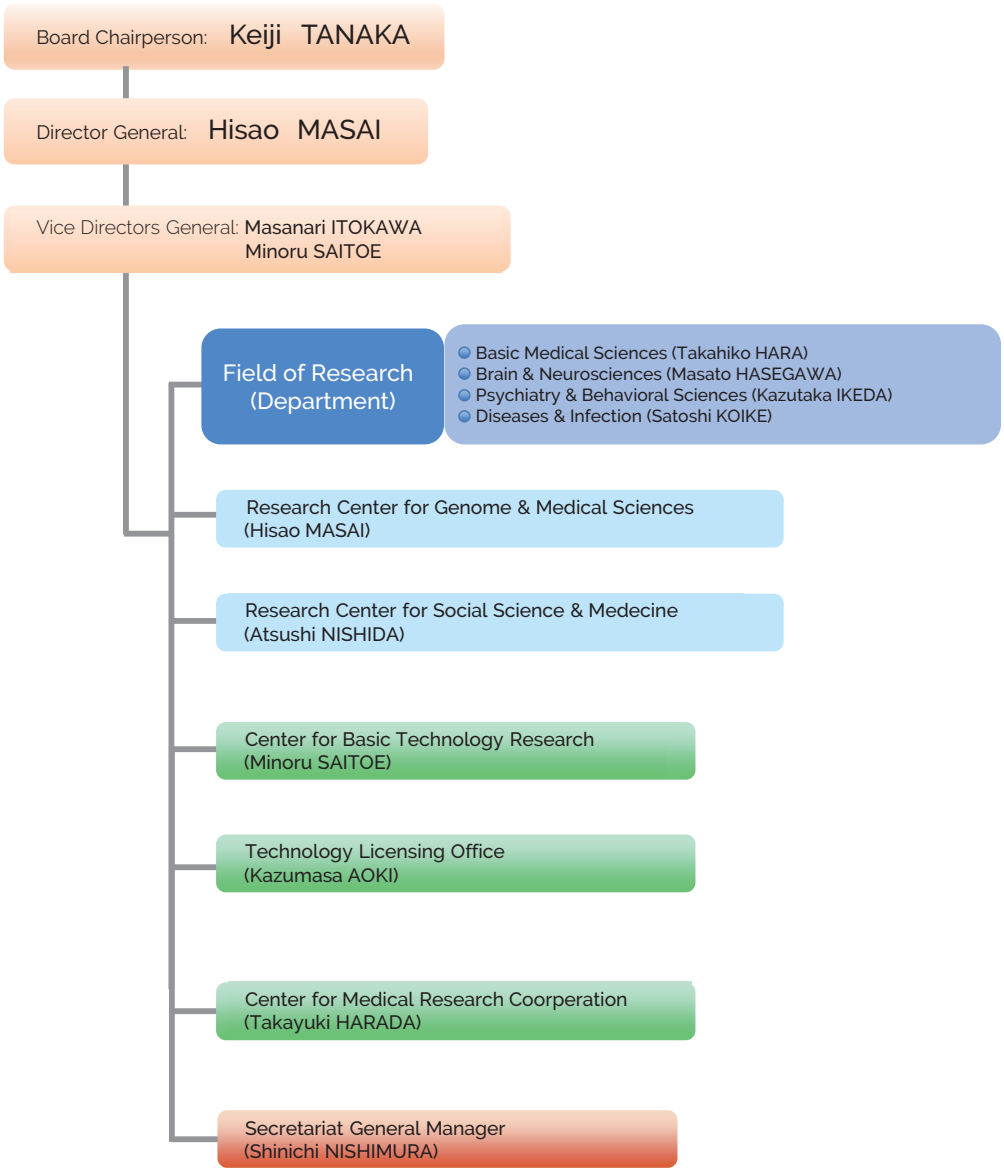
Vice Director General
Masanari ITOKAWA

The recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has caused a worldwide public health emergency. However, SARS-CoV-2 is just the latest of various epidemics and pandemics that have plagued us throughout history. In his "Vitae Parallelae," Plutarch describes the three Cs of, closed spaces, crowded places and close-contact settings that influence contagions, demonstrating humankind's long and ongoing efforts to combat disease transmission. In addition, many types of folklore and traditional tales have been handed down describing the correct behaviors for preventing the spread of disease. The differences between our responses to recent infections compared to those of the past is that since the beginning of bacteriology in the 19th century, we can utilize our knowledge that infectious phenomena are caused by small invisible organisms such as bacteria and viruses.

TMIMS is an organization consisting of over 100 scientists. We are working to address the SARS-CoV-2 pandemic by vastly increasing the collaborative efforts of our medical research teams and increasing the support from our administrative offices and support divisions. As a Tokyo Metropolitan Institute, we are coordinating the largest hospital cooperative effort in Tokyo to date encompassing 7,000 beds in 14 metropolitan and public hospitals in order to protect the citizens of Tokyo from this pandemic.

Joint Meeting of the Task Forces for Antibody Testing and Research Support

Organizational Chart



Our People at a Glance

Position	Number
Researchers	163
Postdoctoral Fellows	51
Students	152
Visiting Scientists	144
Guest Scientists	145
Administrative Staffs	27
Total	682

January 1, 2021

Meet our scientists!

When cellular proteins become old and defective, they are degraded. These proteins are first tagged with ubiquitin, a molecule that can be covalently attached to proteins. Specific types of ubiquitination target proteins to proteasomes, cellular structures that degrade proteins. Sayaka Yasuda, a senior scientist in the Protein Metabolism Project, has been studying how proteasome-dependent degradation occurs and has obtained intriguing results. She found that when cells are subjected to certain types of stress, proteasomes congeal into liquid droplet structures in cells, which likely enhances their ability to degrade substrates. Her results are published in "Stress- and ubiquitin-dependent phase separation of the proteasome," Nature, 2020 Feb;578(7794):296-300. She spoke to us about her work.

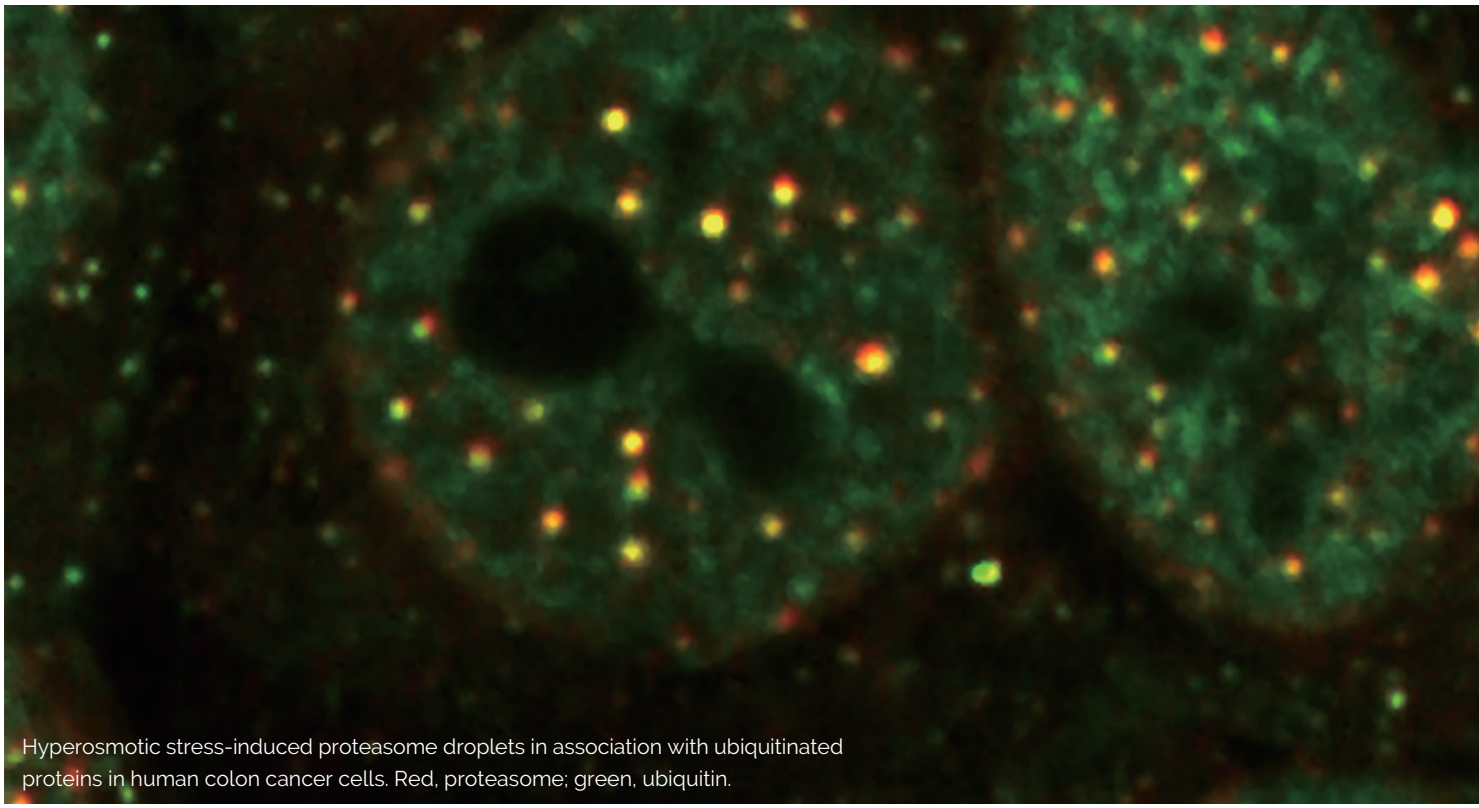
Sayaka YASUDA

How did you start this project?

I first learned imaging techniques when I was in graduate school. When I later joined the Protein Metabolism Project, proteasome dynamics hadn't really been studied before, so I decided to image proteasomes in cells under a microscope in different conditions. Proteasomes are usually found diffusely within a cell, but I found that when cells are stressed, proteasomes congeal into punctate liquid droplet structures. That was the start of this work.

What are liquid droplets and why are they important?

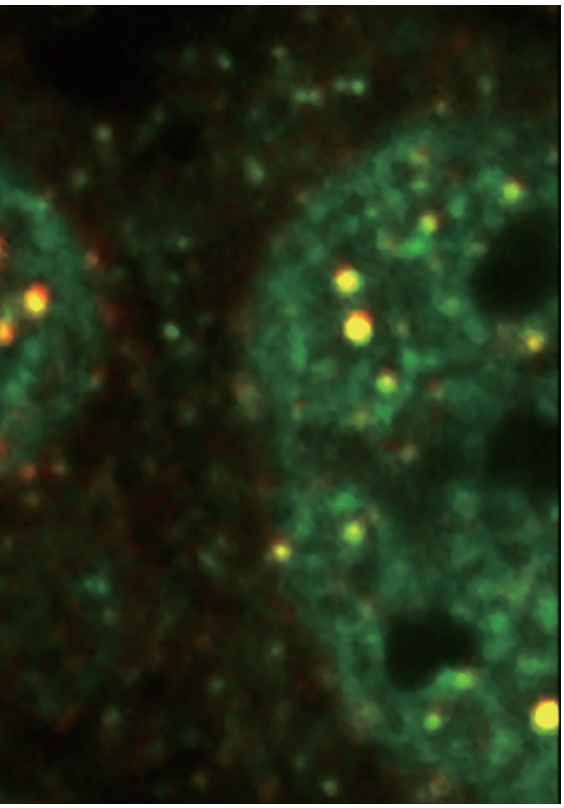
They really look like small droplets of oil in water. Proteasome droplets contain ubiquitinated proteins, RAD23B (a molecule that shuttles ubiquitin to proteasomes and bridges their interaction), proteasomes, and P97 (a molecule required for proteasomal degradation). We think that protein



Hyperosmotic stress-induced proteasome droplets in association with ubiquitinated proteins in human colon cancer cells. Red, proteasome; green, ubiquitin.

degradation occurs in these droplets, and droplets increase the efficiency of proteasomal degradation by bringing all the components and targets for degradation together in a specific location.

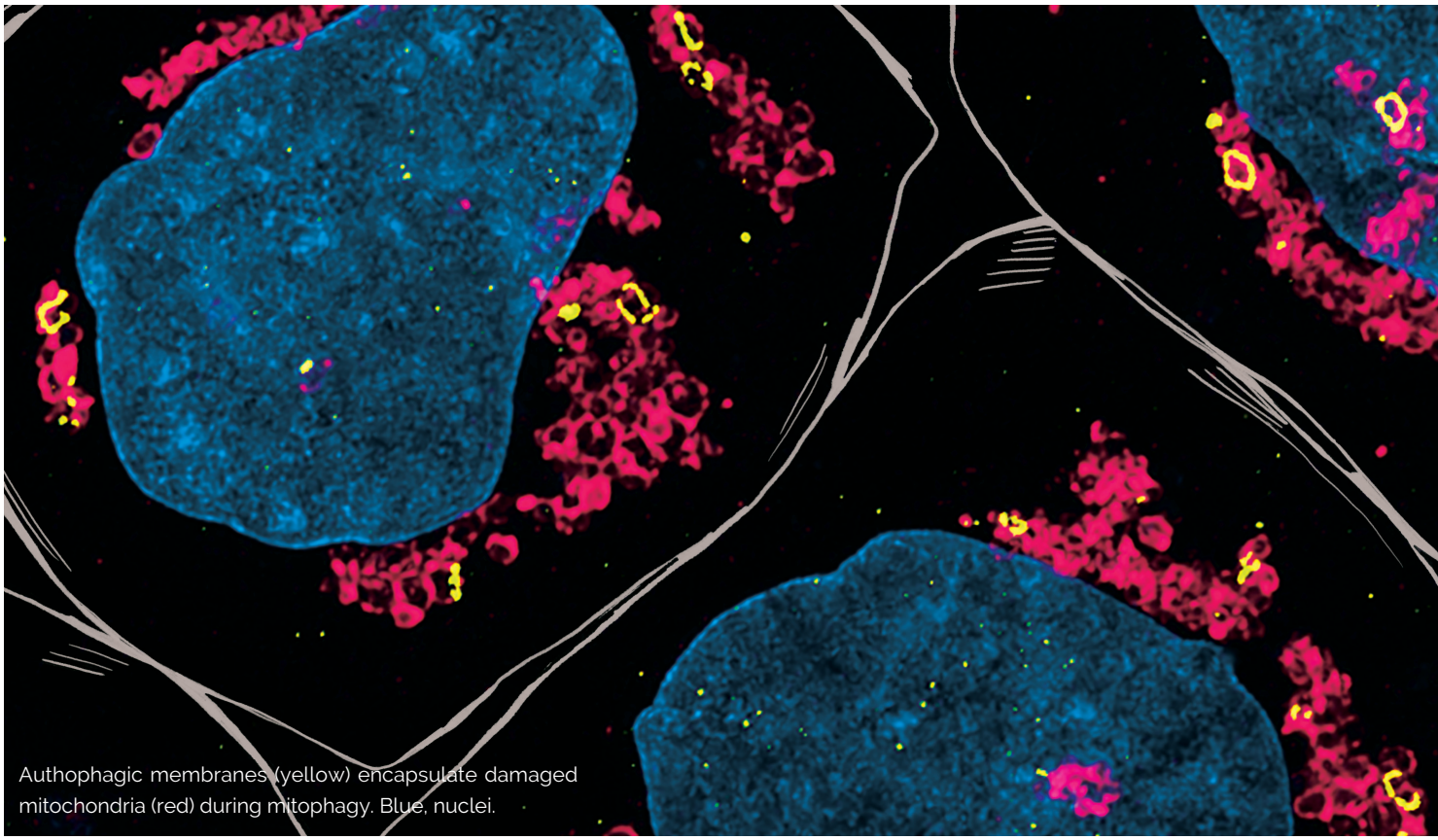
Does protein degradation become more important when cells are under stress?
The primary targets that are degraded in our droplets are ribosomal proteins. When cells are subjected to hyperosmotic stress, ribosomal proteins aggregate, and we think that droplets are where these aggregates are degraded. We've shown *in vitro* that ubiquitinated proteins and RAD23B can form droplets on their own. Proteasomes are recruited to droplets, but they aren't necessary for formation. However, if we add proteasome inhibitors once droplets are formed, they don't disperse as readily. Droplets are transient structures that disperse once ubiquitinated proteins are degraded. They last longer than usual if we inhibit degradation and they disperse faster if we accelerate degradation. That's why we think degradation occurs in droplets.



How is droplet formation beneficial to cells?
We thought that droplet formation should increase the likelihood that a cell would survive hyperosmotic stress, so we performed cell death assays. However, our RAD23B knockout lines increase cell death regardless of stress. So, while we think that droplet formation should improve protein degradation and increase cell survival, but we haven't been able to prove that yet. Recently we've identified a sequence in RAD23B that is required for liquid droplet formation. We're planning to put a mutation within this sequence to make mutated RAD23B that is unable to form droplets, and we're planning to use this mutated protein to prove whether there is a significant survival benefit to liquid droplet formation in cells.

What is the significance of your work and how does it differ from previous reports on liquid droplets?
Liquid droplet formation or liquid-liquid phase separation is a subject that is gaining a lot of attention these days. A relatively well-characterized mechanism for liquid phase separation is electrostatic interactions between proteins or RNAs. The idea is that electrostatic interactions cause proteins or RNAs to bind together and form a different phase, separate from other cellular components. Our results are distinct from previous results because we find that interactions between a particular domain of RAD23B and ubiquitin are responsible for phase separation, not just general electrostatic interactions. Since ubiquitination is a regulated post-translational modification, our results suggest that increases in ubiquitination regulate phase separation. This explains how proteasome droplets are initially formed, and also explains how they disperse when ubiquitinated proteins are degraded.

Meet our scientists!



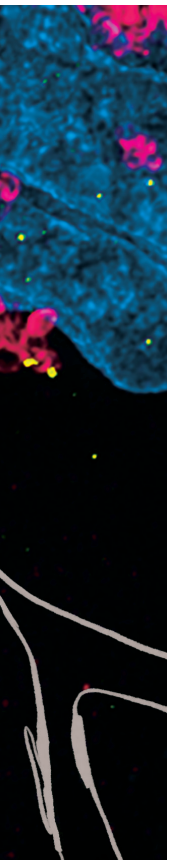
Authophagic membranes (yellow) encapsulate damaged mitochondria (red) during mitophagy. Blue, nuclei.

How are old, damaged proteins and organelles degraded in cells? Defects in degradation cause devastating diseases including Parkinson's disease in humans. Koji Yamano, a senior scientist in the ubiquitin project at TMIMS has been working to understand the mechanisms involved in degradation of defective mitochondria. We spoke to him about his latest research, "Critical role of mitochondrial ubiquitination and the OPTN-ATG9A axis in mitophagy," J Cell Biol 2020 Sep 7.219(9).

Koji YAMANO

Why did you decide to become a research biologist?
As a scientist, we can uncover novel biological mechanisms by using our hands and by using our ideas and creativity. Every day is full of scientific activities with many discussions and many experiments. These kind of things drove me to become a scientist. When I was a high school student, I was very interested in chemistry; I didn't care about biology. But during my Ph.D. studies, I realized that biology is much more important for our health. That's why I decided to become a molecular biologist.

