TMiMS

Annual Reports 2021

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.

Between 2020 and 2021, 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" two years ago and in cooperation with the Tokyo Metropolitan Government, we have been making every effort to develop effective strategies to eliminate this disease. Particularly, epidemiological studies such as monitoring of the resident population in the major downtown areas of Tokyo have contributed greatly to the Tokyo Metropolitan Government's countermeasures against COVID-19 disease, and we have also started our own highly original vaccine development research against SARS-CoV-2. 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 2022.

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 around the world. 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.

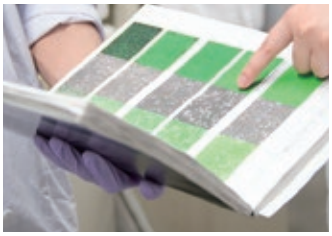
I am of the opinion that scientific research is a symbol of culture. A society cannot be considered cultured if it has no interest and knowledge of science and research. Accordingly, TMIMS aims to be acclaimed both academically and culturally for the knowledge and wisdom of its excellent researchers.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

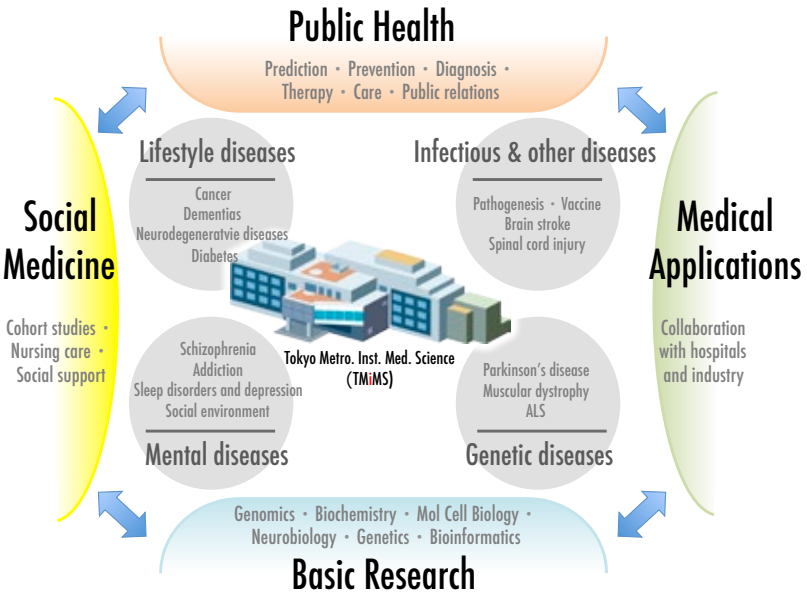
Our medical researchers are energetically pursuing their research to develop preventive medicine and new therapeutic methods to protect citizens' health. During this process, TMIMS also takes on a role in educating young researchers who will continue to develop human knowledge and contribute to social 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 our director: TMIMS 2021

Director
Hisao Masai

2021 forced us once again to fight against COVID-19. More than two years since the start of the outbreak, the world is still suffering from the pandemic. Although the infection rate in Japan fortunately decreased in early September 2021, we still do not know the exact cause. Now a new strain is threatening the world and it is hard to predict how the situation will change. Indeed, we have experienced a sharp rise of cases in early 2022. As a medical institute whose goal is to improve the health and medical care of people, we have been helping the public by providing the latest information related to infections, diseases and vaccinations. In addition, we are testing our own novel, potent vaccines against SARS-CoV-2, and are further pursuing strategies for the rapid development of vaccines for new viruses that will almost certainly appear in the future (see page 6 for details on our activities for combating COVID-19).

Science in 2021

Power of Science: In 2021, we witnessed the power of science in the battle against diseases. SARS-CoV-2 vaccines were developed less than one year after its outbreak and saved millions of lives. No one, even the most knowledgeable virologists or immunologists, could have predicted these events at the beginning of 2020. One of the technologies used for this venture, mRNA vaccines, opened up a new avenue for the generation of drugs utilizing RNA to target various diseases including cancers.

Novel Prize 2021: The 2021 Nobel Prize in Physiology or Medicine was awarded to Professors David Julius and Ardem Patapoutian for their discoveries of the sensing mechanisms for temperature and touch. The first breakthrough came from the search for a gene that can react to capsaicin from chili peppers. Julius and colleagues identified TRPV1 and subsequently identified other family members that sense the temperature. Patapoutain and colleagues identified receptors for mechanical stimuli by screening for genes responsible for responses when cells are poked with a micropipette. Piezo1, named after the Greek word for pressure, and its relative Piezo2 were shown to be ion channels directly activated by the exertion of pressure on cell membranes. Piezo2 turned out to be a key protein for proprioception (sensing of body position and motion). Understanding how cells sense heat, cold and mechanical stimuli helped us understand how we perceive and adapt to the world around us.

A basic principle of life: Professor Tuneko Okazaki was awarded the Order of Culture in 2021 for her ground-breaking discoveries in the basic mechanism of DNA replication. Professor Okazaki, in collaboration with her husband, Professor Reiji Okazaki, solved one of the great mysteries of DNA replication, namely, how can both strands of anti-parallel DNA be replicated by a polymerase that can synthesize DNA in only one direction? While replication of one strand, the leading strand, could be understood easily, unwinding of the opposite strand, the lagging strand, should be "backwards" with respect to polymerase synthesis. In a relentless series of experiments, Tuneko and Reiji demonstrated that the lagging strand is replicated by the polymerase as short pieces of DNA synthesized in the opposite direction as unwinding. These short DNA fragments are then joined together to generate mature daughter DNA strands. This discontinuous mode of DNA replication was shown to be a universal principle of DNA replication, and the short pieces of DNA were named "Okazaki fragments". Reiji, who had been exposed to radiation in the Hiroshima atomic bomb, died of leukemia at the age of 44 in 1975. Under the difficult conditions facing female scientists nearly 50 years ago in Japan, Tuneko, a mother of two, led the laboratory and continued her studies on mechanisms of discontinuous DNA replication, and is now regarded as a pioneering role model for female Japanese scientists. The discovery of discontinuous DNA replication and initiation of DNA synthesis by RNA primers

was a foundation for the development of DNA amplification by PCR (polymerization chain reaction), and has had profound implications in other important biological issues such as evolution and left-right asymmetry. The discovery of Okazaki fragments demonstrates how uncovering a basic principles of life can lead to development of truly useful new technologies and bring new insights into many other general biological problems.

Life science and global warming: In 2021, scientists were pushed more than ever into global issues. Rising global temperatures are causing devastating weather changes throughout the world, including the recent giant tornados that wiped out large areas in central USA. The concentration of greenhouse gases continues to increase. CO_2 emissions have now returned to pre-pandemic levels and will continue to increase. The sea-level will continue to rise (3.7mm/ year) and world-wide efforts to adapt will be important. Scientists from all fields need to unite to develop efficient strategies to curb global warning, and help affected people adapt to changes.
What can we, as life science researchers, do to mitigate these crises? Life science research can contribute to green recovery in many different manners. For example, cattle farming is responsible for the release of a large amount of methane, and therefore, new cattle feed that produces less methane as well as plant-based meat alternatives will provide promising solutions to the problem. To achieve net zero emissions of CO_2, utilization of algae or bacteria to remove carbon from the atmosphere and the oceans could be excellent tools to develop industrial systems for removal of greenhouse gases. Cutting-edge science in combination with rapid industrialization made accelerated production of vaccines possible during this pandemic. Similar efforts by life science researchers will undoubtedly be crucial for restoring the planetary health and achieving sustainable development goals.

TMIMS 2021
Our institute is now in its second decade after its establishment in 2011. Our research projects have 5 year terms, and we are now in the second year of the 4th term. This year, we started two new projects, the Circadian Clock Project led by Dr. Hikari Yoshitane and the Cancer Immunology Project led by Dr. Hidetaka Tanno, and we now have 23 projects and two laboratories in 4 departments. We also have two research centers that were started in 2020.

In 2021 we had in-house scientific gatherings featuring presentations from select scientists and graduate students from the institute. Although we could not invite any foreign scientists to physically visit the institute this year, we had various renowned foreign scientists present institutional seminars online (see page 60-61). We also continued our outreach activities including eight lectures for the public and three Science cafés, which were conducted online.

Our clinical collaborations with hospitals are critical for connecting our basic research findings to the development of novel therapies and treatments. We started two new collaborations with hospitals in 2021, and now have a total of 7 ongoing collaborative projects.

Also in 2021, we reached agreements with Ochanomizu Women's University and the National Center of Neurology and Psychiatry (NCNP) for mutual visits, collaborations, sharing of resources and equipment and education of students and young researchers. This will increase the research and educational opportunities available to students and enhance scientific and educational collaborations between the institutions.

Research achievements in 2021
Despite the difficulties imposed by the pandemic, many new findings were reported last year from the institute. I've listed some of the most notable below. The Dementia Research Project led by Dr. Masato Hasegawa clarified the relationship between structural features of protein precipitates responsible for dementia/ neurodegenerative diseases and their pathological consequences. In a collaboration between TMiMS, NCNP, Brain banks from Japan and overseas, and the MRC (Medical Research Council, United Kingdom), research groups elucidated the structures of protein fibers of tau, α-synuclein, and TDP-43 isolated from diseased brains. These findings were reported in four Nature articles during the past two years. Dr. Shinobu Hirai from the Neural Development Project found that high-sucrose diets impaired glucose uptake from blood vessels and augmented brain dysfunctions related to psychosis in mice. These results were reported in ***Science Advances***. Dr. Daisuke Yamane from the Viral Infection Control Project discovered that iron-dependent fatty acid desaturation induces cell death through ferroptosis and inhibits hepatitis C virus replication (reported in ***Cell Chemical Biology***). Kotaro Nakamura, a graduate student in the Stroke Renaissance Project (led by Dr. Takashi Shichida), identified DJ-1 as a DAMP (Damage-Associated Molecular Patterns) which induces inflammation in the ischemic brain, and showed it can be a therapeutic target for ischemic brain. This was reported in ***PLoS Biol***. Dr. Yukiko Yoshida form the Ubiquitin Project and her collaborators elucidated the mechanism of pathogenesis of NGLY1-deficient syndrome, a rare human disease. The group showed that accumulation of aberrantly ubiquitinated glycosylated polypeptides in NGLY1-deficient cells causes proteasome dysfunction, leading to disease phenotypes (reported in ***PNAS***). Dr. Guo from the Sleep Project (led by Dr. Takayuki Harada) used conditional knockout mice to show that a feedback loop between microglia and astrocytes involving the ASK1 protein causes and maintains neuroinflammation (***PNAS*** in press).

Outlook for 2022
Synergy, sharing and internationalization will continue to be the keys for the future development of the institute. TMiMS was originally formed by combining three previously separate research institutes, and during the past ten years the three different cultures of medical science have been merging constructively. Now we need to harness the growing seeds from this merger into larger trees with ripe fruit. From our strong basic research activities, we aim to identify the hidden principles of life. This will help us understand diseases pathogenesis, which will ultimately lead to the development of truly useful technologies and therapies. In 2022, we will continue to strive for new discoveries that will contribute to the health and welfare of the public.
With the uncertainties of the COVID-19 pandemic in 2022, we will continue our efforts in novel vaccine development and conduct research to better understand the nature of the virus and its epidemiology in order to develop new drugs and treatments. We will also contribute to policy-making by the Tokyo Metropolitan Government through providing social dynamics data.
I strongly hope that 2022 will bring us back to a more normal life where we do not need to worry about the numbers of the cases everyday, where we can travel freely, have in person discussions, and even have parties!

Special Team for COVID-19 Countermeasures: Message from Team Director

M.D., Ph.D.
Masanari ITOKAWA

Samurai-Scientist

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is worldwide public health emergency. We have had plenty of tragic pandemic in history of the earth. We are surprised at finding the depiction of three Cs, closed spaces, crowded places and close-contact settings, in "Plutarchi Vitae Parallelae" which is a famous Roman history book. Many folklores and legendary rules contain right behaviors from a point of view for prevention of infectious diseases. We, however, have known pandemic as infectious phenomenon derived by the small invisible living organism such as viruses since the beginning of Bacteriology in 19 centuries. Tokugawa shogunate had prohibited learning European science and philosophy to maintain feudalism for over 200 years. Science and medicine have been imported from European countries because the shogunate changed the prohibition policy since the mid 18 centuries. A lot of samurai became "Samurai-Scientists" by learning Dutch medicine. Their first lime-lighted fine performance was emergency medical care for the patients of the cholera pandemic at the end of 19 centuries.

The special team constructed of full TMIMS specs

TMIMS is the organization constructed by over 600 scientists. We are confronting against SARS-CoV-2 by gathering all our scientific activities, full capability of administrative office and supporting division. We are demonstrating our strength as the Metropolitan Institute in order to protect the life and safety for citizens of Tokyo by performing the largest hospital cooperation as 7,000 beds in 14 metropolitan and public corporation hospitals.