How did you become interested in mitochondrial elimination?
Mitochondria have a membrane potential that it uses to produce ATP. This membrane potential is also important for protein import. Without a membrane potential, mitochondrial matrix proteins cannot go into the mitochondria. This is a fundamental principle of mitochondrial protein import. But in 2008, an interesting paper came out from Richard Youle's group at the NIH in the United States. They found



that a cytosolic protein called Parkin is selectively recruited to damaged mitochondria that don't have a membrane potential and triggers elimination of these damaged mitochondria by autophagy. I'm very interested in this process. How do mitochondria without a membrane potential recruit Parkin? I wanted to know the molecular mechanism of Parkin translocation so I started studying mitochondrial elimination.

What is the relationship between Parkinson's disease and mitochondrial elimination?

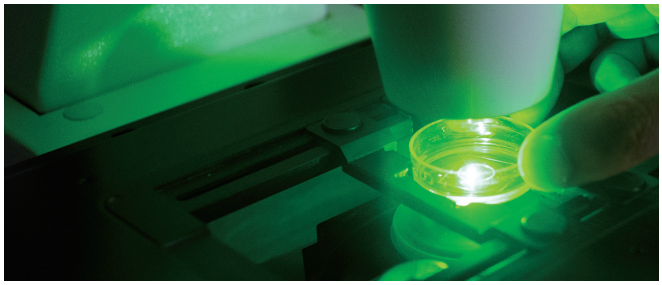
To keep cellular homeostasis, synthesis of new mitochondria is of course important, but the degradation of bad mitochondria is also important. In 2008, Richard Youle's group found that Parkin is essential for mitochondrial elimination. Two years later, in 2010, several groups including ours, independently identified that PINK1 is also essential for elimination and functions upstream of Parkin translocation. Surprisingly, Parkin and PINK1 have both been identified as products of genes mutated in Parkinson's disease. Parkinson's disease is one of the most frequent neurodegenerative diseases. Several papers suggest that accumulation of damaged mitochondria in neuronal cells causes the Parkinson's disease phenotype.

What it the relationship between ubiquitination and mitochondrial elimination?

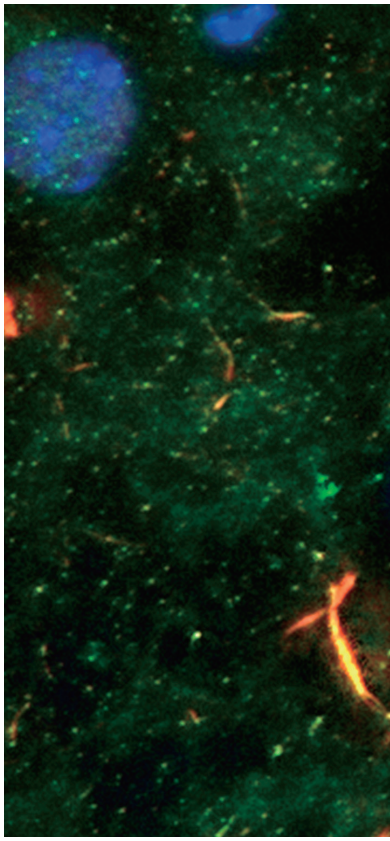
Parkin is an E3 ubiquitin ligase, which means that Parkin is an enzyme that puts ubiquitin onto substrates. In this case it puts ubiquitin onto proteins on damaged mitochondria. Ubiquitin was primarily known to be important for degradation of individual proteins by targeting them to the proteasome, but recently, we and others found that in some cases, ubiquitination is essential for the autophagy degradation pathway. Proteasomes degrade proteins one by one, but autophagy degrades bigger targets such as protein complexes, aggregates, and even organelles. We call autophagy of mitochondria, mitophagy.

What are the new findings published in your JCB paper?

We and others so far investigated how Parkin and PINK1 work together to put ubiquitin on damaged mitochondria. But we still didn't know how ubiquitin-coated mitochondria are recognized by the autophagy machinery. Autophagy adaptors may be a key to linking ubiquitin to the autophagy machinery. Mammalian cells have five different autophagy adaptors, and all five adaptors contain ubiquitin binding domains and are recruited to the mitochondria. Furthermore all five adaptors contain ATG8 interacting motifs. ATG8 is a part of the autophagic machinery that is covalently attached to autophagic membranes. So many groups thought that autophagy adaptors could act as a bridging molecule, recruiting ATG8 and autophagic membranes to ubiquinated mitochondria. However, only two adaptors, called NDP52 and optineurin, are essential for mitochondrial elimination. We found that optineurin binds to not only ATG8, but also to another autophagy core protein, ATG9, and another group found that NDP52 binds FIP200. ATG9 and FIP200 are also essential autophagy proteins and they are important for the de novo synthesis of autophagic membranes. So now we think that optineurin and NDP52 are recruited to ubiquitinated mitochondria and begin synthesis of autophagic membranes to encapsulate the mitochondria. ATG8 is also important for encapsulation, but we found that ATG9-dependent initiation of *de novo* membrane synthesis is an important earlier step in this process.



Meet our scientists!



Neurodegenerative diseases are thought to be caused by the accumulation of toxic protein aggregates. For example, aggregates of a protein called α-synuclein cause diseases known as α -synucleinopathies, which include Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. But how do aggregates of one particular protein cause three different diseases with different toxicities and symptoms? Genjiro Suzuki, a senior scientist in the Dementia Research Project has been studying this problem and recently published his work in a paper, "α-synuclein strains that cause distinct pathologies differentially inhibit proteasome," eLife 2020;9:e56825. We spoke to him about his work.

Genjiro SUZUKI

How did you become interested in science?

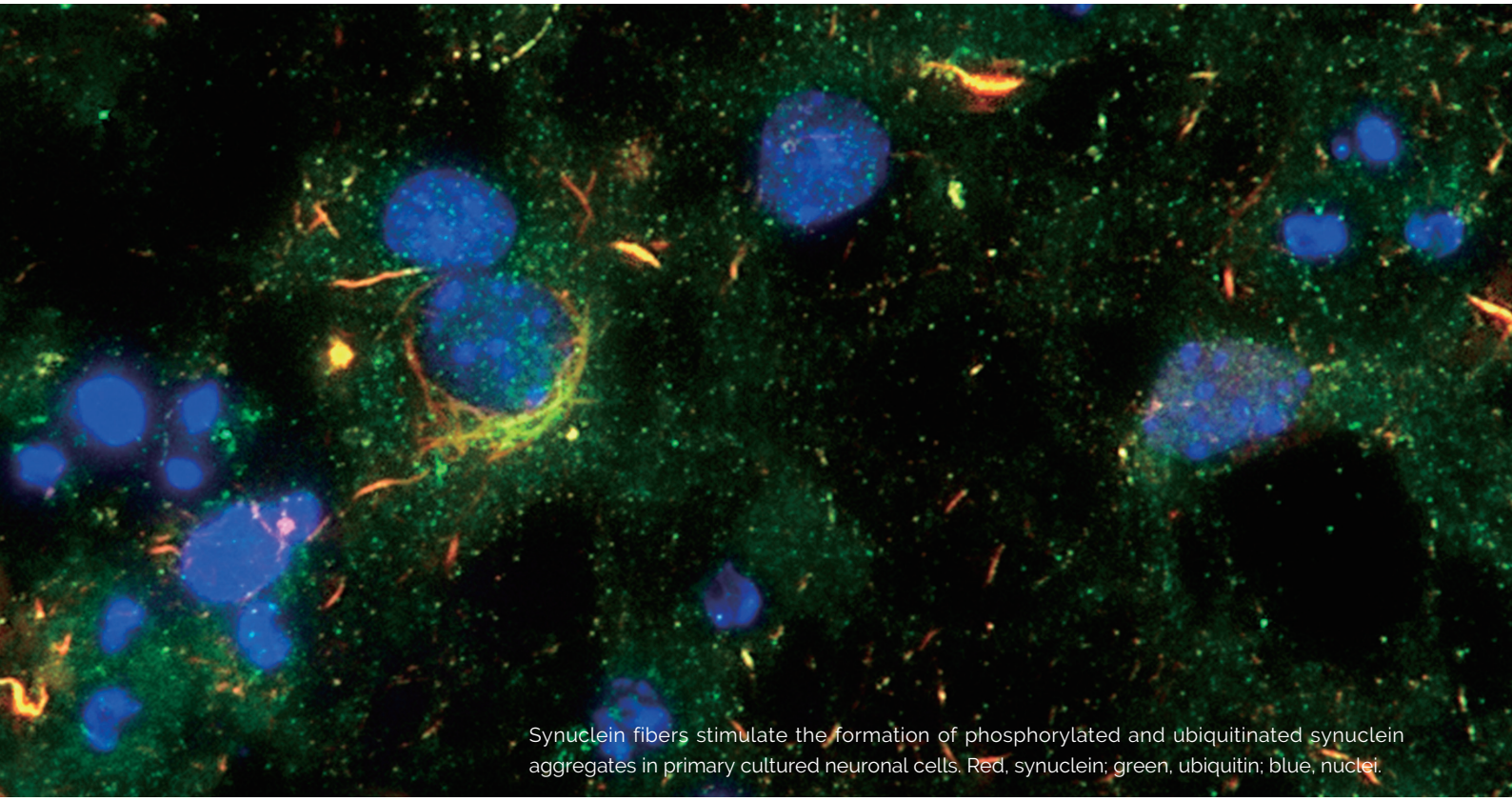
When I was a child, my father bought the science magazine, Newton, each month for me and my brother. This sparked my interest in science and led me to study Biology as an undergraduate at the University of Kyoto and as a graduate student at the University of Tokyo.

What is the relationship between prion protein propagation and neurodegenerative diseases?

Aggregates of proteins such as a-synuclein, tau, and TDP43 are almost always seen in neurodegenerative diseases, and mutations that increase the aggregation of these proteins cause familial forms of these diseases. That means that these neurodegenerative diseases are likely caused by these aggregates, similar to how prion diseases are caused by prion protein aggregates. In neurodegenerative diseases, degeneration doesn't occur immediately throughout the brain, but instead starts at a particular location and spreads in a particular manner. Again, this is similar to the spread of prion protein aggregates. That's why we believe that neurodegenerative disease spread in the brain in a manner similar to prion propagation.

What are prion proteins?

When a protein is made, it folds into a particular conformation that allows it to perform its function. However, in some cases, there are different conformations that a protein can fold into. Prion proteins normally fold in a native conformation that doesn't cause disease, but they can also fold into other harmful conformations. Prion proteins in harmful conformations can bind to other prion proteins in the native conformation and shift to the harmful conformation. This causes the spread of harmful proteins and these proteins get transferred to other cells to spread the disease to other regions of the nervous system.



Synuclein fibers stimulate the formation of phosphorylated and ubiquitinated synuclein aggregates in primary cultured neuronal cells. Red, synuclein; green, ubiquitin; blue, nuclei.

What are the new findings in your eLife paper?

There are at least three different synucleinopathies, Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. This suggests that α-synuclein can fold into at least three different conformations besides the native conformation. In order to test this idea, we made α-synuclein *in vitro* and then aggregated it under different salt conditions to show that different aggregates are formed with different characteristics. Our work shows how aggregation of one protein can cause different diseases with different symptoms and toxicities.

What is the proteasome and how is it related to toxicity of aggregated proteins?

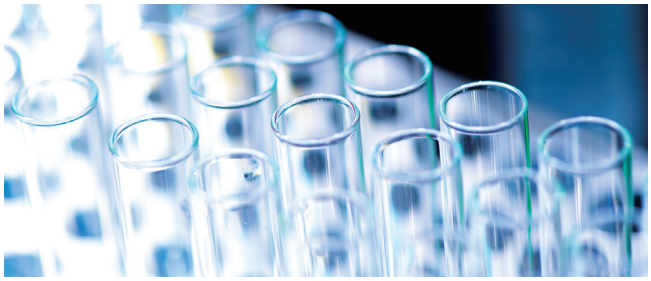
Damaged, or deleterious proteins are tagged by ubiquitin and this ubiquitin tag directs them to the proteasome where they are degraded. However, in many neurodegenerative diseases, we see many ubiquitinated protein aggregates. We believe that cells try, but fail, to degrade these aggregates, so we decided to measure the effects of our aggregates on proteasome activity. We found that our more toxic aggregate abolished proteasome activity while our less toxic aggregate didn't. This shows that one aggregate may be more toxic than the other because of the effect it has on the proteasome and protein degradation.

How do you plan to continue this work?

The α-synuclein aggregates we made *in vitro* are structurally different from aggregates found in disease patients. One of my future plans is to make *in vitro* aggregates that are very close to those found in disease patients. This would allow us to analyze how disease aggregates inhibit proteasome activity. It would also be very useful in screening studies to develop new treatments for these diseases.

Are non-toxic aggregates found in people, and do you think they could be used to treat diseases?

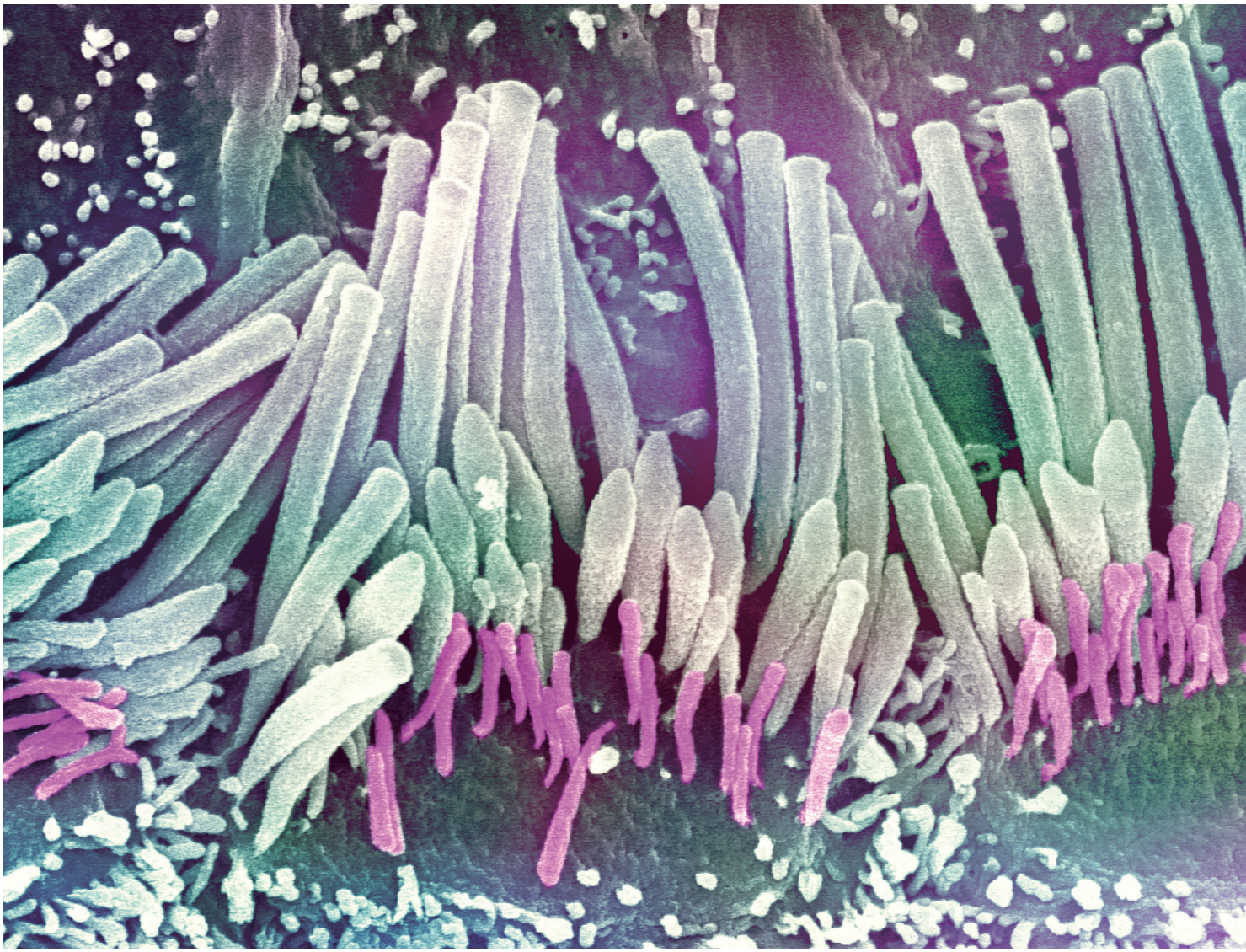
I don't think α-synuclein aggregates have been found in people without neurodegeneration, but there are reports of accumulation of tau aggregates in people without neurodegeneration. So maybe Alzheimer's patients have tau aggregates that are toxic and inhibit the proteasome, while healthy older people can have tau aggregates that aren't toxic and might even function protectively. It would be fascinating if we could make non-toxic protein aggregate seeds that we could use to inhibit the formation of toxic aggregates.



Our Goal

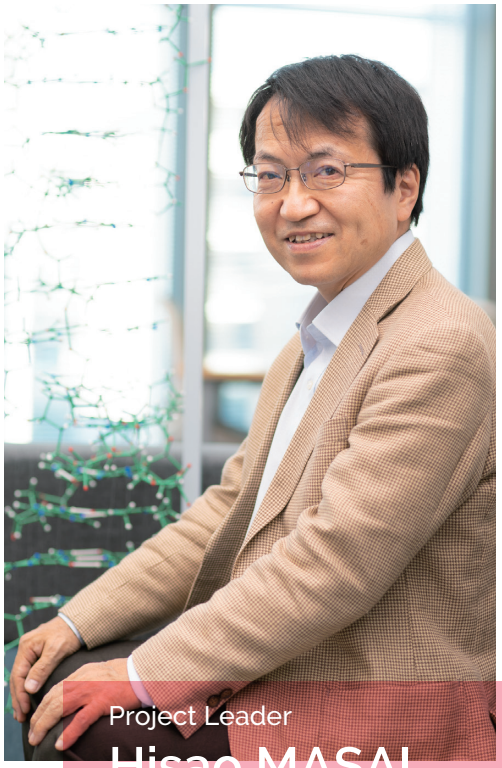
Our goal is to be a leading and role model institute for the life/medical science by conducting cutting-edge basic and clinical researches, that will help prediction, prevention, diagnosis, and treatment of various diseases and improve the care of patients, leading to longer healthy life.

Research Activities



Mouse cochlear inner hair cells, conventional sensory receptors that transmit most of the acoustic information to the brain. Red cilia represent those lost during aging.

Basic Medical Sciences



Project Leader
Hisao MASAI

Hisao Masai is the director of TMIMS and the head of the Genome Dynamics Project. After graduating from the University of Tokyo in 1981, he worked as a graduate student under the supervision of Dr. Ken-ichi Arai at DNAX Research Institute in Palo Alto, California, USA, and received his Ph.D. in 1987 from the University of Tokyo. He has spent his career studying how genetic information is duplicated and inherited, and what happens when these processes fail. His current interests include understanding diversified modes of DNA replication, how failure to respond to replication stress leads to cancerous growth, and the roles of unusual nucleic acid structures, including G-quadruplexes and RNA-DNA hybrids, in shaping chromosomes, copying and reading genetic information, and in causing detrimental diseases.