Watching the antibody against COVID-19

Dr. Michinori Kohara and colleagues of the TMiMS COVID-19 team had screened randomly selected blood samples of more than 27,000 people for antibodies against SARS-CoV-2 collaborating with the 14 hospitals owned by the Tokyo Metropolitan government since June 1, 2020 through the end of March, 2021. Monitoring the IgG and IgM against COVID-19 levels in the local general population helps access the infection spread. Dr. Kohara found larger amount of asymptomatic population than that of PCR-detected in Tokyo(1).

Toward the lifelong immunity

Dr. Kohara has also developed a vaccine based on highly attenuated recombinant vaccinia virus. The preclinical testing showed not only enough amount but also prolonged duration of antibody suggesting long-term protection against ever-evolving SARS viruses.

We are also developing novel antivirals and investigating factors associated with increase of severity of COVID-19. Dr. Hisao Masai has been analyzing SARS-CoV-2 genomes by collaborating with the National Institute of Genetics to recognize variations including novel ones. Dr. Yasushi Saeki has been analyzing patient proteomes to detect cellular changes derived from infection.

Social dynamics and COVID-19

Dr. Atsushi Nishida and colleagues estimated populations between 10 PM and midnight in seven Tokyo metropolitan areas by using mobile phone location data. Mobile phone trajectories were used to distinguish and extract on-site dining from stay-at-work and stay-at-home behaviors. Dr. Nishida found an increase in the number of symptom onsets after 1 week from the increased volume of the nighttime population(2).

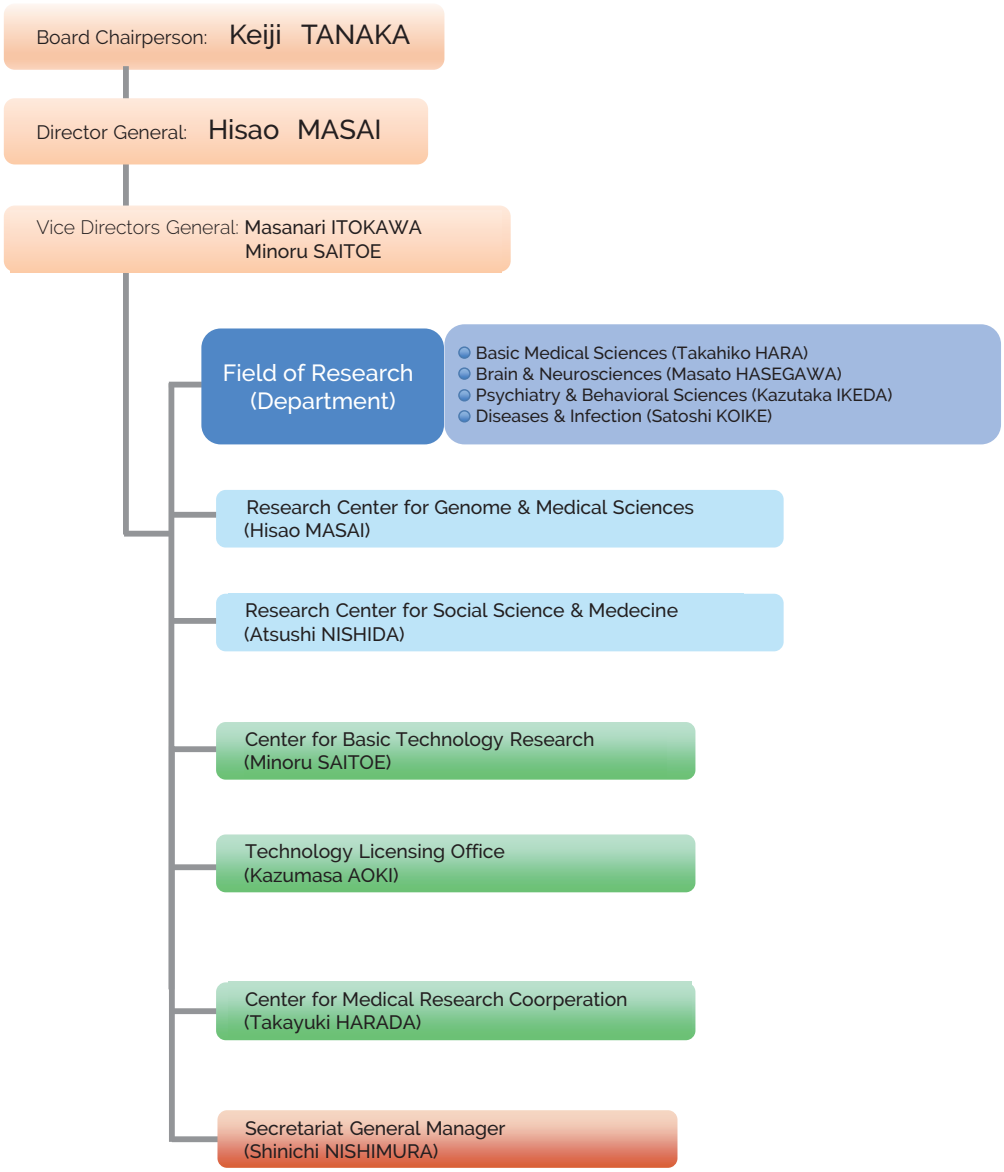
We, TMiMS COVID-19 team, are confronting against SARS-CoV-2 to protect the people's life and health in Tokyo by using scientific research and technologies as descendants of the Samurai-Scientists.

References

1. Sanada T, Honda T, Yasui Fumihiko, Yamaji K, Munakata T, Yamamoto N, Kurano M, Matsumoto Y, Kono R, Toyama S, Kishi Y, Horibe T, Kaneko Y, Kakegawa M, Fukui K, Kawamura T, Daming W, Qian C, Xia F, He F, Yamasaki S, Nishida A, Harada T, Higa M, Tokunaga Y, Takagi A, Itokawa M, Kodama T, Kohara M* Serologic survey of IgG against SARS-CoV-2 among hospital visitors without a history of SARS-CoV-2 infection in Tokyo, 2020-2021 *J. Epidemiol* (in press)
2. Nakanishi M, Shibasaki R, Yamasaki S, Miyazawa S, Usami S, Nishiura H, Nishida A. On-site Dining in Tokyo During the COVID-19 Pandemic: Time Series Analysis Using Mobile Phone Location Data *JMIR Mhealth Uhealth* 9(5)e27342, 2021 |