Genome Dynamics

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

Staff

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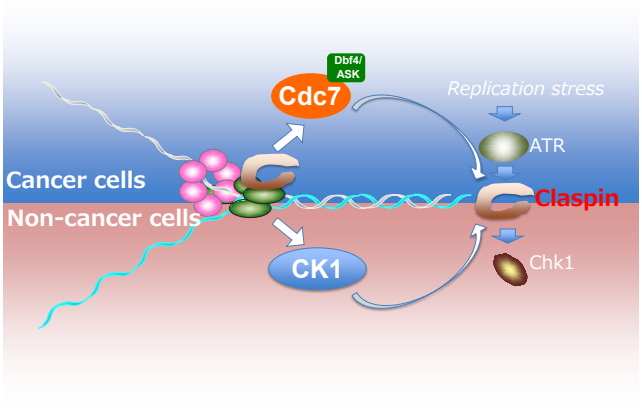
Hikari MIYAMOTO
Shoha KINOSHITA
Trinh Thi To NGO

Research Summary

Our goal is to understand the molecular mechanisms responsible for faithful inheritance of genetic materials and stable maintenance of the genome. To achieve this, we are studying various aspects of chromosome dynamics with particular emphasis on regulation of DNA replication during S-phase in E. coli, fission yeast, and mammalian cells. We work to elucidate how chromosomes replicate and how the inheritance of replicated chromosomes is regulated to enable stable maintenance of the genome through generations. Answers to these questions will shed light on how defects in these processes contribute to the development of diseases, including cancers, and to senescence. They will also help to identify novel target proteins for cancer therapies. We are addressing the following questions.

1) How are the timing and location of DNA replication determined, and how are these coordinated with other chromosomal processes?
2) What are the biological functions of G-quadruplex structures, particularly in regulating DNA replication?
3) How are cellular responses to replication stress regulated, and how are these responses related to other cellular stress response pathways?
4) What are the roles of replication factors in development of individual organs and tissues, and how are these replication systems diversified to regulate development of different parts of our bodies?



Different mechanisms of replication stress responses in cancerous and non-cancerous cells. In cancer cells, Cdc7 is primarily responsible for phosphorylation of Claspin, a mediator of replication checkpoint, whereas in non-cancer cells, casein kinase 1γ1 is the primary kinase. This differential mechanism can be exploited to develop a strategy for cancer cell-specific cell killing by targeting Cdc7 kinase.

Selected Publications

Masai H, et al. (2020) "Detection of cellular G-quadruplex by using a loop structure as a structural determinant." ***Biochemical and Biophysical Research Communications,*** 531, 75-83.

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

Kobayashi S, et al. (2019) "Both a unique motif at the C terminus and N-terminal HEAT repeat contribute to G4 binding and origin regulation by Rif1 protein." ***Mol Cell. Biol.*** 39(4). pii: e00364-18

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

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

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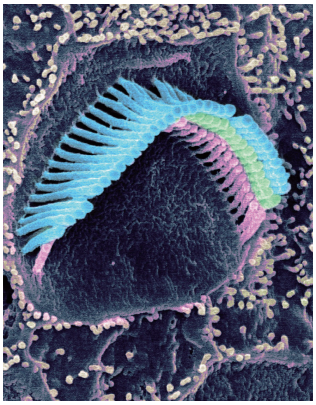
Research Summary

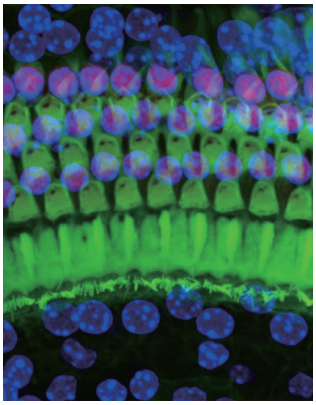
Hearing loss is a very common sensory disorder that severely affects human quality of life. In order to develop effective therapeutic strategies for deafness, it is critical to understand the mechanisms regulating its onset. Our aim is to discover novel genes associated with deafness. In particular, 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

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.

Yasuda SP, et al. (2018) "Effects of genetic background on susceptibility and the acceleration of hearing loss in mice." ***An Excursus into Hearing Loss*** 3–23.

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.

Kikkawa Y and Miyasaka Y. (2016) "Genetic modifiers of hearing loss in mice: The case of phenotypic modification in homozygous *Cdh23*^{ahl} age-related hearing loss." ***Monogr. Hum.*** Genet. 20: 97–109.

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
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Research Assistants
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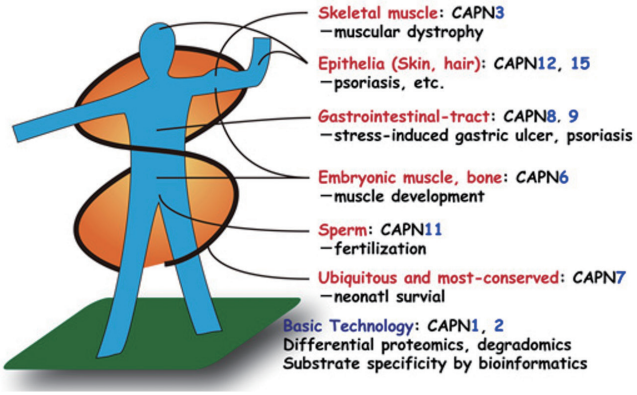
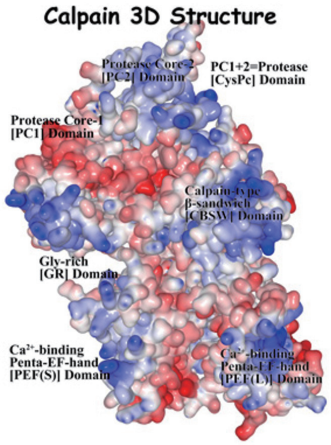
Research Summary

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

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

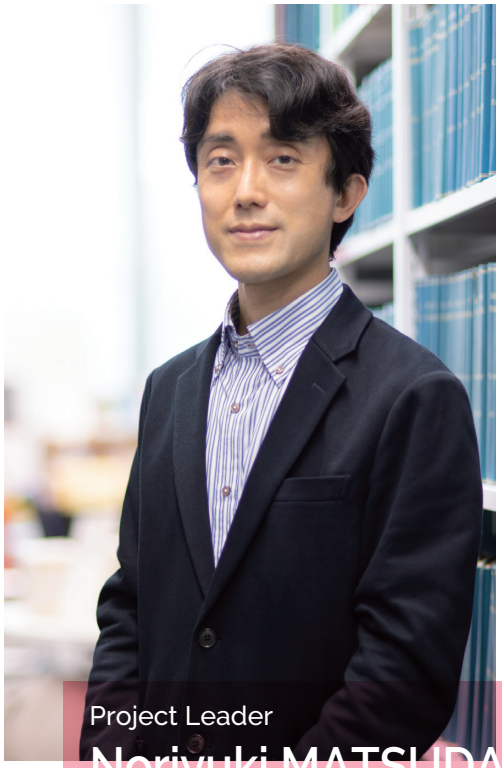
Hata S, et al. (2020) "A muscle-specific calpain, CAPN3, forms a homotrimer." ***Biochim. Biophys. Acta, Proteins Proteomics***, 7: 140411.

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
Noriyuki MATSUDA

Noriyuki Matsuda has been the leader of the Ubiquitin Project since 2015. He received his Ph.D in 2001 from the University of Tokyo Graduate School of Science for identification of the membrane-bound RING finger-type ubiquitin ligase, Rma1/Rnf5, from *H. Sapiens* and *A. thaliana* (Matsuda, *J. Cell. Sci.* 2001). He then worked as a postdoctoral fellow studying mechanisms and functions of ubiquitylation under the supervision of Dr. Keiji Tanaka at the Tokyo Metropolitan Institute of Medical Science. His current interests are to understand how ubiquitin is conjugated on damaged mitochondria, how these mitochondria are degraded in a mitochondria-specific autophagic process known as mitophagy, and how mitophagy prevents detrimental diseases such as Parkinson's disease.

Ubiquitin

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

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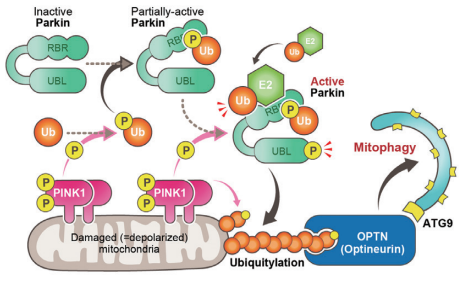
Rhota HAYASHIDA

Research Summary

Parkinson's disease (PD) is a common movement disorder characterized by loss of dopaminergic neurons. The majority of PD cases are sporadic, however, the discovery of genes linked to hereditary forms has provided important insights into molecular mechanisms associated with PD pathology. For example, functional analysis of recessive familial PD-related genes has identified a link between PD and mitochondrial quality control. However, the molecular mechanisms underlying this relationship have been obscure.

We focused on two genes associated with hereditary recessive PD, PINK1 and PARKIN. PINK1 encodes a Ser/Thr kinase and PARKIN encodes a RING-IBR protein. We found that when the mitochondrial membrane potential decreases, a sign of mitochondrial damage, PINK1 phosphorylates ubiquitin at Ser65. Phosphorylated ubiquitin activates the ubiquitin ligase (E3) function of Parkin (Koyano *Nature* 2014). Moreover, ubiquitin chains phosphorylated by PINK1 function as Parkin receptors and recruit Parkin to damaged mitochondria (Okatsu *J.Cell.Biol.* 2015). Consequently, the trio of PINK1, Parkin, and phospho-ubiquitin induced rapid ubiquitination of mitochondrial outer membrane proteins. Since a bewildering array of substrates are ubiquitinated by Parkin during this process, Parkin substrate specificity remained poorly understood. We found, using artificial mitochondria-targeted proteins, that substrate specificity of Parkin is not determined by specific amino acid sequences but instead by mitochondrial localization (Koyano *J.Biol.Chem.* 2019). Ubiquitin is well-known for directing proteins for degradation. However, increasing evidence indicates that ubiquitination is also involved in quality control of larger structures including organelles, by tagging and directing damaged organelles for autophagic degradation. We found that ubiquitin chains on depolarized mitochondria are recognized by OPTN, an adaptor protein that recruits ATG9, a downstream autophagic protein, to damaged mitochondria (Yamano *J.Cell.Biol.* 2020). Impairment of this process prevents mitochondrial degradation and induces a predisposition to familial PD. Our work identifies a mechanism for PD pathology.



Schematic model for how PINK1, Parkin, and ubiquitin cooperate in the degradation of damaged mitochondria.

Selected Publications

Yamano K, et al.(2020) "Critical role of mitochondrial ubiquitination and the OPTN-ATG9A axis in mitophagy." ***J. Cell Biology*** 219: e201912144.

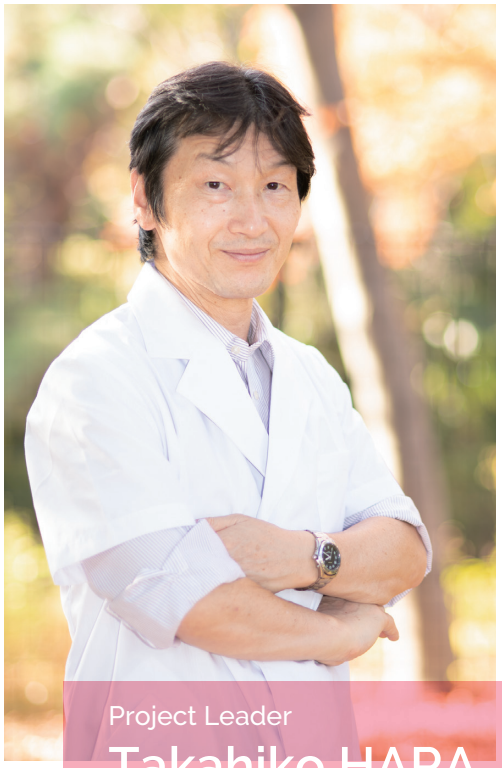
Koyano F, et al.(2019) "Parkin recruitment to impaired mitochondria for nonselective ubiquitylation is facilitated by MITOL." ***J Biol Chem*** 294: 10300-10314.

Koyano F, et al.(2019) "Parkin-mediated ubiquitylation redistributes MITOL/March5 from mitochondria to peroxisomes." ***EMBO Rep***. 20: e47728.

Yamano K, et al.(2018) "Endosomal Rab cycles regulate Parkin-mediated mitophagy." ***eLife*** 7: e31326

Okatsu K, et al.(2015) "Phosphorylated ubiquitin chain is the genuine Parkin receptor." ***J. Cell Biology*** 209: 111-128

Koyano F, et al.(2014) "Ubiquitin is phosphorylated by PINK1 to activate Parkin." ***Nature*** 510: 162-166.



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

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Chihiro NAKATA
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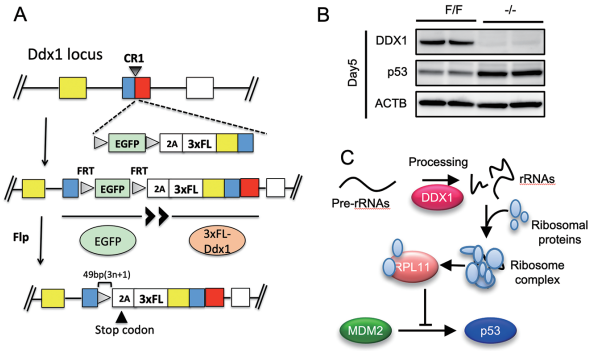
Kaho ISHIGE
Mako HAMASAKI
Satoko TAKAGI
Shota HOYANO
Shoma YAMAGUCHI
Risa SAITO

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. We are vigorously investigating physiological roles of CXCL14 and its action mechanisms. CXCL14 is a promising tool for developing novel anti-cancer and anti-diabetes drugs.

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

Suzuki T, et al. (2020) "A novel all-in-one conditional knockout system uncovered an essential role of DDX1 in ribosomal RNA processing." ***Nucl. Acid Res.,*** (in press.)

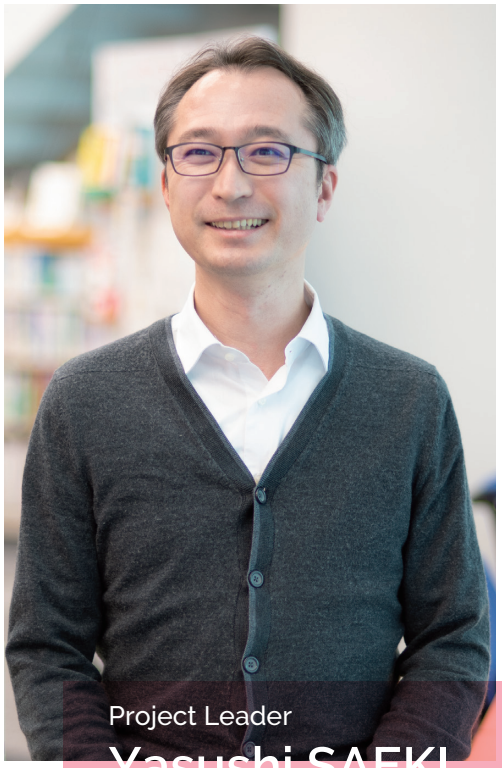
Sato K, et al. (2020) "Nitric oxide and a conditioned medium affect the hematopoietic development in a microfluidic mouse embryonic stem cell/OP9 co-cultivation system." ***Micromachines,*** 11: 305.

Nakajima M, et al. (2019) "In vitro differentiation of mouse T cell-derived hybrid cells obtained through cell fusion with embryonic stem cells." ***Biochem. Biophys. Res. Commun.*** 513: 701-707.

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.

Tanegashima K, et al. (2017) "Epigenetic regulation of the glucose transporter gene Slc2a1 by *β*-hydroxybutyrate underlies preferential glucose supply to the brain of fasted mice." ***Genes Cells*** 22: 71-83.



Project Leader
Yasushi SAEKI

Yasushi Saeki has been the leader of the Protein Metabolism Project since 2019. He received his Ph.D. in 2003 from the Graduate School of Pharmaceutical Sciences, Hokkaido University. After working as a JSPS research fellow at the Univ. of Tokyo, he joined the laboratory of Dr. Keiji Tanaka in 2007. He has been studying the ubiquitin-proteasome system and has identified the last proteasome subunit, multiple proteasome-specific chaperones, and key regulators for proteasomal degradation. He has also developed methods for analyzing proteasome activity and ubiquitin chain topology. Since 2018, he has also led the Grantin-Aid Scientific Research on Innovative Area 'New frontier for ubiquitin biology driven by chemo-technologies' and works to promote collaborative research on ubiquitin in Japan.

Protein Metabolism

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

Staff

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Visiting Scientists
Fumiaki OHTAKE
Sayaka YASUDA

Supervisor
Keiji TANAKA
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Kyoko UEDA

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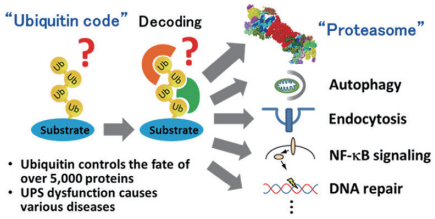
Miho SAKUMA
Kenta KISAI

Research Summary

The ubiquitin-proteasome system (UPS) is a crucial protein degradation system that affects almost all cellular functions in eukaryotic cells. Since protein homeostasis is essential to human health, malfunctions of the UPS cause various diseases including cancers, inflammation, and neurodegeneration. Thus, UPS regulators are attracting attention as drug discovery targets. However, there is still much unknown about the UPS. Our goal is to elucidate the fundamental mechanisms of ubiquitin signaling and proteasomal degradation and to integrate this information into pathophysiology to develop therapeutic strategies for UPS-related diseases. To this end, we are currently focusing on the following research projects.

1) Deciphering the ubiquitin code: The structural diversity of ubiquitin chains with distinct topologies, called the 'ubiquitin code,' regulates the diverse functions of ubiquitin. We have shown that the branching and length of ubiquitin chains provide additional specificity to this code (Mol Cell 2016, Nat Commun 2018). To further investigate the ubiquitin code, we are developing methods to analyze the high-order structure of ubiquitin chains using advanced mass spectrometry.
2) Decoding mechanisms for proteasomal degradation: We have identified the p97-UFD1-NPL4 complex and RAD23 family as ubiquitin decoders that direct substrates to the proteasome (Mol Cell 2017, Nat Commun 2019). Currently we are investigating the substrate selectivity of these ubiquitin decoders using advanced proteomics and by developing chemical tools to manipulate proteasomal degradation.
3) Biological significance of proteasome phase separation: Recently, we found the ubiquitin-dependent liquid-liquid phase separation (LLPS) of the proteasome under hyperosmotic stress (Nature). This compartmentalization appears to be advantageous for the rapid removal of stress-damaged proteins, and we are further investigating proteasome phase separation under various stress conditions.
4) Generation of proteasome mutant mice: Recently, gene mutations in the proteasome have been identified in patients with autism and immune disorders. To understand the pathophysiological mechanism of "proteasomopathy", we generated proteasome mutant mice and are analyzing their phenotypes.



Selected Publications

Yasuda S, Tsuchiya H, Kaiho Ai, et al. (2020) "Stress- and ubiquitylation-dependent phase separation of the proteasome." ***Nature*** 578, 296-300.

Sato Y, Tsuchiya H, et al. (2019) "Structural insights into ubiquitin recognition and Ufd1 interaction of Npl4." ***Nat. Commun.*** 10, 5708.