The weekly monitoring conference of Tokyo Center for Infectious Disease Control and Prevention (A). Drs. Kohara (B) and Nishida (C) are reporting their data.
[Image: From" Tokyo Metropolitan Government Official Video Channel (https://tokyodouga.jp/) "]

Organizational Chart

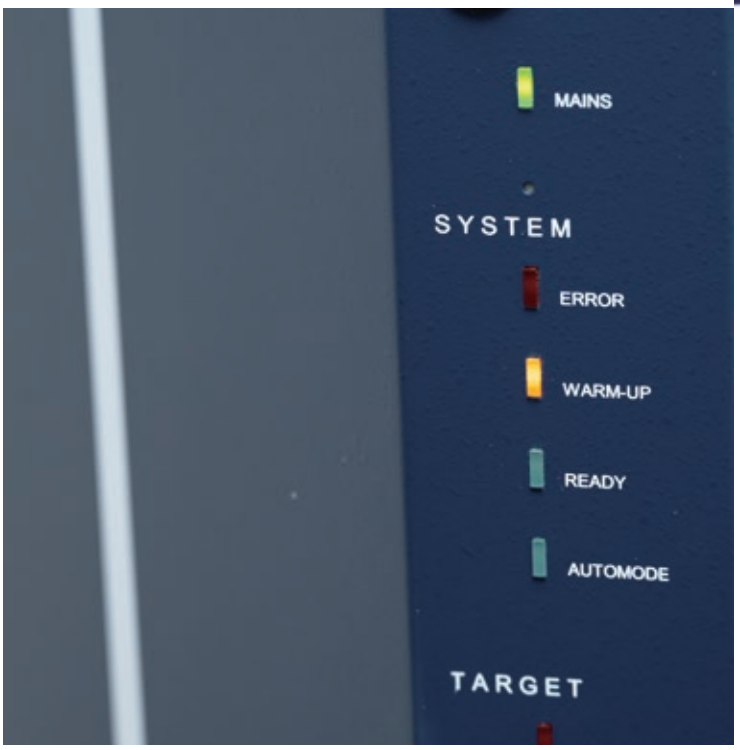


Our People at a Glance

Position	Number
Researchers	160
Postdoctoral Fellows	53
Students	149
Visiting Scientists	138
Guest Scientists	138
Administrative Staffs	30
Total	668

February 1, 2022

Meet our scientists!



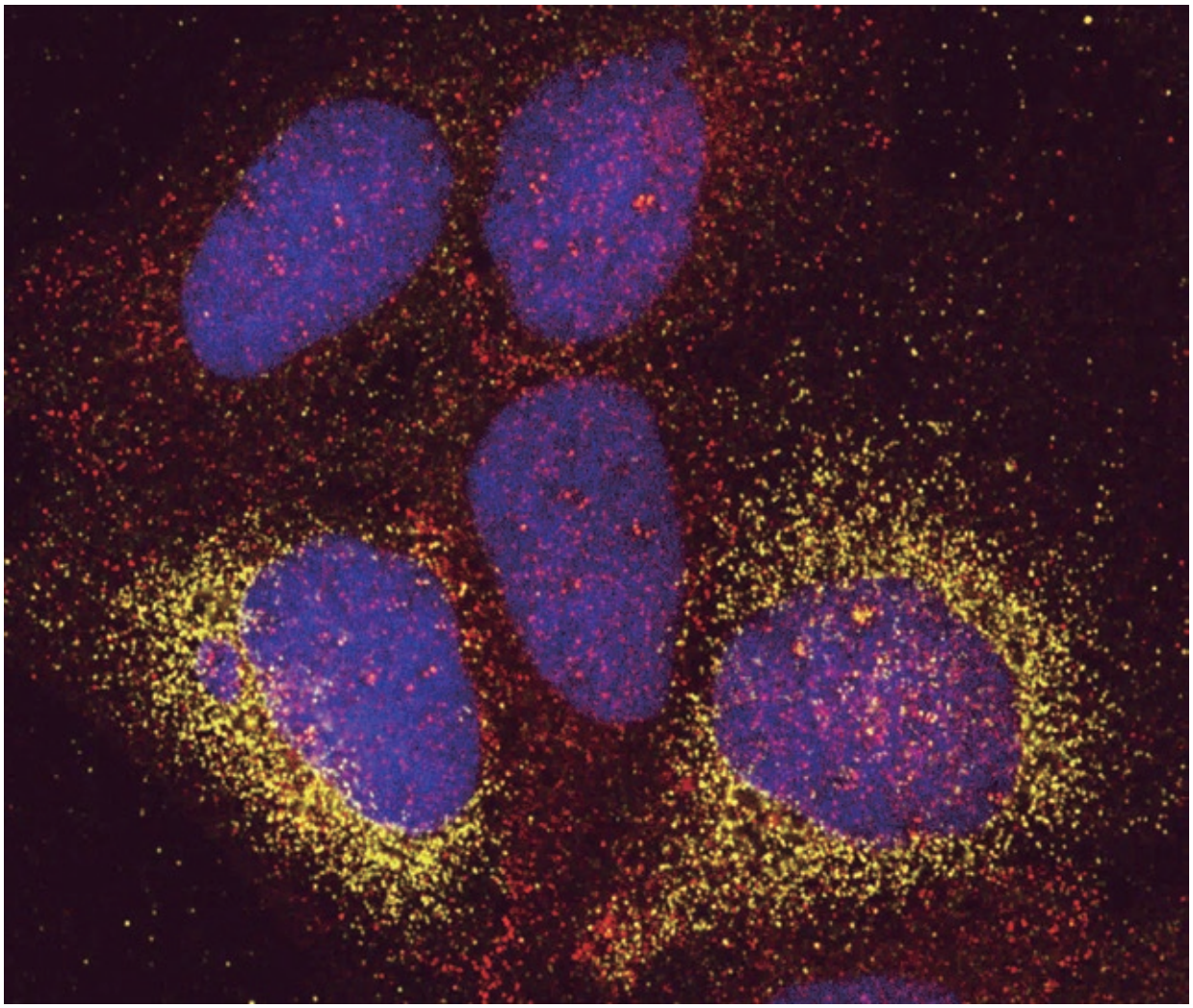
Meet our scientists!