Tsuchiya H, et al. (2018) "Ub-ProT reveals global length and composition of protein ubiquitylation in cells." ***Nat. Commun.*** 9, 524.

Ohtake F, et al. (2018) "K63 ubiquitylation triggers proteasomal degradation by seeding branched chains." ***Proc. Natl. Acad. Sci. USA.*** 115, E1401-E1408.

Tsuchiya H, et al. (2017) "In vivo ubiquitin linkage-type analysis reveals that the Cdc48-Rad23/Dsk2 axis contributes to K48-linked chain specificity of the proteasome." ***Mol. Cell*** 66, 485-502.

Ohtake F, et al. (2016) "The K48-K63 branched ubiquitin chain regulates NF-κB signaling." ***Mol. Cell*** 64, 251-266.

Laboratory Head
Kohji KASAHARA

Biomembrane

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

Kohji Kasahara has been the head of the Laboratory of Biomembranes at TMIMS since 2020. He obtained a BSc in Chemistry from the Tokyo Institute of Technology in 1986, a MSc in 1988, and a PhD from the University of Tokyo in 1992. After graduating, he worked at TMiMS as a research scientist from 1992 to 2003, as an independent scientist from 2003 to 2005, as a project subleader from 2005 to 2010, and as a team leader from 2010 to 2020. He also worked at PRESTO, Japan Science and Technology Agency from 2001 to 2005.

Staff

Researchers
Ikuo KAWASHIMA
Kiyoshi OGURA
Tetsuya HIRABAYASHI
Keisuke KOMATSUYA
Norihito KIKUCHI

Students
Mai KAWAGUCHI
Jun KANBE

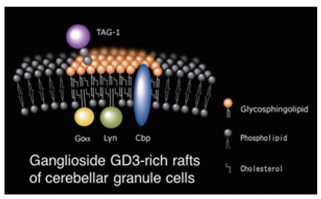
Research Summary

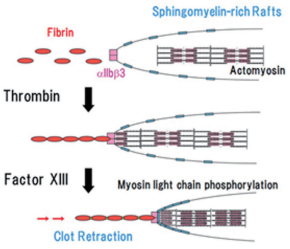
We are studying the function of lipid rafts. Lipid rafts are dynamic assemblies of glycosphingolipids, sphingomyelin, cholesterol, and proteins that can be stabilized in microdomains on cell surfaces. They are involved in the regulation of a number of cellular processes including axonal guidance, cellular migration, and blood clot formation and retraction.

In order to understand how lipid rafts receive external signals and transduce them to internal changes, we have been identifying protein interactions of glycosphingolipids in cerebellar granule cells from the nervous system, and in platelet cells from the blood.

In cerebellar granule cells we found that anti-ganglioside GD3 antibodies co-precipitate the GPI-anchored neural cell adhesion molecule TAG-1, the src-family kinase Lyn, its substrate Cbp, and the trimeric G protein Goα. TAG-1 is important for axonal guidance, and cellular migration. However, GPI anchors have no direct contact with the cytoplasm so it was unclear how TAG-1 activation causes internal cellular changes required for axonal guidance or migration. We demonstrated that TAG-1 transduces signals through interactions with Lyn/Cbp proteins found in ganglioside GD3-rich rafts of cerebellar granule cells. We further found that the chemokine SDF-1α triggers the chemoattraction of cerebellar granule cells during cerebellar development. SDF-1α stimulates GTPγS binding to Goα, and causes Goα translocation to lipid rafts, leading to growth cone collapse of cerebellar granule cells.

In blood platelets, sphingomyelin-rich lipid rafts are important for both blood clot formation and retraction through interaction with fibrin. We have identified a factor XIII-dependent fibrin-integrin αIIbβ3-myosin axis in sphingomyelin-rich membrane rafts that is important in clot retraction.





Selected Publications

Komatsuya K et al.(2020) "Function of Platelet Glycosphingolipid Microdomains/Lipid Rafts." ***Int. J. Mol. Sci.*** 21(15) :5539.

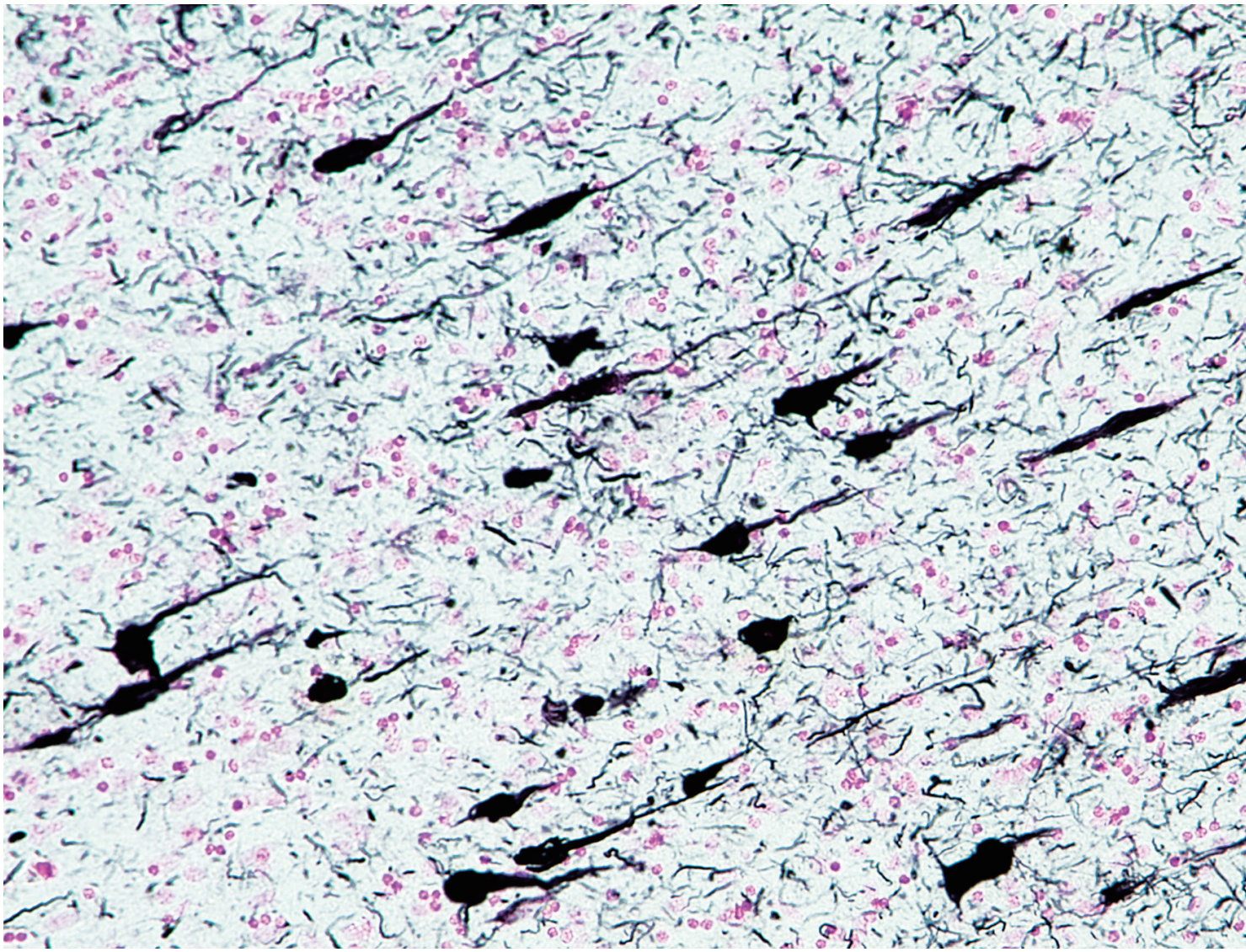
Kasahara K, et al. (2013) "Clot retraction is mediated by factor XIII-dependent fibrin-αIIbβ3-myosin axis in platelet sphingomyelin-rich membrane rafts." ***Blood*** 122, 3340-3348.

Kasahara K, et al. (2010) "Impaired clot retraction in factor XIII A subunit-deficient mice." ***Blood*** 115, 1277-1279.

Yuyama K, et al. (2007) "Translocation of activated heterotrimeric G protein Gαo to ganglioside-enriched detergent-resistant membrane rafts in developing cerebellum." ***J.Biol.Chem.*** 282, 26392-26400.

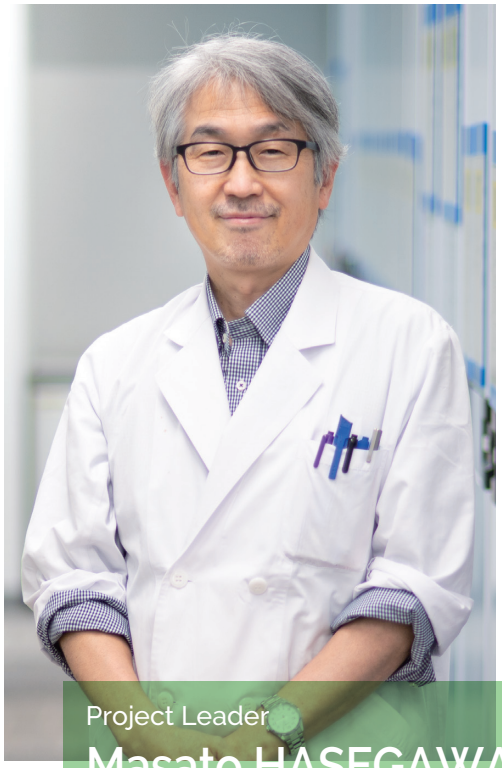
Kasahara K, et al. (2000) "Involvement of gangliosides in GPI-anchored neuronal cell adhesion molecule TAG-1 signaling in lipid rafts." ***J.Biol.Chem.*** 275, 34701-34709.

Kasahara K, et al. (1997) "Association of src family tyrosine kinase Lyn with ganglioside GD3 in rat brain. Possible regulation of Lyn by glycosphingolipid in caveolae-like domains." ***J.Biol.Chem.*** 272, 29947-29953.



Neurofibrillary changes in Alzheimer's disease brain.
Black, tau aggregates stained by Gallyas-Braak staining; pink, nuclei.

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/

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Ito KAWAKAMI

Postdoctoral fellows
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Research Assistants
Reiko OOTANI

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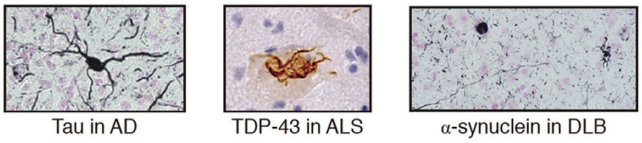
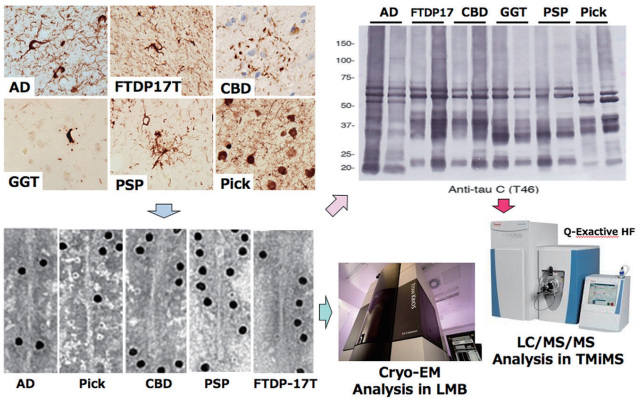
Sei IMURA
Yuuya HANZAWA
Mina TAKASE

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

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

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

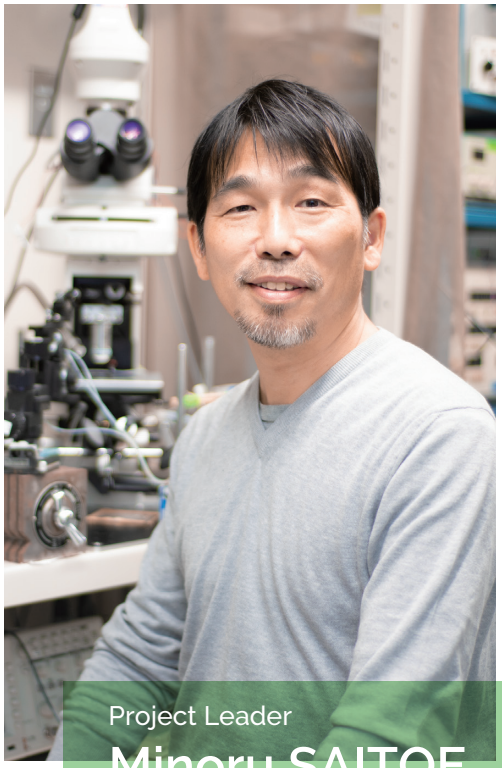
Suzuki G, et al. α-Synuclein strains that cause distinct pathologies differentially inhibit proteasome. ***eLife.*** 2020 Jul 22;9:e56825.

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

Watanabe R, et al. Intracellular dynamics of Ataxin-2 in the human brains with normal and frontotemporal lobar degeneration with TDP-43 inclusions. ***Acta Neuropathol Commun*** 2020 Oct 28;8(1):176.

Kametani F, et al. Comparison of common and disease-specific post-translational modifications of pathological tau associated with a wide range of tauopathies. ***Front Neurosci 2020,*** 581936.

Hasegawa M. Experimental models of prion-like protein propagation. ***Neuropathology.*** 2020 Jun 1.



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

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Motomi MATSUNO
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Yoshinori SUZUKI

Postdoctoral fellows
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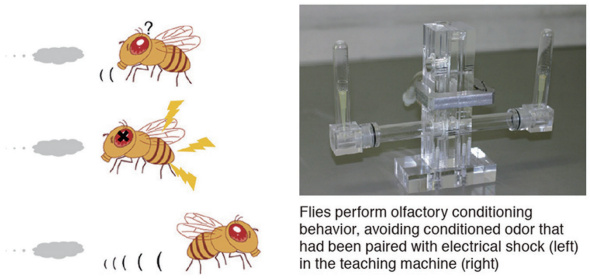
Emi KIKUCHI
Saki KOMIYA
Tomoko TAKAMISAWA

Students
Nozomi UEMURA

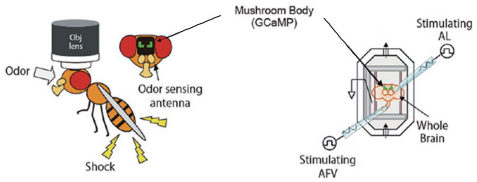
Research Summary

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.



Flies perform olfactory conditioning behavior, avoiding conditioned odor that had been paired with electrical shock (left) in the teaching machine (right)



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

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

Yukio Nishimura, PhD has led the Neural Prosthetics Project since 2017. He received a B.S. in Sports Sciences from Nihon University, a M.S. in Education from Yokohama National University and a PhD from Chiba University Medical School in 2003. He was a post-doctoral 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 in 2016 as an Associate Professor. His overall research is in neural control of limb movements in humans and non-human primates. His present research focuses on neural mechanisms of functional recovery after neural damage and restoration of lost functions using brain computer interfaces.

Neural Prosthetics

Laboratory HP: https://www.igakuken.or.jp/english/project/detail/neuroprosth1.html
https://www.igakuken.or.jp/neuroprosth/

Staff

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Toshiki TAZOE
Osamu YOKOYAMA
Sho K. SUGAWARA
Michiaki SUZUKI

Postdoctoral fellows
Miki KANESHIGE
Rumiko OKAMOTO
Noboru USUDA

Research Assistants
Naoko YOSHIDA
Shoko HANGUI
Yukie AIZAWA
Sachiko SHIMAKAWA
Tomomi GOTO

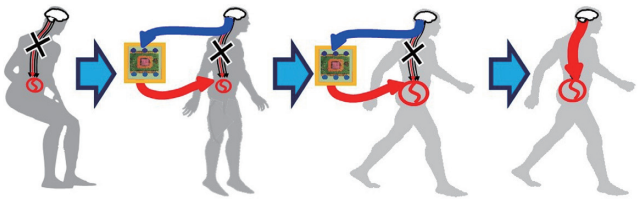
Students
Kei OBARA
Naoya KABE
Kouichi UAMARU

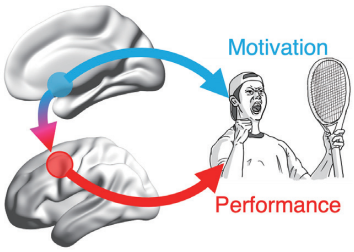
Research Summary

Our goal is to conceive of innovative ideas for neuro-rehabilitation of lost functions 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 supra-spinal systems with spinal networks distal to the lesion to restore lost functions. We are conducting clinical trials to assess the effectiveness of ANCs in restoring motor function in paralyzed patients. We are also investigating 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 remains unknown. We are identifying these neuronal substrates using humans and animal models.





Selected Publications

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.

Nishimura Y, et al. (2009) "A subcortical oscillatory network contributes to recovery of hand dexterity after spinal cord injury." ***Brain*** 132(Pt 3):709-721

Nishimura Y, et al. (2007) "Time-dependent central compensatory mechanisms of finger dexterity after spinal cord injury." ***Science***. 318(5853):1150-1155

Project Leader
Hiroshi SAKUMA

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

Child Brain

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

Staff

Researchers
Kuniko KOHYAMA

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Tomonori SUZUKI
Naoyuki TANUMA
Masaharu HAYASHI

Research Assistants
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Students
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Hiroya NISHIDA
Kengo MORIYAMA
Motoshi FUJITA
Rie NAKAI
Takayuki MORI

Research Summary

Our research focuses on childhood autoimmune and inflammatory neurological diseases (AINDs). These diseases are a significant social burden because of poor prognosis and high mortality. We have created a multicenter registry of patients and sample repository for AINDs, based on nationwide collaborations, which we are using for cohort studies. We perform multi-omics analyses 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. We have developed transgenic animal models to determine how glial cells contribute to pathomechanisms of AINDs by regulating brain metabolism and inflammation. These studies will help us develop novel therapeutic strategies.

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

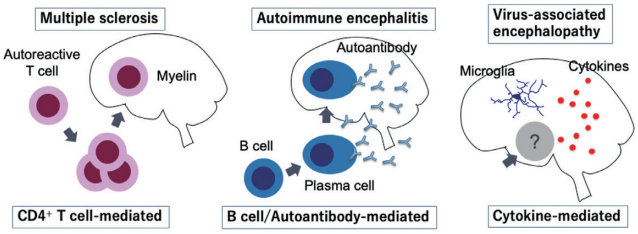


Figure Pathomechanisms of inflammatory and autoimmune neurological diseases
Multiple sclerosis has been regarded as a CD4 T-cell mediated disease in which autoreactive T cells are activated, proliferate, migrate to the brain, and cause myelin damage. Autoimmune encephalitis is caused by autoantibodies against neuronal surface antigens, produced by plasma cells in both the periphery and the 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

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

Mizuguchi M, et al. (2020) "Guidelines for the diagnosis and treatment of acute encephalopathy in childhood." ***Brain Dev***. In press.

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

Igarashi A, "et al. (2018) "Cytokine-induced differentiation of hematopoietic cells into microglia-like cells in vitro." ***Clin. Exp. Neuroimmunol.*** 9:139-149.

Saika R, et al. (2017) "MicroRNA-101a regulates microglial morphology and inflammation." ***J. Neuroinflammation*** 14:109

Nakahara E, et al. (2015) "A diagnostic approach for identifying anti-neuronal antibodies in children with suspected autoimmune encephalitis." ***J. Neuroimmunol.*** 285:150-155.

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
Takashi SHICHITA

Takashi SHICHITA has been the project leader of the Stroke Renaissance Project since 2017. After graduating from the Faculty of Medicine, Kyushu University in 2004, he practiced internal medicine and was affiliated with the Cerebrovascular Center, Kyushu Medical Center. He conducted research at Kyushu University and Keio University and received a Ph.D in 2010 from Kyushu University for clarifying molecular and cellular mechanisms underlying inflammation after ischemic stroke. His current interest is to clarify the precise molecular mechanisms for the neural repair in brains damaged by stroke and dementia. His group will develop therapeutic methods which sustain the reconstruction of neural circuits for accelerated recovery from stroke and dementia.

Stroke Renaissance

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

Staff

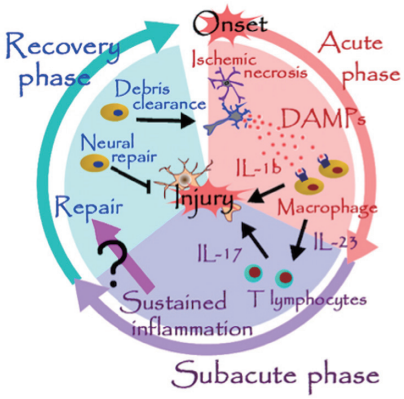
Researchers	Research Assistants	Students
Seiichiro SAKAI	Yoshiko YOGIASHI	Koutaro NAKAMURA
Jun TSUYAMA	Kumiko KURABAYASHI	Akari NAKAMURA
		Kento OTANI

Research Summary

Stroke is a common cause of severe disability and death worldwide; however, few therapeutic agents have been shown to improve the neurological deficits of stroke patients.

In this Project, we are studying the detailed molecular mechanisms underlying the neural repair after stroke and dementia. New research methods and techniques which have been recently developed in the field of immunology or neuroscience are allowing us to investigate the precise process of inflammation and repair in the injured brain after stroke and dementia. The purpose of our project is to develop a new therapeutic method for promoting the recovery of neurological function in patients with cerebrovascular diseases.

Sterile Inflammation After Ischemic Stroke



"What triggers neural repair after stroke?"

We have identified peroxiredoxin family proteins as DAMPs (damage associated molecular patterns) which trigger post-ischemic inflammation (Nat. Med. 2012). DAMPs induce IL-23 production from infiltrating macrophages and neutrophils, and this sustains the inflammation after ischemic stroke by promoting IL-17 production of γδT lymphocytes (Nat. Med. 2009). Cerebral post-ischemic inflammation resolves several days after the stroke onset. The clearance of DAMPs from ischemic brain through MSR1, a scavenger receptor, plays a pivotal role in the resolution of sterile inflammation after ischemic stroke (Nat. Med. 2017). Currently, we are studying how cerebral post-ischemic inflammation switches into the process of neural repair.

Selected Publications

Tsuyama J, et al. (2018) "Pivotal role of innate myeloid cells in cerebral post-ischemic sterile inflammation." ***Semin. Immunopathol.*** 40(6): 523-538.

Shichita T, et al. (2017) "Mafb prevents excess inflammation after ischemic stroke by accelerating clearance of danger signals through MSR1." ***Nat. Med.*** 23(6): 723-732.

Shichita T, et al. (2012) "Peroxiredoxin family proteins are key initiators of post-ischemic inflammation in the brain." ***Nat. Med.*** 18(6): 911-917.

Shichita T, et al. (2009) "Pivotal role of cerebral interleukin-17-producing gammadelta T cells in the delayed phase of ischemic brain injury." ***Nat. Med.*** 15(8):946-950.

Project Leader
Chiaki Ohtaka-MARUYAMA

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

Developmental Neuroscience

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

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Takuma KUMAMOTO

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Aiko ODAJIMA
Yoshiko TAKAHSAHI
Kaori MIURA

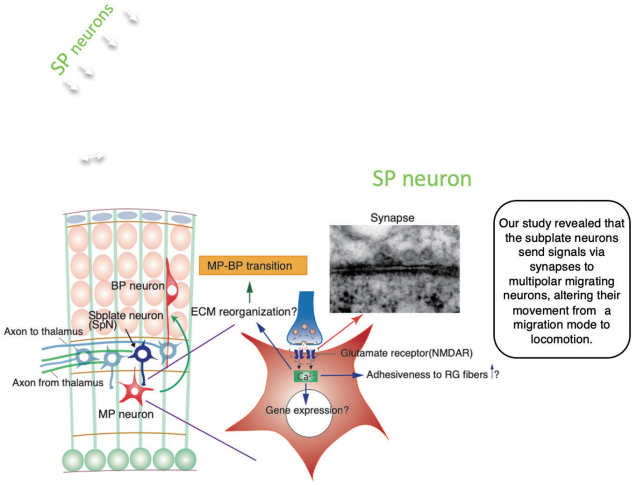
Students
Hitomi ACHIWA
Kyosuke WADA
Xiang SONG
Saki ONODERA
Mayu OZAKI

Research Summary

Mechanisms of Neural Network Formation: Neocortical development and synapse formation

How does the mammalian neocortex acquire the unique six-layered structure that is thought to be the structural basis for the remarkable evolution of complex neural circuits? We focus on subplate (SP) neurons that develop extremely early during cortical development and disappear postnatally. Recently, we found that SP neurons interact directly with young migrating neurons and play an essential role in radial neuronal migration. 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 studies of the SP layer should lead to a better understanding of brain development during evolution.

"We are interested in the roles of the subplate layer in the development of the cerebral cortex. Subplate neurons are a transient cell population that plays a crucial role as a "control tower" during neocortical formation and also exerts effects on adult cortical function."



Selected Publications

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

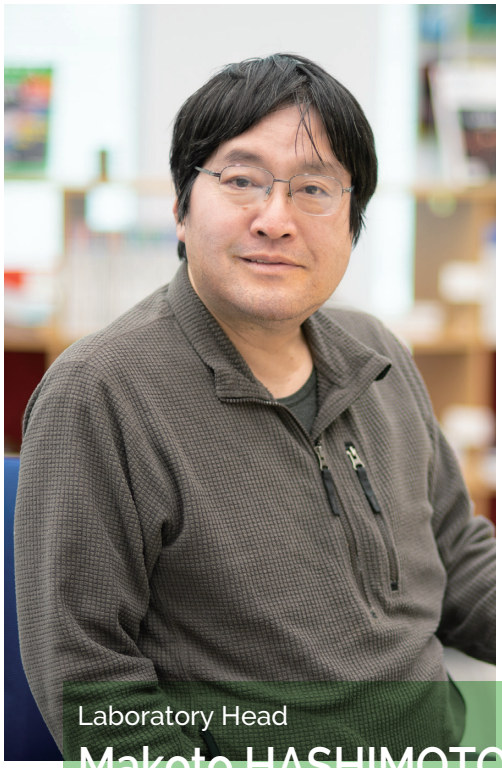
Nomura T, et al. (2020) "Changes in Wnt-dependent neuronal morphology underlie the anatomical diversification of neocortical homologs in amniotes." ***Cell Reports, 31***,107592.

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.



Laboratory Head

Makoto HASHIMOTO

Makoto Hashimoto has been the head of the Laboratory of Parkinson's Disease since 2011. He obtained his MD from the University of Tokyo School of Medicine in 1986, after which he worked at the University of Tokyo Hospital until 1988. In 1992 he graduated from the Graduate School of Medicine at the University of Tokyo with a PhD in Biochemistry. He then worked as a research associate at the Salk Institute from 1992 to 1995 and as a postdoctoral fellow in the Dept of Neurosciences at the University of California, San Diego from 1995 to 2000. From 2004 to 2011 he worked as a deputy councilor researcher at the Tokyo Metropolitan Institute for Neuroscience before joining the staff at TMIMS.

Parkinson's Disease

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

Staff

Researchers
Yoshiki TAKAMATSU

Research Assistants
Ryoko WADA

Research Summary

Our goal is to develop effective disease-modifying therapies for age-associated neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD).

1. Despite extensive investigation, the physiological functions of amyloidogenic proteins (APs) associated with neurodegenerative diseases, including amyloid β for AD and α-synuclein for PD, are currently unclear. We recently proposed that APs may protect the brain from multiple stressors through a heritable proteinaceous adaptation mechanism we call evolvability (Fig.1) (Hashimoto M, et al. J. Alzheimers Dis. 2018, J. Parkinsons Dis. 2018). Further studies of evolvability should contribute to the development of novel therapy strategies for neurodegenerative diseases.

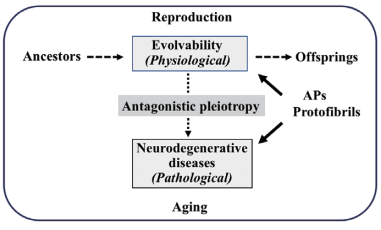


Fig 1. Evolvability and neurodegenerative disease: antagonistic pleiotropy of AP protofibrils

2. We are also identifying small molecules that could be useful for the prevention of neurodegenerative diseases using *Drosophila* molecular genetics (Fig. 2), cell biology, and transgenic mice studies. Molecules identified in our study may also be applicable to other diseases, including AD and Huntington's disease.

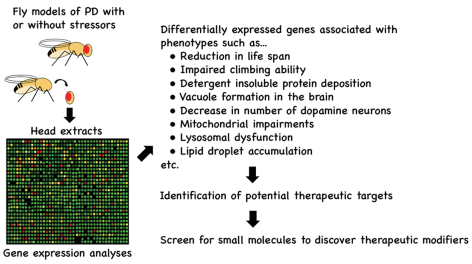


Fig. 2 *Drosophila* molecular genetics

Selected Publications

Takamatsu Y, et al. (2020) "Adiponectin Paradox as a therapeutic target of the cancer evolvability in aging. " ***Neoplasia.*** in press

Hashimoto M, et al. (2020) "Understanding Creutzfeldt-Jacob Disease from a Viewpoint of Evolvability". ***Prion.*** 14(1):1-8.

Ho G, et al. (2020) "Connecting Alzheimer's Disease with Diabetes Mellitus through Amyloidogenic Evolvability ***Front Aging Neurosci.***12:576192.

Takamatsu Y, et al. (2020) "Amyloid Evolvability and Cancer. ***Trends Cancer.*** 6(8):624-627.

Fujita M et al. (2020) "Possible Role of Amyloidgenic Evolvability in Dementia with Lewy Bodies; Insights from Transgenic Mice Expressing P123H β-synuclein" ***Int J Mol Sci.*** 21(8):2849.

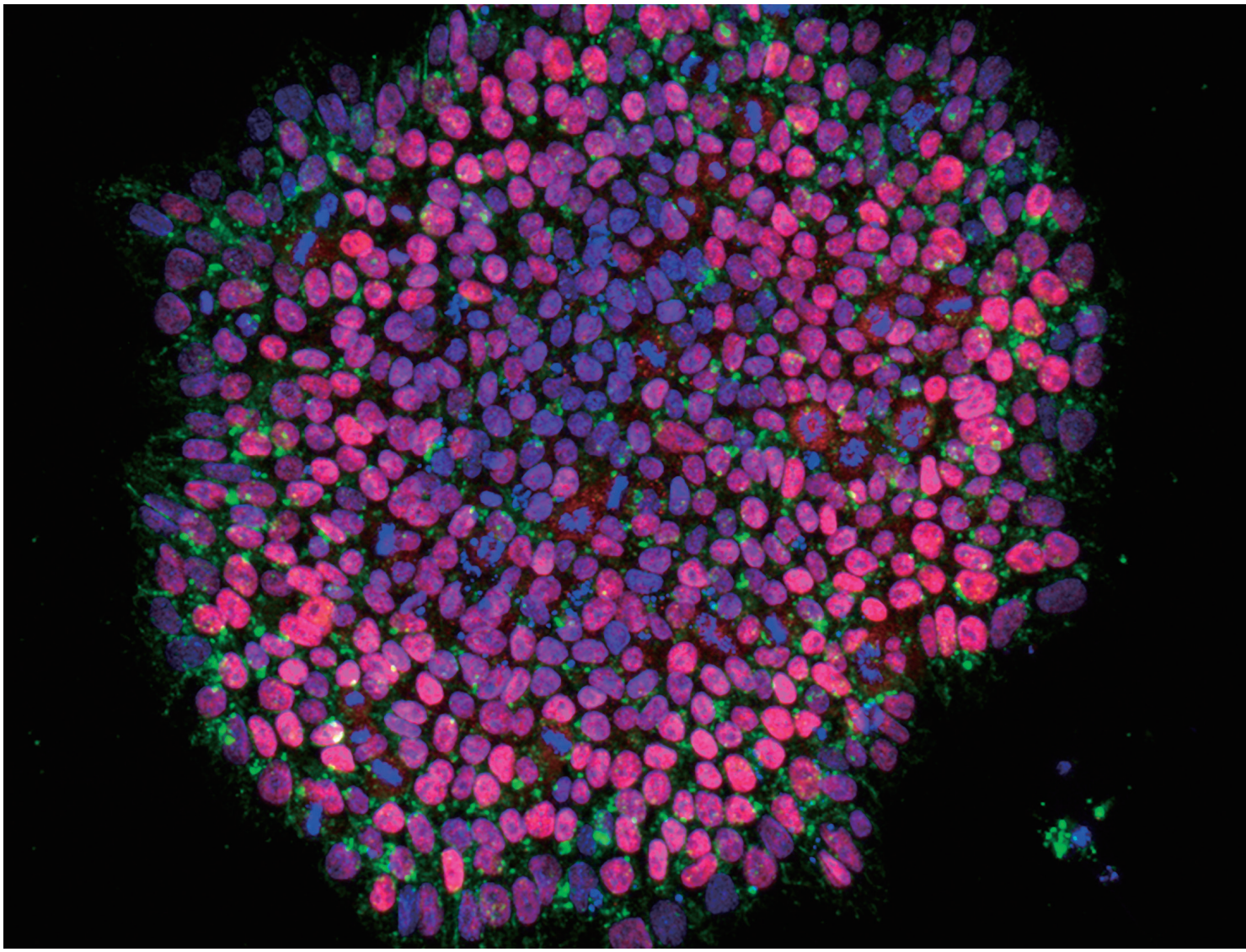
Waragai M, et al. (2020) "Adiponectin Paradox as a Therapeutic Target Alzheimer's Disease." ***J Alzheimers Dis.*** 76(4):1249-1253.

Waragai M, et al. (2020) "Adiponectin Paradox in Alzheimer's Disease; relevance to Amyloidgenic Evolvability? ***Front Endocrinol (Lausanne)*** :108. 101.

Hashimoto M, et al. et al. (2019) "Possible Role of Amyloid Cross-Seeding in Evolvability and Neurodegenerative Disease. ***J Parkinsons Dis.*** 9(4):793-802

Takamatsu Y, et al. (2017) "Combined immunotherapy with "anti-insulin resistance" therapy as a novel therapeutic strategy against neurodegenerative diseases." ***NPJ Parkinson's Disease*** 3: 4.

Takamatsu Y, et al. (2016) "Protection against neurodegenerative disease on Earth and in space." ***NPJ Microgravity*** 2: 16013.



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

Psychiatry & Behavioral Sciences

Project Leader
Makoto ARAI

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

Schizophrenia Research

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

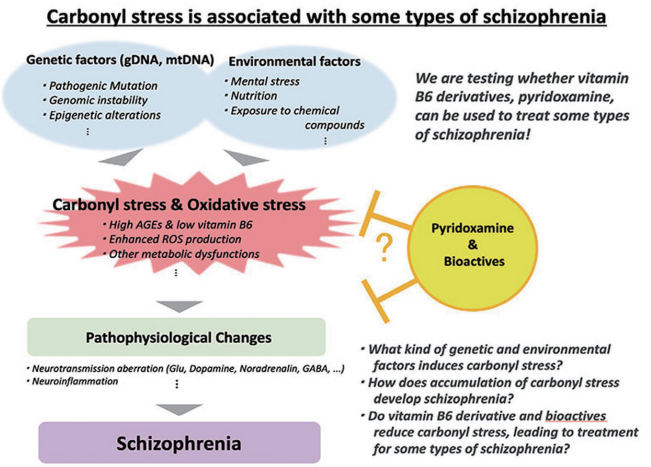
Staff

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

Research Summary

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

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



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

Selected Publications

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

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

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

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

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

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

Project Leader
Yoshitaka TATEBAYASHI

Affective Disorders Research

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

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

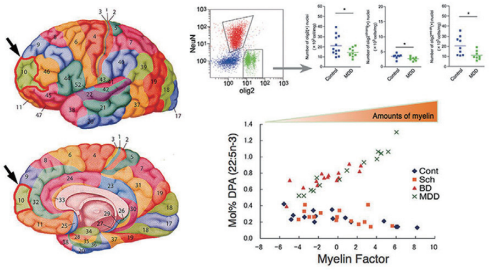
Staff

Researchers

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

Research Summary

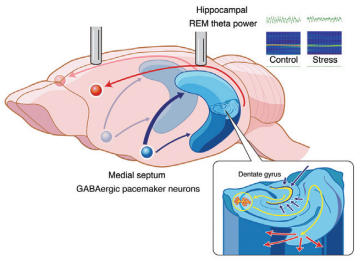
Major depressive disorder (MDD) and bipolar disorder (BD), collectively known as affective disorders, are relapsing and remitting disorders of affect with nearly full recovery between episodes. We use human postmortem brains and animal and cell culture models to identify the processes in which stress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



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

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

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



Selected Publications

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

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

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

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

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

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

Project Leader
Makoto HONDA

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

Sleep Disorders

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

Staff

Researchers
Taku MIYAGAWA
Akiyo NATSUBORI

Research Assistants
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Yoshiko HONDA

Visiting Scientist
Mihoko SHIMADA

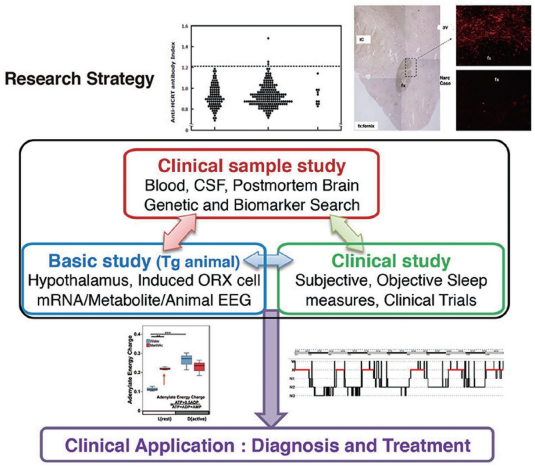
Students
Momoka MIYAZAWA
Takuma OGAWA
Shun SUZUKI

Research Summary

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

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

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



Selected Publications

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

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

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

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

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

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

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

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

Project Leader
Kazutaka IKEDA

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

Addictive Substance

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

Staff

Researchers
Shinya KASAI
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Seii OHKA
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Yuki MORIYA

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Junko HASEGAWA
Etsuko KAMEGAYA
Yukiko MATSUSHIMA
Yuki SERITA
Yuko EBATA
Kyoko NAKAYAMA

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Yukiko OCHIAI
Yoshihisa KATO
Aimi YAMAGISHI
Yoshihiko KOSAKI
Moe SOEDA
Rie INOUE
Shoka MATSUYAMA

Research Summary

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

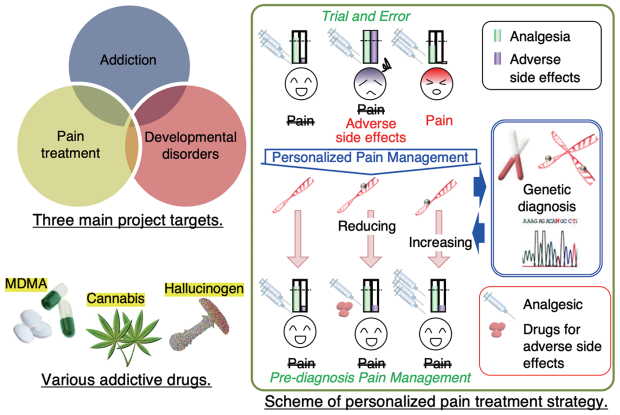
Some addictive drugs are also widely used as analgesics and for the treatment of developmental disorders. Some molecules that are involved in the actions of addictive drugs may be shared between analgesia and developmental disorders. The goals of our project are the following:

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

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

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

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



Scheme of personalized pain treatment strategy.