The hepatitis C virus (HCV) is a leading cause of chronic liver disease. While effective treatments exist, up to 5% of infected people do not respond to these treatments, resulting in tens of millions of people worldwide suffering from incurable liver disease. Daisuke Yamane, a senior scientist in the Department of Diseases and Infection at TMIMS, has been studying HCV. He previously discovered a curious phenomenon. HCV viral replication is strongly inhibited by lipid peroxidation, the metabolic oxidative degradation of cellular lipids (Nature Medicine 2014 20:927-35.). In his current work, entitled "FADS2-dependent fatty acid desaturation dictates cellular sensitivity to ferroptosis and permissiveness for hepatitis C virus replication," (Cell Chemical Biology 2021 S2451-9456(21)00362-7.) he uncovered metabolic pathways that inhibit viral replication and identified therapeutic targets for novel HCV treatments.

Daisuke YAMANE

How did you become interested in science?
When I was in elementary school, I learned about viruses such as Ebola and HIV. I became very curious and wanted to know what they look like and how they behave in our bodies to cause disease. That was my first motivation to become a scientist and study viruses.

What do you enjoy most about research?
I enjoy discovery. I can come up with a hypothesis and I can test it. If the hypothesis turns out to be true, the



Hepatitis C virus induces remodeling of host membranes into specialized structures enriched in lipids (Red, Caveolin-2) to create viral replication factories (Green, hepatitis C virus antigen). Blue, Nucleus.

findings lead to a new paper that can sometimes influence people. I just really want to know what the truth is.

How did you become interested in hepatitis C?

I went to veterinary school and first studied a bovine virus, bovine viral diarrhea virus, which is closely related to hepatitis C virus (HCV). From there, I became interested in HCV. However, HCV clinical isolates are very difficult to grow in cell culture. Their replication efficiency is very low. I tried to improve culture conditions and found that HCV is very sensitive to exogenous polyunsaturated fatty acids (PUFAs). When I added PUFAs to cell culture, it induced lipid peroxidation and this impaired viral replication. I also did the reverse experiment where I inhibited lipid peroxidation using vitamin E, a physiological lipid-soluble antioxidant. When I treated cells with vitamin E, I found that lipid peroxidation was reduced and viral replication was dramatically increased ~10 fold. From these results, I realized that cellular lipid peroxidation rates strongly influence HCV replication.

What is lipid peroxidation?

Lipid peroxidation is a process that degrades fatty acids, specifically PUFAs. PUFAs have multiple double bonds that can be attacked by free radicals. This process of attacking double bonds is amplified by chain reactions between multiple double bonds, leading to degradation of PUFAs. Lipid peroxidation is always going on at low levels in cells. Membranes have to turn over. However, when we age, lipid peroxidation increases and, in this case, it may be part of a pathological condition.

Why does replication of hepatitis C virus virus depend on the lipid metabolism state?

There are lipid peroxidation-resistant variants of HCV. These variants replicate efficiently in vitro, but in vivo, these viruses replicate too fast and are easily recognized by the immune system and eliminated. In contrast, peroxidation-sensitive viruses are more stealthy. They can infect liver cells and hide from the immune system, replicating only when the lipid peroxidation is low. They replicate gradually and slowly hijack the host cell. In fact, HCV can also induce lipid peroxidation itself. When it replicates to a threshold level, it induces lipid peroxidation which downregulates its own replication in an autoregulatory circuit. Thus, we consider that the sensitivity to lipid peroxidation may provide an advantage for the virus to persist in the host.

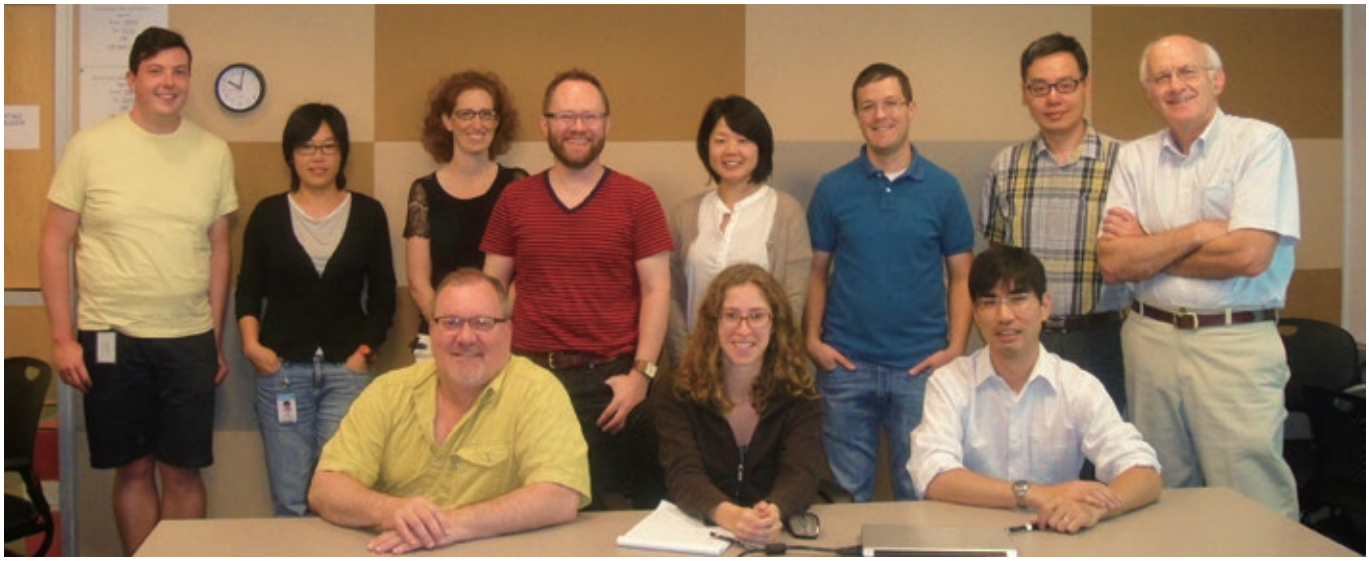
What is a significant finding in your Cell Chemical Biology paper?

Our paper has multiple significant findings. One is that ferroptosis inducers inhibit HCV replication. Ferroptosis is a type of cell death induced by iron. Iron acts as an oxidant and attacks the double bonds present in PUFAs to induce lipid peroxidation. We found that low concentrations of ferroptosis inducers that didn't kill cells were sufficient to inhibit HCV replication. Furthermore, we found that ferroptosis inducers combined with direct antiviral agents that target the viral protease, a component of the viral replication machinery, exerted synergistic effects and eliminated the virus much more efficiently. Overall, we determined how hepatocytes restrict HCV replication through lipid metabolism and discovered how we may manipulate this pathway to improve therapy for hepatitis C patients.

What are your future plans?

HCV clinical isolates are still difficult to grow in culture so we are trying to develop a better cell culture system that is more similar to liver tissue in order to grow the virus more efficiently. We believe this will be important for antiviral testing and vaccine development. Despite the availability of oral drugs, HCV is still a major worldwide health concern and we think the development of vaccines is necessary for the complete elimination of HCV.