Selected Publications

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

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

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

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

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

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

Laboratory Head
Kanato YAMAGATA

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

Synaptic Plasticity

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

Staff

Researchers
Tadayuki SHIMADA
Chihiro HISATSUNE
Hiroko SUGIURA
Keiko MORIYA-ITO

Research Assistants
Fumie MASUDA
Tomoko KAWANO

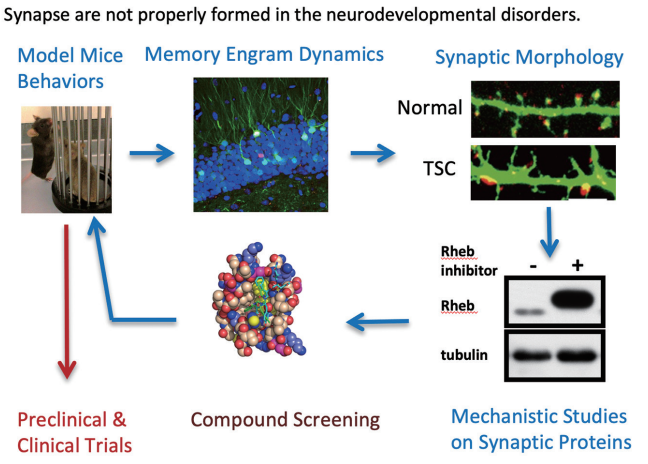
Students
Hirono KOBAYASHI
Yuka KAWAMOTO
Shiho SAKAI

Research Summary

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

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

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



Selected Publications

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

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

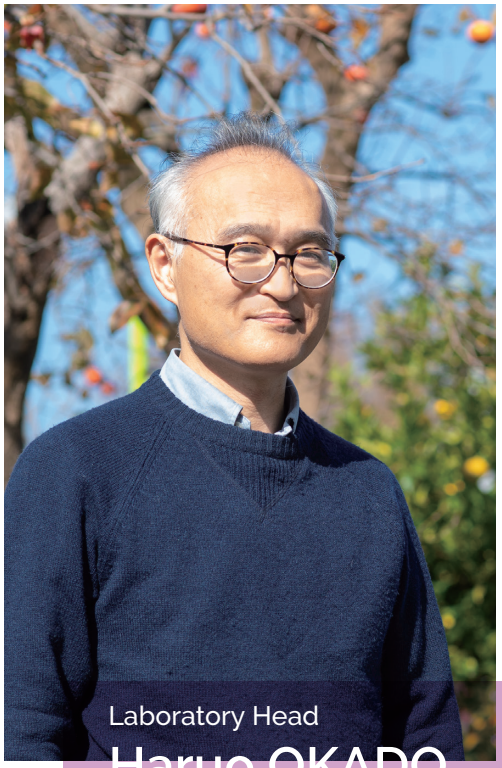
Shimada T and Yamagata K. (2018) 442:296-310. "Pentylenetetrazole-Induced Kindling Mouse Model." ***JoVE*** (136).

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

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

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

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



Laboratory Head
Haruo OKADO

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

Neural Development

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

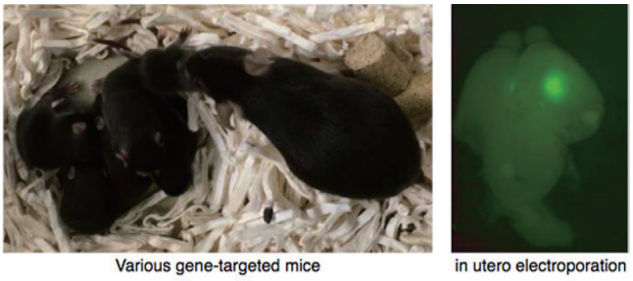
Staff

Researchers
Shinobu HIRAI
Tomoko TANAKA

Research Assistants
Katsuko TAKASAWA
Hiroko SHIMBO
Fumika KAWANO

Research Summary

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



Various gene-targeted mice　　in utero electroporation

Our major projects include

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

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

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

Selected Publications

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

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

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

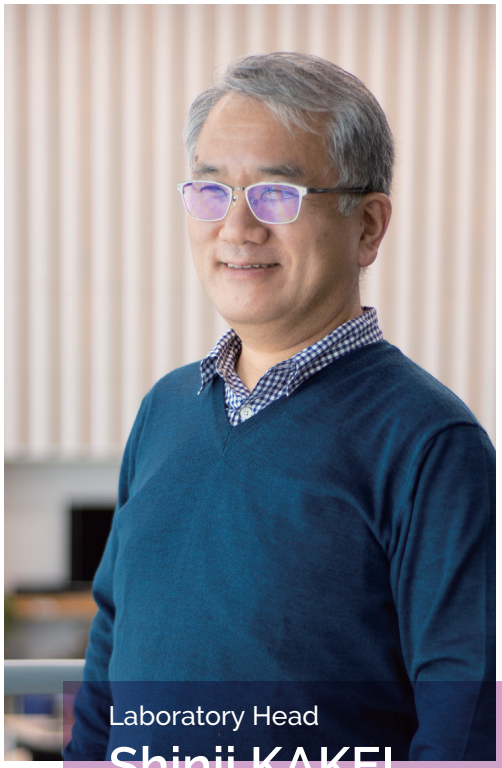
Nakajima K, et al. (2015) "Benzodiazepines induce sequelae in immature mice with inflammation-induced status epilepticus." ***Epilepsy & Behavior*** 52: 180-186.

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

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

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

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



Laboratory Head
Shinji KAKEI

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

Movement Disorders

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

Staff

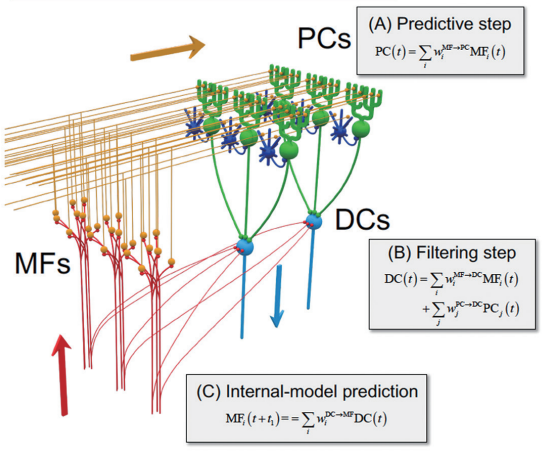
Researchers
Kyuengbo MIN
Takahiro ISHIKAWA
Takeru HONDA

Students
Masaya WATANABE

Research Summary

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

The Cerebellum as a Kalman Filter



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

Selected Publications

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

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

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

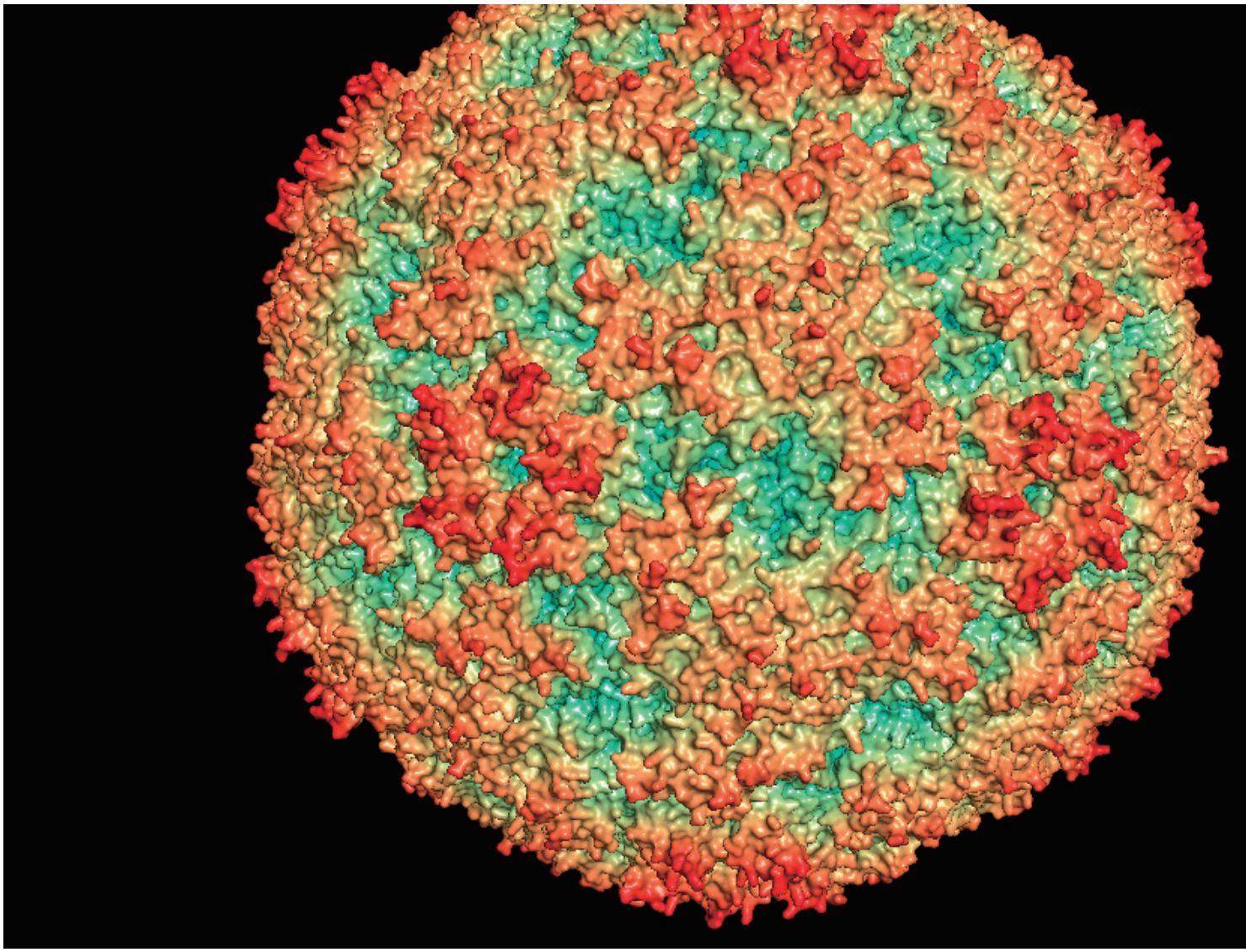
Tanaka H, et al. (2019) "Neural Evidence of the Cerebellum as a State Predictor." ***Cerebellum.*** 18(3):349-371.

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

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

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

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



A particle structure model of Enterovirus 71 generated from the Protein Data Base 4AED. Red and green indicate surface and interior compartments, respectively.

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.

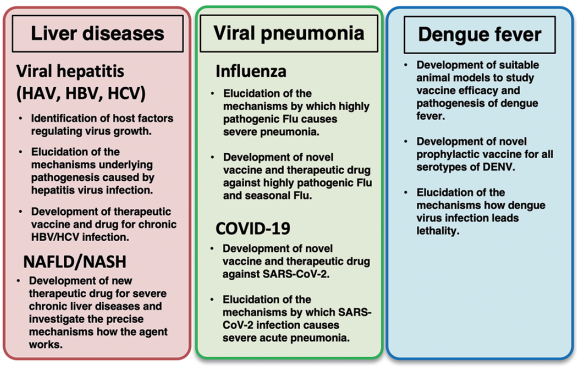
Staff

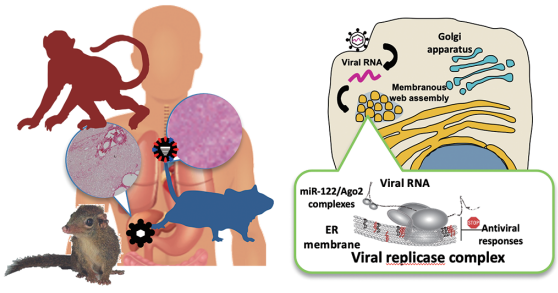
Researchers
Michinori KOHARA
Tsubasa MUNAKATA
Daisuke YAMANE
Kenzaburo YAMAJI
Yuko TOKUNAGA
Naoki YAMAMOTO
Takahiro SANADA
Yusuke MATSUMOTO
Tomoko HONDA

Research Assistants
Asako TAKAGI
Risa KONO
Masahiko HIGA

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

Saito M, et al. In Press "Targeted macrocycles hamper hemagglutinin adsorption and fusion, and have antiviral effects in murine and macaque models of influenza." ***Nat Commun***.

Sanada T, et al. (2019) "Avian H5N1 influenza virus infection causes severe pneumonia in the Northern tree shrew (Tupaia belangeri)." ***Virology*** 529:101-110.

Tokunaga Y, et al. (2017) "Selective inhibitor of Wnt/-catenin/CBP signaling ameliorates hepatitis C virus-induced liver fibrosis in mouse model." ***Sci. Rep.*** 7: 325.

Sanada T, et al. (2016) "Transmission of HBV DNA mediated by ceramidetriggered extracellular vesicles." ***Cell Mol. Gastroenterol Hepatol.*** 3:272-283.

Yasui F, et al. (2016) "Sensitization with vaccinia virus encoding H5N1 hemagglutinin restores immune potential against H5N1 influenza against H5N1 influenza virus." ***Sci. Rep.*** 6: 37915.

Sanada T, et al. (2016) "Property of hepatitis B virus replication in Tupaia belangeri hepatocytes." ***Biochem. Biophys Res. Commun.*** 469: 229-235.

Yamamoto N, et al. (2016) "Novel pH-sensitive multifunctional envelopetype nanodevice for siRNA-based treatments for chronic HBV infection." ***J. Hepatol.*** 64: 547-555

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
Naoki KAJIWARA

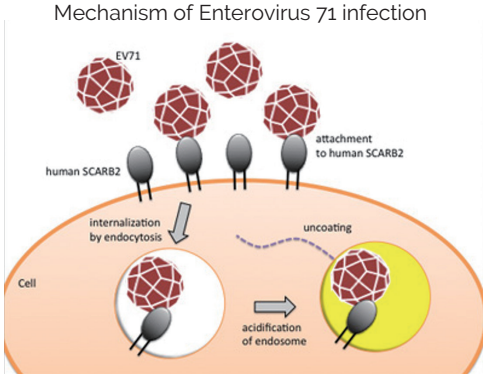
Research Assistants
Ayako TAKASHINO
Masako UKAJI
Namiko NOMURA
Tomoha NISHIZAWA
Wakako MIWATASHI
Minori ISHIDA
Sayaka ESAKI

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.

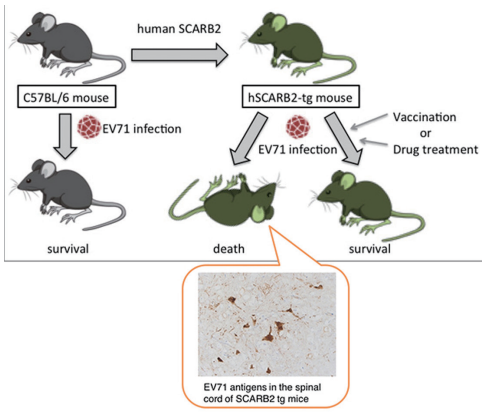
Research Topics

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

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

Fujii K, et al. (2018) "VP1 Amino Acid Residue 145 of Enterovirus 71 Is a Key Residue for Its Receptor Attachment and Resistance to Neutralizing Antibody during Cynomolgus Monkey Infection." ***J. Virol.,*** 92:(15)e00682-18

Fujii K, et al. (2013) "Transgenic mouse model for the study of enterovirus 71 neuropathogenesis." ***Proc. Natl. Acad. Sci. USA.,*** 110: 14753-14758

Yamayoshi S, et al. (2009) "Scavenger receptor B2 is a cellular receptor for enterovirus 71." ***Nature Medicine*** 15:789-801

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

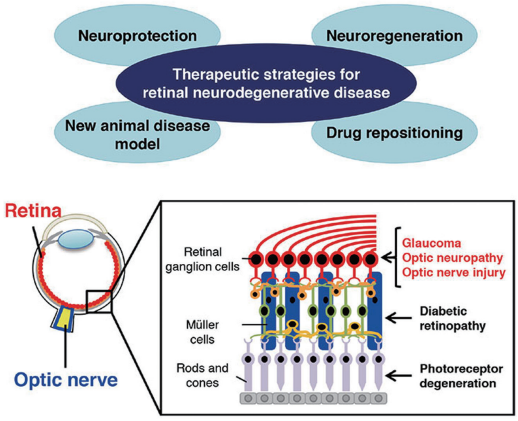
Researchers
Researchers
Kazuhiko NAMEKATA
Xiaoli GUO
Atsuko KIMURA
Chikako HARADA
Takahiko NORO
Euido NISHIJIMA
Yuta KITAMURA
Naoki KIYOTA

Research Assistants
Mayumi KUNITOMO

Students
Kaori SEGURA

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.



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.

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 an animal model of multiple sclerosis (MS). Thus, DOCK10 may be a novel therapeutic target for diseases such as MS and optic neuritis.

Finally, we have been studying the relationship between glaucoma and EAAT1, a glutamate transporter that regulates glutamate signaling. Glutamate is the major excitatory neurotransmitter in the central nervous system and we identified EAAT1 variants that are associated with glaucoma. These loss-of-function variants may contribute to pathogenesis of glaucoma.

Selected Publications

Namekata, K., Guo, X., Kimura, A., Azuchi, Y., Kitamura, Y., Harada, C. and Harada, T. Roles of the DOCK-D family proteins in a mouse model of neuroinflammation. ***Journal of Biological Chemistry*** 295(19), 6710-6720, 2020.

Nishijima, E., Namekata, K., Kimura, A., Guo, X., Harada, C., Noro, T., Nakano, T. and Harada, T. Topical ripasudil stimulates neuroprotection and axon regeneration in adult mice following optic nerve injury. ***Scientific Reports*** 10(1), 15709, 2020.

Harada, C., Noro, T., Kimura, A., Guo, X., Namekata, K., Nakano, T. and Harada, T. Suppression of oxidative stress as potential therapeutic approach for normal tension glaucoma. ***Antioxidants*** 9(9), 874, 2020.

Kimura, A., Noro, T. and Harada, T. Role of animal models in glaucoma research. ***Neural Regeneration Research*** 15(7), 1257-1258, 2020.