Interviewed by Jun Horiuchi



Daisuke Yamane (the first from the right on the the front row) and his former colleagues at the University of North Carolina at Chapel Hill in Prof. Stan Lemon's laboratory.

Meet our scientists!

Psychiatric disorders are complex diseases that have a combination of genetic and environmental causes. While various genes that affect diseases such as schizophrenia and bipolar disorders have been identified, environmental contributions and the interactions between genetic and environmental effects that cause these diseases have not been as well-studied. Shinobu Hirai, a senior scientist in the department of Psychiatry and Behavioral Sciences has been studying how a combination of genetic and environmental influences can result in metabolic changes that cause psychiatric effects. Her latest results were published in a paper entitled, "High-sucrose diets contribute to brain angiopathy with impaired glucose uptake and psychosis-related higher brain dysfunction in mice" (Sci Adv. 7, eabl6077(2021)). We spoke to her about her work.

Shinobu HIRAI

How did you first become interested in science?
My parents were both scientists. My father was a synthetic organic chemist, and my mother was a microbiological engineering chemist. When I was a child, they kept asking me questions about the world to stimulate my curiosity and increase my love for learning. In school, I loved my biology classes so I entered this field.

How did you become interested in diet and psychiatric diseases?
When I was in college, I lived on my own, and started eating a lot of sweets instead of eating a balanced diet. Because of this, I got sick, and my doctor told me to stop eating so poorly. After that I started eating more carefully and I became interested in how diets affect our mental health.

What was the start of your research for your Science Advances paper?
Patients with psychiatric diseases such as schizophrenia or bipolar disease eat much more sugar than healthy individuals, and those who eat more sugar tend to have more severe symptoms. Schizophrenia and bipolar disorders are caused by a complex interaction of genetic and environmental risk factors. From these observations, I decided to examine the connection between excess sugar consumption and psychosis-related behaviors.

Is there a connection between excess sugar consumption and psychiatric illnesses?
Yes! In my experiments, I used two different types of mice, one was a normal control and one expressed reduced amounts of GLO1, a protein that protects cells from oxidative damage. Reductions of GLO1 have been associated with schizophrenia. I fed these mice two types of diets. One was a high sucrose diet, and the other was

a control starch-based diet. So, altogether I had a total of four different experimental conditions. When I looked at various behaviors, I found that GLO1 mutant mice fed high sucrose diets exhibited behaviors associated with schizophrenia and bipolar disorders, while mice in the three other conditions didn't. Human schizophrenia and bipolar patients have changes in dopamine signaling in the brain and alterations in activity of certain neurons, called parvalbumin-positive neurons, and I found that GLO1 mutant mice fed high sucrose had similar changes. From these results, I concluded that a high sucrose diet can work in combination with a genetic predisposition to cause psychiatric disease.

How do high sucrose diets contribute to psychiatric diseases?

Both excess sucrose consumption and decreased GLO1 activity increase oxidative damage in our bodies. So, I thought that a combination of sucrose and decreased GLO1 could have additive or synergistic effects, and a large increase in oxidative stress could cause psychiatric illness. Indeed, I found a strong increase in oxidative damage, in blood vessels in brains of GLO1 mutant mice fed high sucrose. I also found that these mice had increased neuroinflammation and increased activation of immune cells and glia. These changes were accompanied by damage to the brain vasculature and decreased brain glucose. Interestingly, I found similar damage to the brain vasculature in the postmortem brains of schizophrenic and biopolar disorder patients. Overall, I think that oxidative damage to blood vessels decreases the amount of glucose transported to the brain. This leads to changes in brain activity and psychiatric illness.

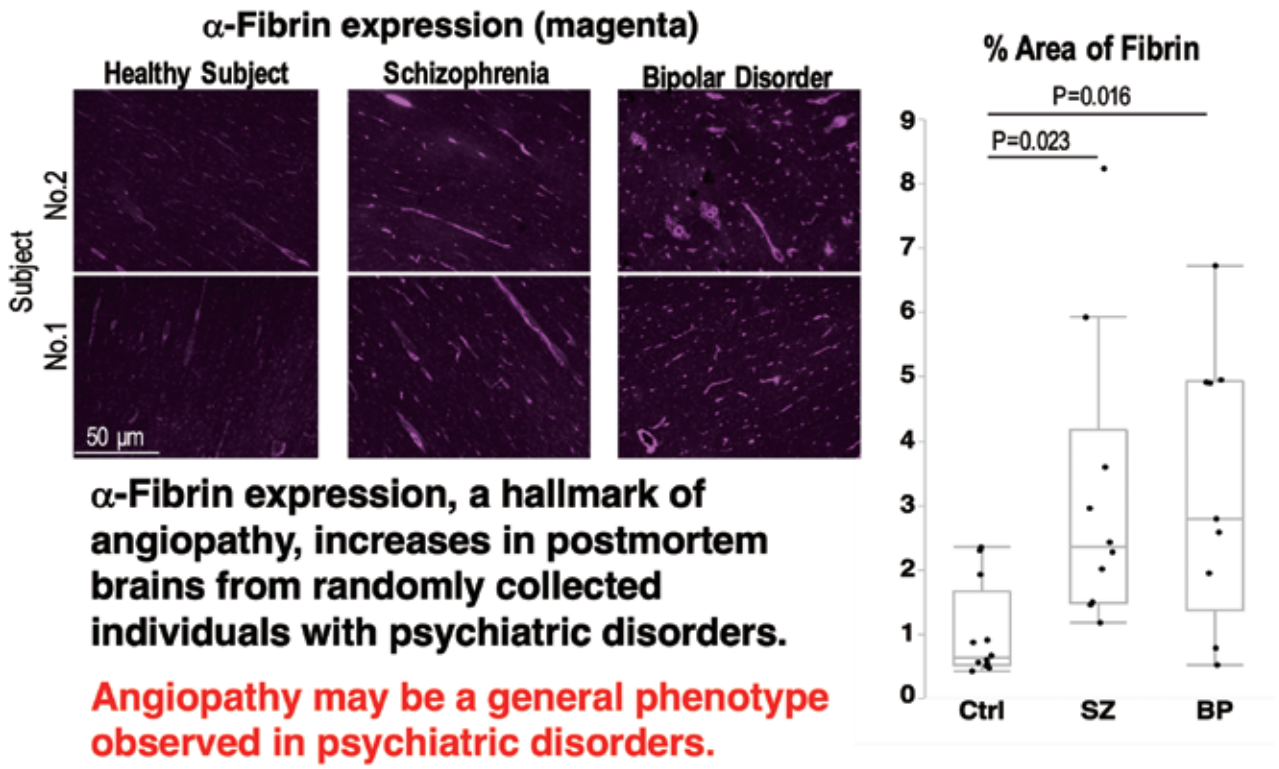
How can we prevent damage to the brain vasculature?

Interestingly, I found that chronic low dose aspirin treatment prevents damage to the brain vasculature and rescues glucose uptake to the brain. It also decreased psychiatric behaviors. Aspirin suppresses inflammation and smoothens blood flow. I think it may also decrease accumulation of AGEs (Advanced Glycation End products).

What are your future plans?

Recently I've been studying how glucose is transported into the brain and I've obtained some fascinating results about a possible role for astrocytes. I'm really excited to pursue this research!

Interviewed by Jun Horiuchi



Meet our scientists!

Inflammation can be a protective response by the body to harmful stimuli such as pathogens, tissue damage, and irritants, but it can also have adverse effects. For example, inflammation can increase the severity of various diseases, including cerebral pathologies. Koutarou Nakamura, a graduate student in the Stroke Renaissance Project, studies the inflammatory response to ischemic stroke and identified a novel signaling pathway through which strokes induce inflammation. He further found that inhibition of this pathway decreases the damage caused by strokes. We spoke to him about his recent results, published in a paper entitled, "Extracellular DJ-1 induces sterile inflammation in the ischemic brain," PLOS Biology| https://doi.org/10.1371/journal.pbio.3000939 May 20, 2021.

Koutarou NAKAMURA

How did you become interested in science?

When I was in high school, I had an excellent biology teacher who was so enthusiastic about biology that he taught us using university textbooks even though we were still in high school. In his class, I became impressed with the beauty of the immune system - how T cells, B cells, neutrophils, and many other cell types communicate with each other in a coordinated manner to protect our bodies from pathogens. When I was a third-year undergraduate student in university, I met Dr. Shichita, who was starting a new research lab at TMIMS. He invited me to join as a Master's student. It was a great opportunity for me. Dr. Shichita's goal was to combine the fields of immunology and neurosciences, and I was very excited to join his group to study inflammatory responses in ischemic strokes.

What are ischemic strokes?

Ischemic stroke is a brain disease where clogged blood vessels decrease cerebral blood flow. This blockage causes brain cells, including neurons, to die, leading to impaired brain functions, such as loss of movement or loss of verbal functions. One of the consequences of ischemic strokes is severe inflammation and this drastically worsens disease pathology. However, the detailed mechanisms that cause inflammation have not been sufficiently clarified, and we wanted to tackle this problem.

Why does inflammation occur?
Inflammation has both protective and harmful effects on the body. When pathogens or viruses invade our bodies, pattern recognition receptors on natural immune cells recognize these invaders. This activates natural immune cells and causes them to produce inflammatory cytokines, which protect our bodies and recruit other immune cells to the area of invasion, triggering further inflammatory immune responses. However, this inflammation also leads to severe brain edema and brain deficits after strokes. So, while inflammation has protective roles, it can also harm our bodies and worsen the pathology of diseases such as strokes.

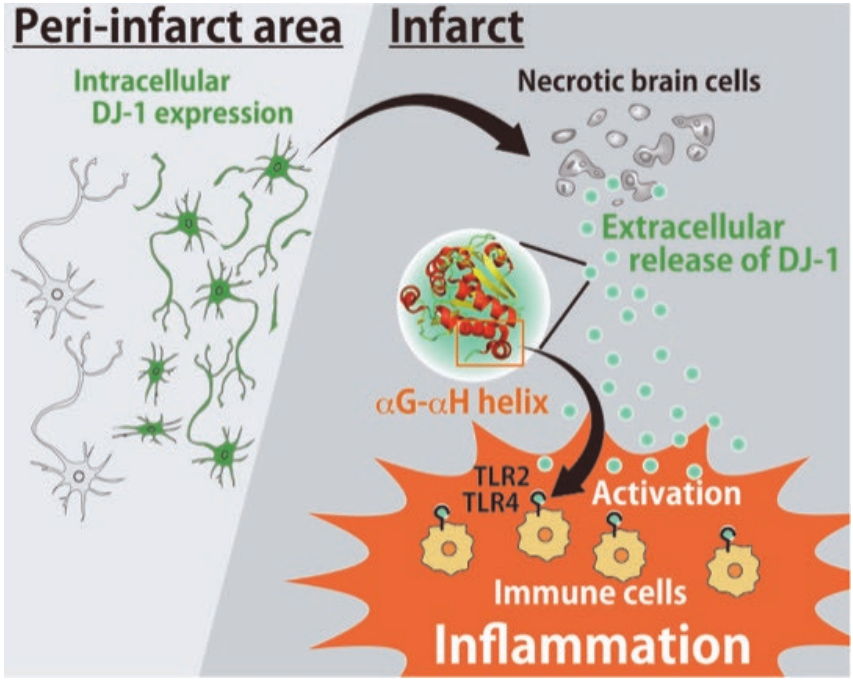
Could you explain your results published in PLOS biology?
Even though we know that inflammation worsens the pathology of strokes, the detailed mechanisms causing inflammation were unclear. We wanted to reveal these mechanisms. In this paper, I found a molecule called DJ-1, which triggers severe inflammation after strokes and worsens stroke pathology.

Interestingly, we've found that DJ-1 has two opposing functions: one is cytoprotective, and the other is inflammatogenic. When DJ-1 is inside cells, it functions as a potent antioxidant that protects cells from oxidative stress and reactive oxygen species (ROSs). In ischemic strokes, reduced blood flow increases oxidative stress in neurons, leading to the production of harmful ROSs. In intact neurons, DJ-1 would catabolize ROSs, protecting cells from oxidative damage. However, we found that in more severe strokes where neurons have died from necrosis, DJ-1 is released into the extracellular space and functions as a signaling molecule to infiltrating immune cells to induce inflammation. Those endogenous molecules which induce inflammation are called DAMPs (Damage Associated Molecular Patterns) and we showed that DJ-1 is one of the major DAMP in ischemic stroke.

When we knocked out DJ-1 in mice, we observed that inflammation after ischemic stroke was strongly suppressed. However, DJ-1 knock-out mice had similar damage after stroke compared to normal mice. We think that is because DJ-1 has both protective and deleterious effects and knocking out DJ-1 removes both effects. So, we next developed neutralizing antibodies to DJ-1, which would mainly affect the harmful extracellular DJ-1. When we injected these antibodies into mice, we found that they reduced inflammation and greatly improved pathology after ischemic stroke.