Yanagisawa, M., Namekata, K., Aida, T., Katou, S., Takeda, T., Harada, T., Fuse, N., the Glaucoma Gene Research Group, and Tanaka, K. EAAT1 variants associated with glaucoma. ***Biochemical and Biophysical Research Communications*** 529(4), 943-949, 2020.

Kikuchi, K., Dong, Z., Shinmei, Y., Murata, M., Kanda, A., Noda, K., Harada, T. and Ishida, S. Cytoprotective effect of astaxanthin in a model of normal intraocular pressure glaucoma. ***Journal of Ophthalmology*** 2020, 9539681, 2020.

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

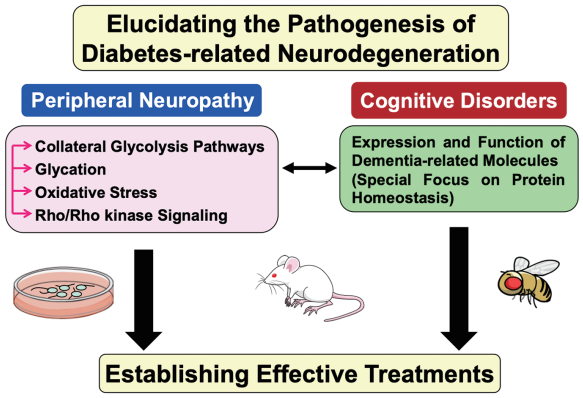
Visiting Scientists
Koichi KATO
Tatsufumi MURAKAMI
Junji YAMAUCHI
Hitoshi KAWANO
Ken MURAMATSU
Keiichiro MATOBA
Tomoyo AKAMINE
Tomoko ISHIBASHI

Students
Yosuke NAGAI
Masaki OBA
Nozomi SAKATA

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

Mizukami H, et al. "Role of glucosamine in development of diabetic neuropathy independent of aldose reductase pathway." ***Brain Commun***, Oct 9, 2020 (on line).

Akamine T, et al. (2020) "Glycolaldehyde induces sensory neuron death through activation of the c-Jun N-terminal kinase and p-38 MAP kinase pathways." ***Histochem. Cell Biol.*** 153:111-119.

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)

Takaku S, et al. (2018) "Establishment of a myelinating co-culture system with a motor neuron-like cell line NSC-34 and an adult rat Schwann cell line IFRS1." ***Histochem. Cell Biol.*** 149:537-543.

Niimi N, et al. (2018) "A spontaneously immortalized Schwann cell line from aldose reductase-deficient mice as a useful tool for studying polyol pathway and aldehyde metabolism." ***J. Neurochem.*** 144:710-722.

Sango K, et al. (2017) "Impaired axonal regeneration in diabetes. Perspective on the underlying mechanism from in vivo and in vitro experimental studies." ***Front. Endocrinol.*** 8:12.

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

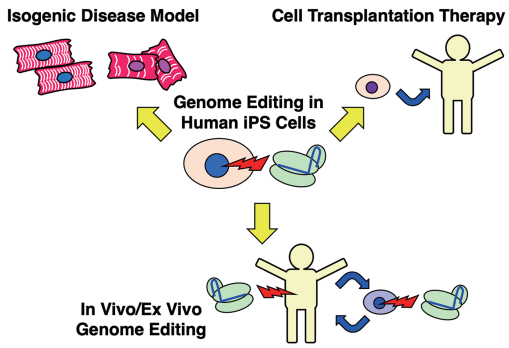
Research Assistants
Szuyin HSU

Students
Daiki KONDO
Ittetsu NAKAJIMA
Terumi ONO
Anri SAITOH
Minato MAEDA

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

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.

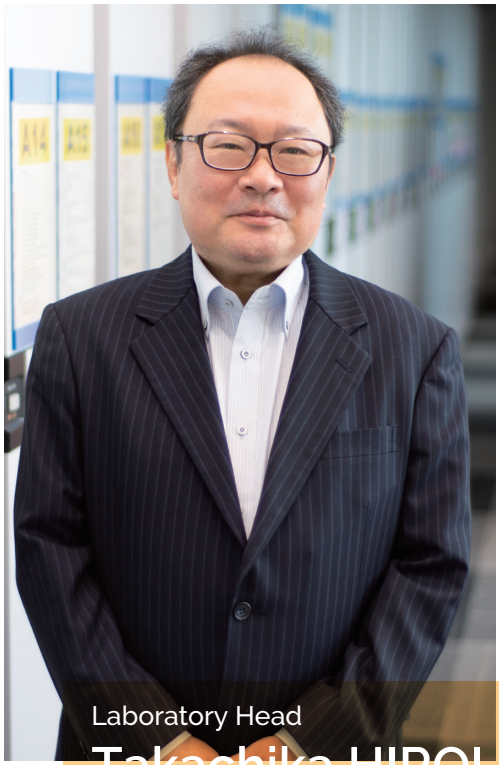
Miyaoka Y, et al. (2018) "Detection and Quantification of HDR and NHEJ Induced by Genome Editing at Endogenous Gene Loci Using Droplet Digital PCR." ***Methods Mol. Biol.*** 1768: 349-362.

Workman MJ, et al. (2017) "Engineered human pluripotent-stem-cell-derived intestinal tissues with a functional enteric nervous system." ***Nat. Med.*** 23: 49-59.

Miyaoka Y, et al. (2016) "Using Digital Polymerase Chain Reaction to Detect Single-Nucleotide Substitutions Induced by Genome Editing." ***Cold Spring Harb. Protoc.*** 2016:688-692.

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.



Laboratory Head
Takachika HIROI

Takachika Hiroi has been the leader of the laboratory of allergy and immunology since 2005. After graduation from Nihon university school of dentistry at Matsudo in 1986 (D.D.S.), he completed graduate school at Nihon university in 1990 (Ph.D). He started to work on mucosal immunology under the supervision of Dr. Hiroshi Kiyono at University of Alabama at Birmingham, Vaccine center, Alabama, USA, in 1992. After returning to Japan, he worked at Osaka University in 1995-2003 and at University Tokyo in 2003-2005. His current research is the study for effective bio-markers of sublingual immunotherapy (SLIT) for Japanese cedar pollen allergy . Further, the molecular mechanisms of mucosal tolerance still remain unclear. I want to elucidate this immune mechanism and develop drugs for some mucosal diseases in the future.

Allergy and Immunology

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

Staff

Researchers
Mayumi SAEKI
Masanobu WATANABE
Tomoe NISHIMURA

Research Assistants
Noriko KITAMURA

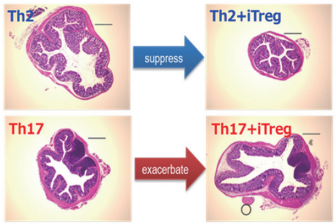
Students
Eriko ANDO
Kohei FUSANO
Satoshi UNO

Research Summary

Recent Topics of Mucosal Immunology

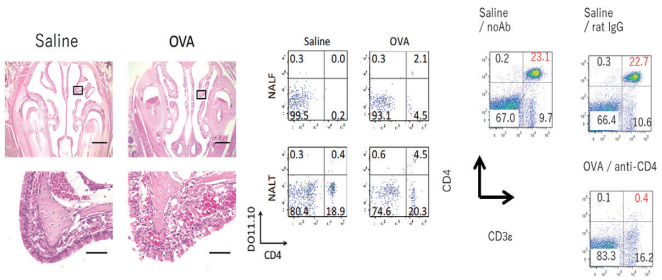
1. Antigen-specific iTreg cells stimulate Th17-mediated colon inflammation

$CD4^+$ helper T cells play a crucial role in allergy and autoimmune diseases including inflammatory bowel diseases (IBDs). Th17 cells and $Foxp3^+$ regulatory T cells (Tregs) are thought to promote and suppress inflammatory responses, respectively. Recently we have developed an antigen-specific and organ-targeted inflammation model by transferring antigen-specific helper T cell subsets followed by antigen administration. By adopting this strategy to colon, we have shown that antigen-specific Tregs stimulate Th17-mediated inflammation in a CTLA4-dependent manner. This finding will call for reconsideration of Treg/CTLA4-based immunological modulation to suppress or treat inflammatory diseases.



2. Essential Contribution of $CD4^+$ T Cells to Antigen-Induced Nasal

Hyperresponsiveness in Experimental Allergic Rhinitis.
Recently, we have reported that $CD4^+$ T cells play a crucial role in the pathogenesis of AR via induction of NHR, independent of IgE-, mast cell-, and eosinophil-mediated responses. (A) (B) Antigen-induced NHR in T cell-transferred mice. (C) Administration of an anti-CD4 mAb to immunized mice depleted peripheral $CD4^+$ T cells almost completely.



Selected Publications

Tachibana M, et al. (2020). "Ablation of IL-17A leads to severe colitis in IL-10-deficient mice: implications of myeloid-derived suppressor cells and NO production." ***Int Immunol.*** 32: 187-201.

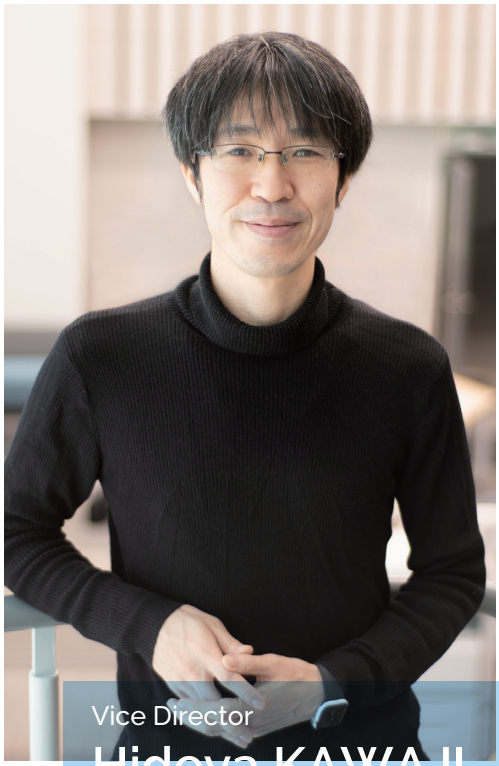
Kitamura N, et al (2020). "Identification of novel interacting regions involving calcineurin and nuclear factor of activated T cells." ***FASEB J.*** 34: 3197-3208.

Takaiwa, F, et al. (2019). "Development of rice-seed-based oral allergy vaccines containing 2 hypoallergenic Japanese cedar pollen allergen derivatives for immunotherapy." ***J Agric Food Chem.*** 67: 13127-13138.

Kaminuma O, et al. (2018). "Downregulation of NFAT3 due to lack of T-box transcription factor TBX5 is crucial for cytokine expression in T cells." ***J Immunol.*** 200: 92-100.

Yokoyama S, et al. (2009) "Antibody-mediated blockade of IL-15 signaling reverses autoimmune intestinal damage in a mouse model of celiac disease." ***Proc. Natl. Acad. Sci. USA*** 106: 15849-15854.

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

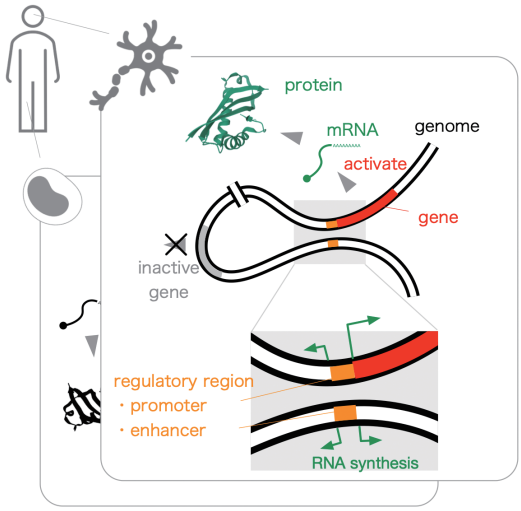
Director
Hisao MASAI
Senior Researcher
Keisuke OBOKI

Researcher
Naoko YOSHIZAWA
Yuichiro HARA
Saki SAITO
Naoki HIROSE

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

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 T, et al. (2019) "Evaluation of off-target effects of gapmer antisense oligonucleotides using human cells. "*Genes Cells.* 24(12):827-835.

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

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

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

Forrest, A.R.R., Kawaji,H., et al. (2014) "A promoter-level mammalian expression atlas. *Nature*, 507, 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

Researcher
Syudo YAMASAKI

Researcher
Miharu NAKANISHI

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

Nakanishi M, et al. (2020) "Time investment for program implementation to manage neuropsychiatric symptoms: an observationallongitudinal study in in-home and residential care settings." *J Alzheimer's Dis*.

Yamasaki S, et al. (2020) "Interaction of adolescent aspirations and self-control on wellbeing in old age: Evidence from a six-decade longitudinal UK birth cohort." *J Positive Psychol*.

Yamasaki S, et al. (2019) "Maternal diabetes in early pregnancy, and psychotic experiences and depressive symptoms in 10-year-old offspring: A population-based birth cohort study." *Schizophr Res*, 206:52-57.

Ando S, et al. (2019) "Cohort profile: The Tokyo Teen Cohort study (TTC)."*Int J Epidemiol*, 48(5):1414-1414g.

Nishida A et al.(2018) "A randomized controlled trial of comprehensive early intervention care in patients with first-episode psychosis in Japan: 1.5-year outcomes from the J-CAP study." *J Psychiatr Res*, 102:136-141.

Unit Leader
Yuki NAKAYAMA

Career
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
Yasuyo KASAHARA

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

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, Article number: 12262

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

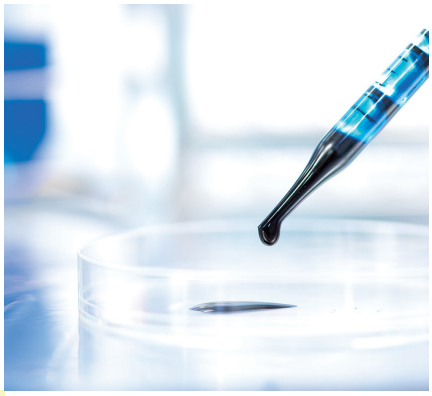
Matsuda C, Shimizu T, Nakayama Y, Haraguchi M. (2019) "Cough peak flow decline rate predicts survival in patients with amyotorophic lateral sclerosis" ***Muscle & Nerve***. 59(2) 168-173.

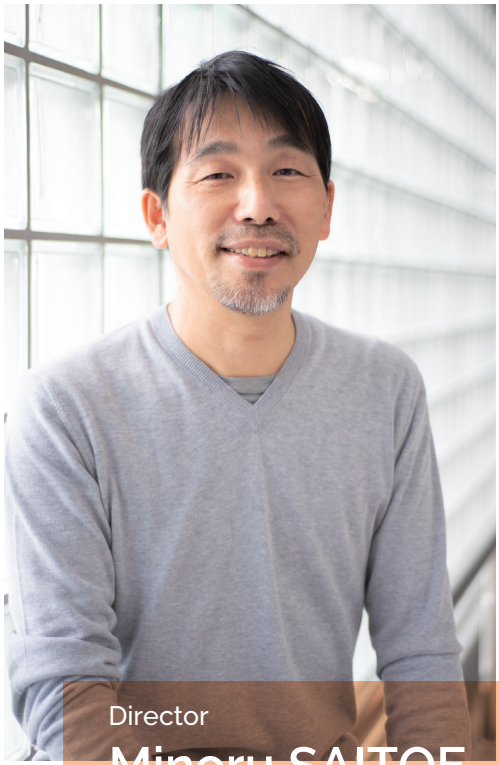
Shimizu T, Nakayama Y, et al. (2018) "Sensory cortex hyperexcitability predicts short survival in amyotrophic lateral sclerosis." ***Neurology*** 1 ;90(18): e1578-e1587.

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





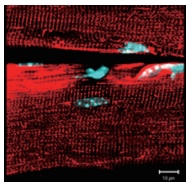
Basic Technology Research

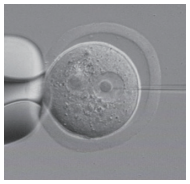
Laboratory HP: https://www.igakuken.or.jp/english/center/basic/basictech.html

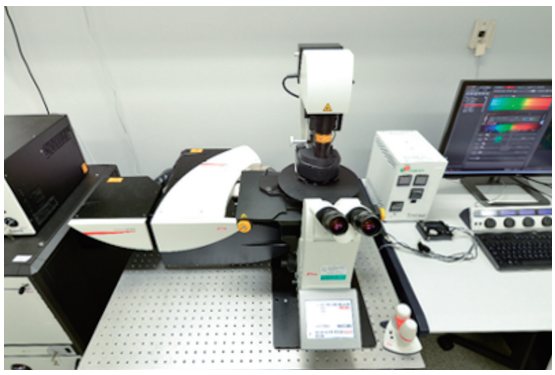
Director
Minoru SAITOE

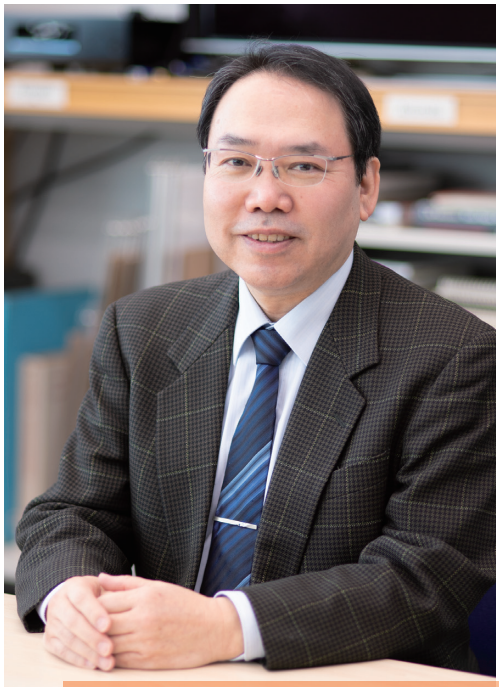
The Basic Technology Research Center provides resources to assist scientists to conduct their research efficiently. We provide state-of-the-art technologies required for biomedical and life science research and maintain various facilities used by researchers.

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.









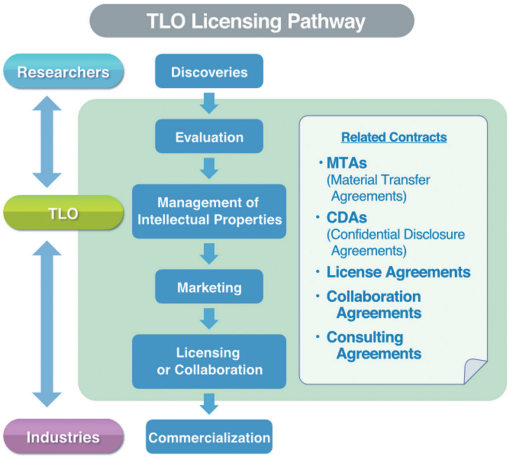
Technology Licensing Office

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

General Manager
Kazumasa AOKI

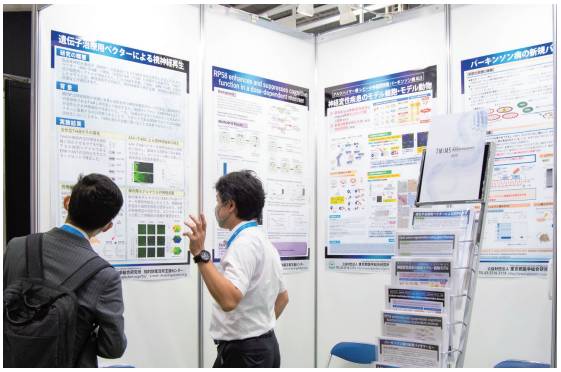
Who we are

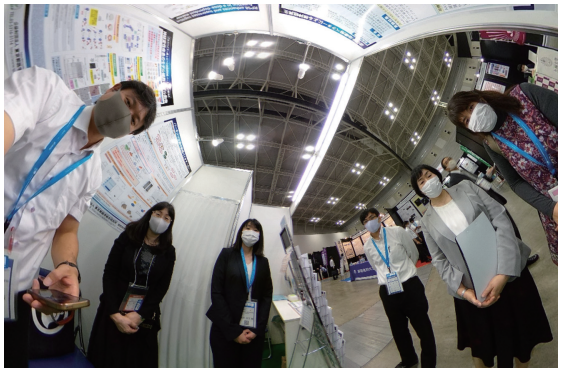
- The Technology Licensing Office (TLO) facilitates the conversion of scientific discoveries to innovative technologies with the ultimate goal of improving public health and welfare.
- We evaluate basic research findings (seeds) as intellectual property assets, and license promising candidates to industries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

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

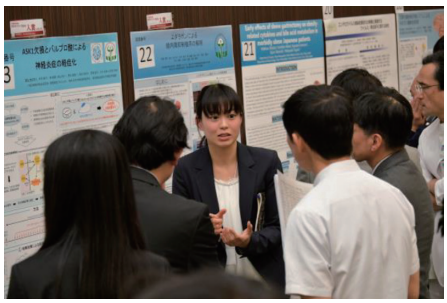
We facilitate collaboration between basic scientists at research institutes and medical doctors at hospitals. We have a supporting budget of 500,000 yen for collaborative clinical studies with medical doctors at Tokyo Metropolitan Hospitals.

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.

Tokyo Metropolitan Institute of Medical Science

7,000 beds of Tokyo Metropolitan Hospitals

Conference with researchers and medical doctors



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

Laboratory Head
Nobutaka ARAI

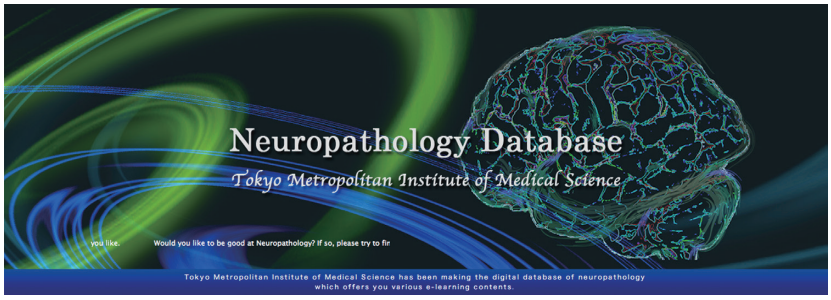
Neuropathology

Laboratory HP: https://pathologycenter.jp/english/en_index.html

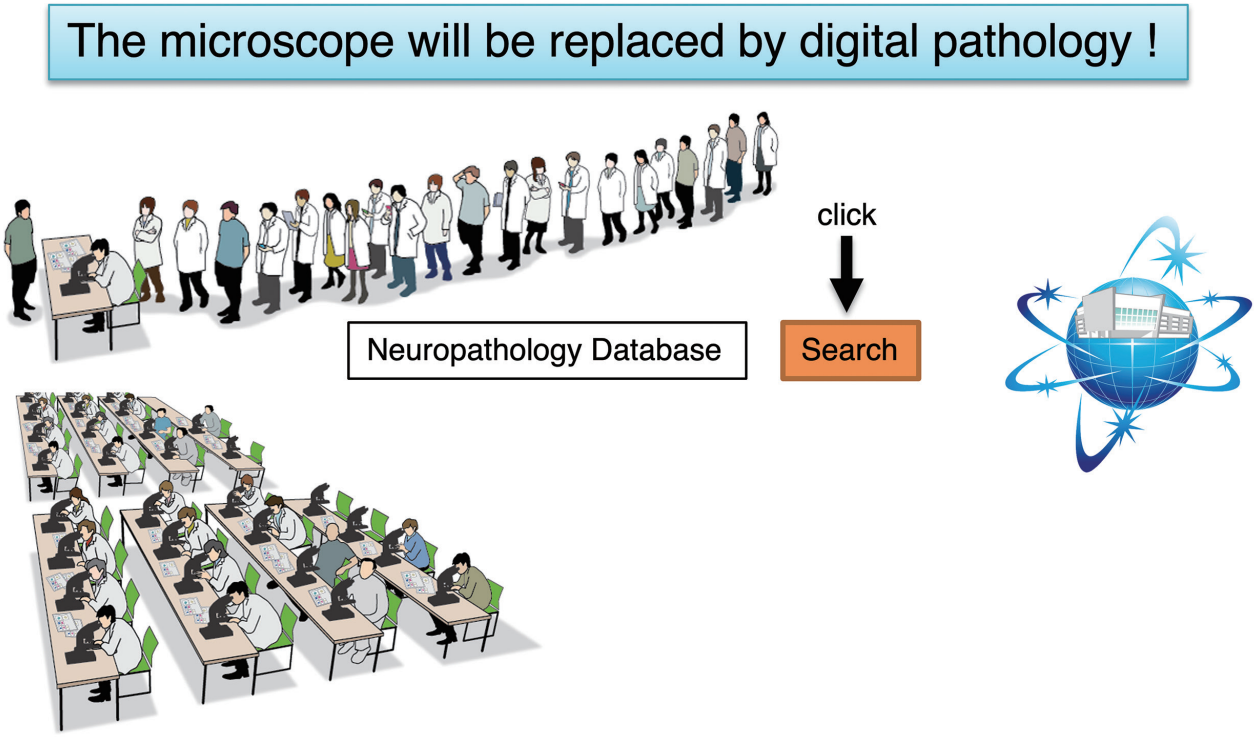
Translational Research using human materials and Management of Database for Essential Brain Anatomy & Neuropathology

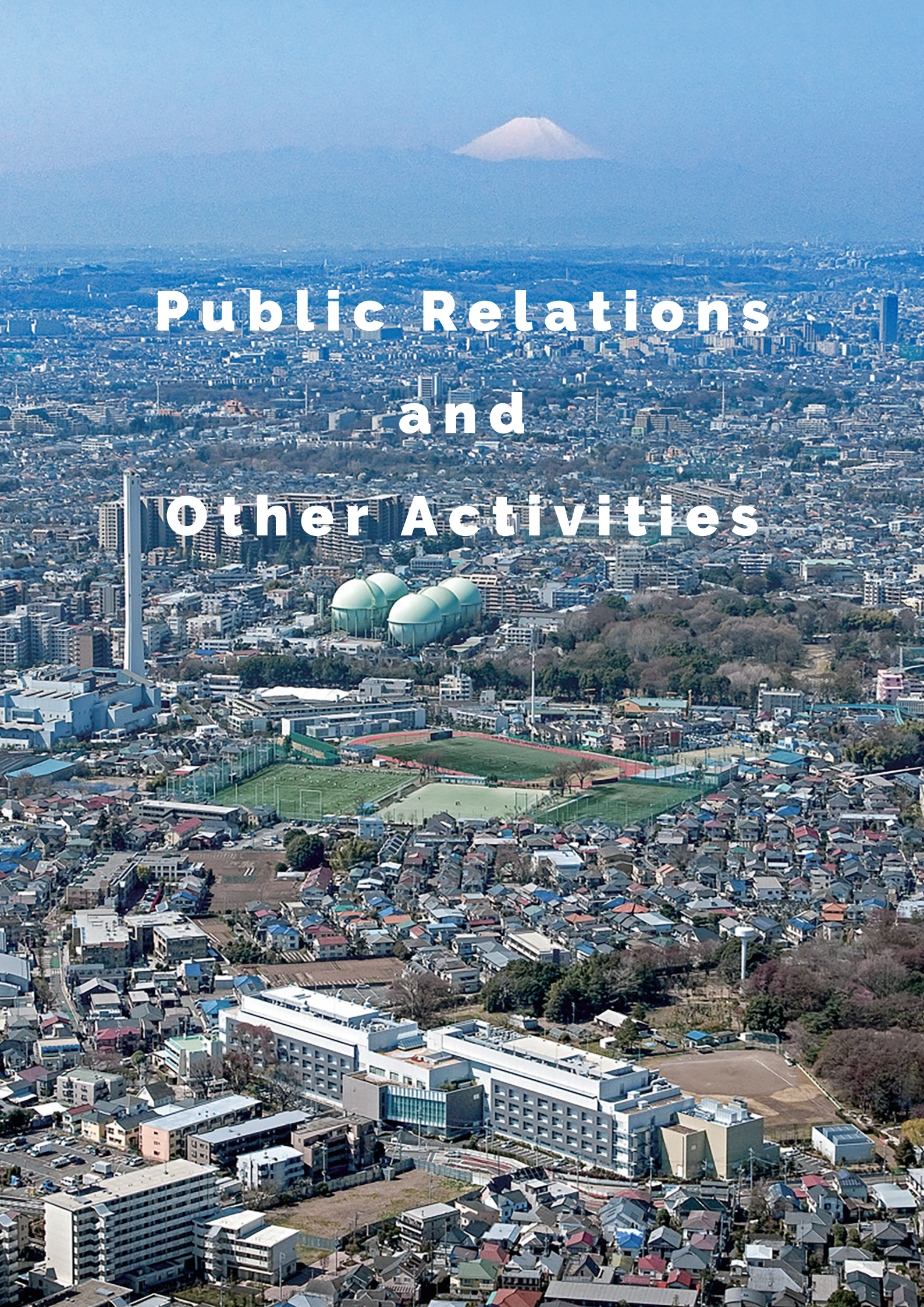
Staff

Erika SEKI	Nobuko UEKI	Keiko AKAMATSU
Rika KOJIMA	Tomoko YAGI	Hiromi EGUCHI
Kazunari SEKIYAMA	Tsunemi YAMANISHI	Yoshitomo UMITSU



The Laboratory of Neuropathology has more than 5,000 sets of human autopsied brain slides with a wide variety of human neurological diseases. In recent years, we have been scanning these slides with virtual slide instruments. Using this digital data and its derivatives, we are constructing a digital neuropathology library.





Public Relations and Other Activities

TMIMS Programs

Public lectures

Each year we present 8 pubic lectures to inform the public of our research progress and enlighten people on various medical issues pertinent to their health and welfare. In 2020, we had to cancel three lectures due to the pandemic, but we had five, including three online. Lecture topics included adolescent mental care, addiction, hearing loss, Parkinson's disease, and memory.

How can you prevent and recover from addictive disorders?
.....Kazutaka IKEDA (TMIMS, Addictive Substance Project)
.....Toshihiko MATUMOTO (NCNP)

How wil mind development during adolescence affect healthy mental state in later stage of life?
.....Atsushi NISHIDA
(TMIMS, Mental Health Promotion Project)
.....Kiyoto KASAI (The University of Tokyo Hospital)

How can you prevent and cure hearing loss?
.....Yoshiaki KIKKAWA
(TMIMS, Mammalian Genetics Project)
.....Masato FUJIOKA (Keio University)

Parkinson's diseases: what we know now from the latest basic and clinical studies
.....Noriyuki MATSUDA (TMIMS, Ubiquitin Project)
.....Taku HATANO (Juntendo University)

Can you create memory?
.....Kaoru INOKUCHI (University of Toyama)




Science café

In the past ten years we have had 32 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 2020, we had three online science cafes on topics such as "what is PCR?", "what do you need to know about virus infections?" and "how does the human brain develop and how is it different from brains of other species?" The participants enjoyed our online quizzes in these events.

PCR: how it works and how it was discovered.
.....Yuichiro MIYAOKA
(TMIMS, Regenerative Medicine Project)

Virus infection: PCR, antigen test and antibody test
.....Satoshi KOIKE
(TMIMS, Neurovirology Project)

Brain: mechanisms of its formation and evolution
.....Chiaki OHTAKA-MARUYAMA
(TMIMS, Neural Network Project)



Institutional seminars (Igakuken Seminars)

We have institutional seminars on a regular basis. In 2020, despite the coronavirus pandemic we had 17 seminars, 10 at the institute and 7 online, by both domestic and international scientists including those from the Sorbonne, France, and Texas, USA.

Development of intergration-dependent genetic switch-on systems
.....Takuma KUMAMOTO (Sorbonne Université)

Roles of olfactory cortex as information-processing hub
.....Hiroyuki MANABE (Doshisha University)

Analyses of morphological phenotypes of mice by X-ray imaging
.....Masaru TAMURA (RIKEN)

Mechanisms of mammalian hibernation; syrian hamster as a model
.....Yoshifumi YAMAGUCHI (Hokkaido University)

The Schedule for the evaluating of the individual Quality of Life-direct weighting: SEIQoL-DW
.....Yoshihiko SAKASHITA (Chiba Cancer Center)
.....Akira YAMAMOTO (R102 Co.,Ltd.)

Development of versatile softwares for novel genome editing systems
.....Hideto MORI (The University of Tokyo)

Rapid induced protein degradation by an improved Auxin-degron system and its application for the studies of genome maintenance mechanisms
.....Masato KANEMAKI (NIG)

Who kills science?
.....Momoko SUDA (The Mainichi Newspapers)

Knowing the biochemical microbrain for memory
.....Yukinori HIRANO (Kyoto University)

Cryo EM analyses of the TOM complex, the gateway to mitochondria
.....Yuhei ARAISO (Kanazawa University)

Chemical genetic analyses of spacial molecular network profiling of tri-point synaps
.....Tetsuya TAKANO (Keio University)

Circadian quartz and clock aging
.....Hikari YOSHITANE (The University of Tokyo)

Comprehensive analyses of antibody/ T cell receptor by high-speed one cell analyses
.....Hidetaka TANNO
(The University of Texas at Austin)

Ghost cytometry technologies and beyond
.....Sadao OTA (The University of Tokyo)

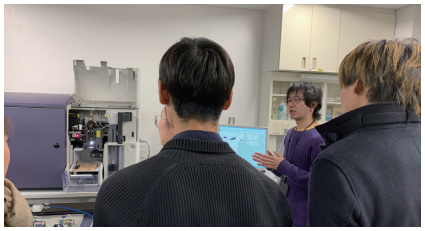
Genetic tracing of formation of cerebral cortex functional area
.....Takayoshi INOUE (NCNP)

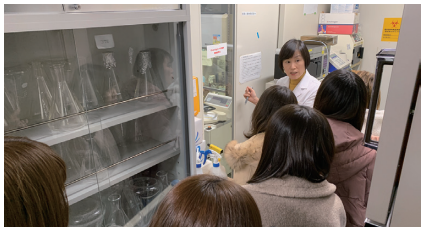
Translational research by MRI brain imaging of small animals
.....Tomokazu TSURUGIZAWA (AIST)

Somatic cell nuclear transfer by micromanipulator and its application
.....Eiji MIZUTANI (University of Tsukuba)

Lectures to students

We give lectures to high-school and university students who visit our institute and we also send staff to visit schools and deliver lectures. This year, face-to-face lectures were difficult so we gave online lectures, including one delivered by Yuichiro Miyaoka on regenerative medicine and gene editing, and the other by Takeru Honda on braininfunctions.





Joint programs with universities

Many scientists at TMIMS have joint appointments as visiting professors or lecturers at various universities. Unfortunately, this year we had to cancel our annual “open institute” events for prospective graduate students due to the coronavirus pandemic, but we currently have 152 students from affiliated universities and other schools, who conduct their research here.

Support for students and young scientists

Research Associate Fellowships

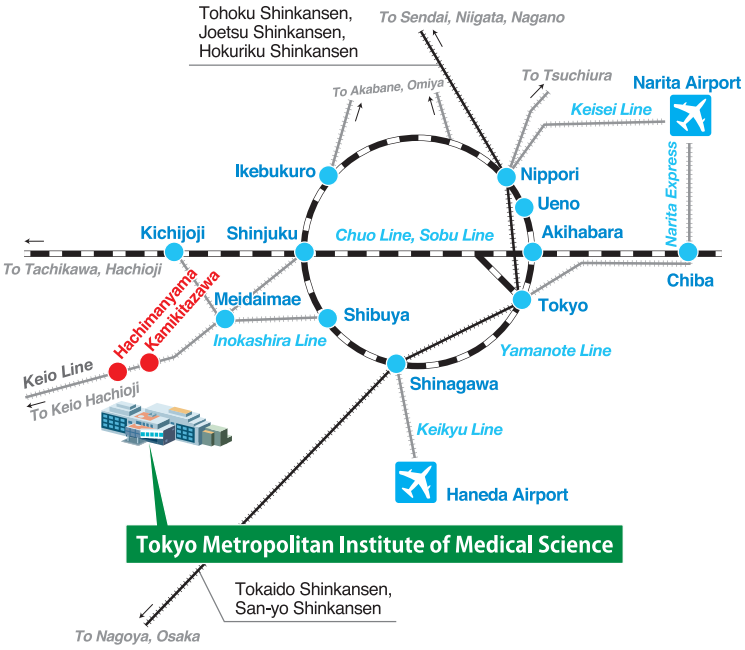
We provide graduate students who conduct their masters/ Ph.D. research at TMIMS with research associate fellowships that provide them with financial support, and allow them to concentrate on their studies and research.

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

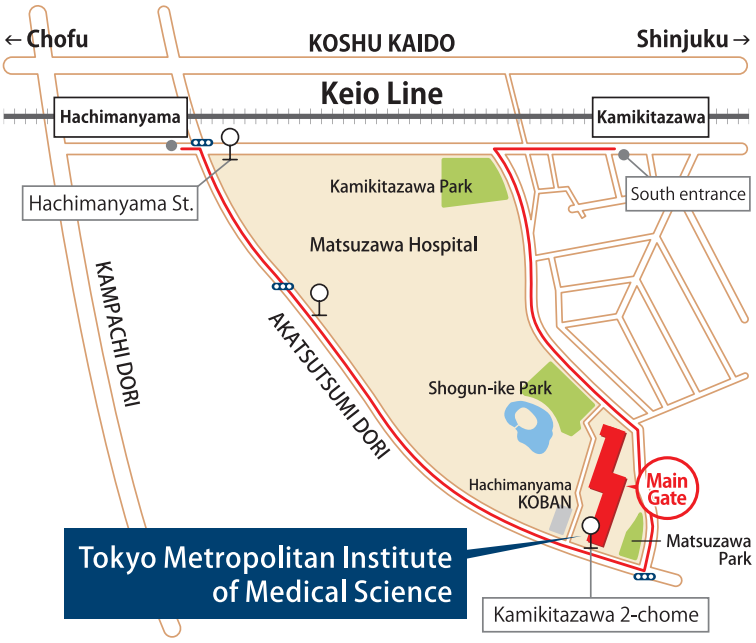
Tokyo Metropolitan Institute of Medical Science	
Address	2-1-6 Kamikitazawa, Setagaya-ku, Tokyo, 156-8506, Japan
Tel	+81-3-5316-3100
Fax	+81-3-5316-3150



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

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

As of March 1, 2021