What are your plans for the future?
I think that DJ-1 is a very promising therapeutic target for developing more effective treatments for stroke and other diseases associated with inflammation. Also, although DJ-1 antibodies are expensive, they could be further developed for treatments of inflammation. For myself, I'm currently interested in studying endogenous repair mechanisms in the brain. Usually the brain isn't thought of as a very repair-friendly organ, but I've recently obtained some interesting results that I'm eager to pursue further.

Interviewed by Jun Horiuchi

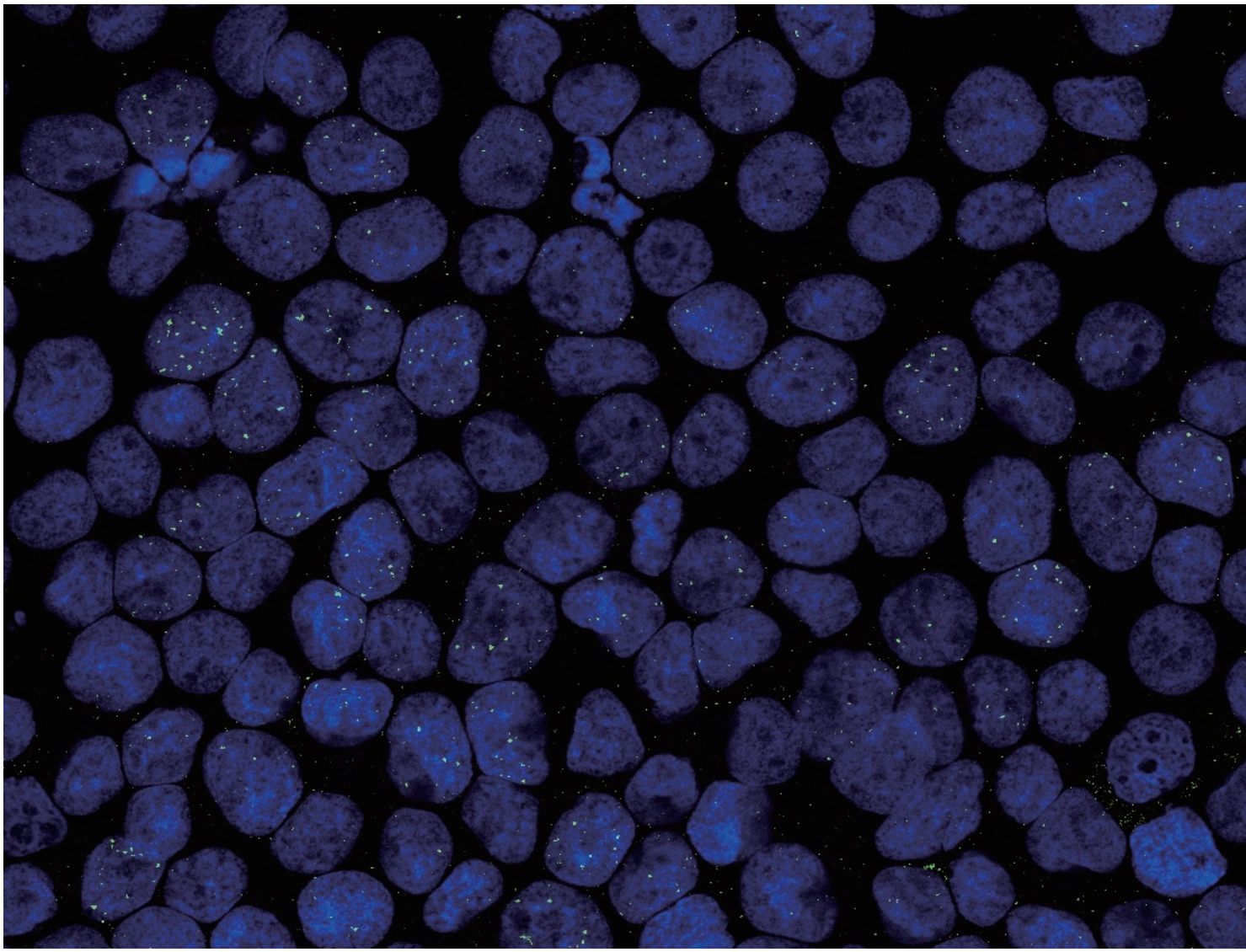


Schematic model of the roles of DJ-1 in the ischemic brain injury. DAMP, damage-associated molecular pattern; ROS, reactive oxygen species.

Our Goal

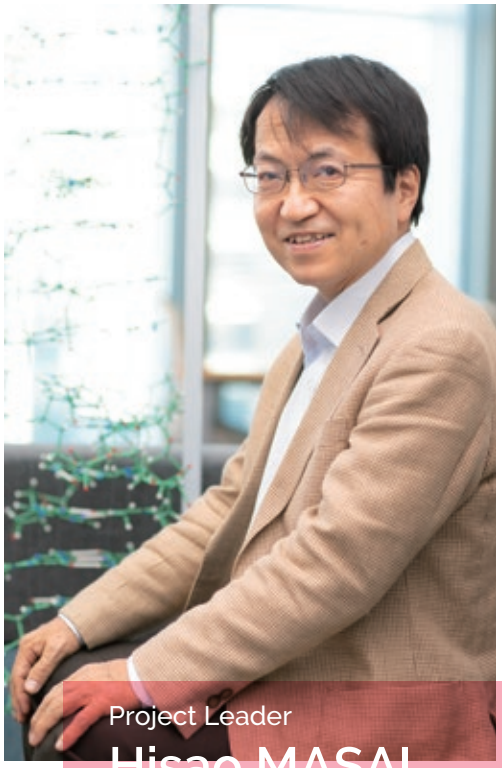
Our goal is to be a leading and role model institute for the life/medical science by conducting cutting-edge basic, clinical and social medical researches, that will help prediction, prevention, diagnosis, and treatment of various diseases and improve the care of patients, leading to longer healthy life.

Research Activities



Rad5 1 foci induced by ionizing irradiation in human B cells

Basic Medical Sciences



Project Leader
Hisao MASAI

Hisao Masai, the director-general of the institute since 2018, has led the Genome Dynamics Project since 2009. After graduating from the University of Tokyo in 1981, he worked on mechanisms of DNA replication as a graduate student under the supervision of Dr. Ken-ichi Arai at DNAX Research Institute in Palo Alto, California, USA, and received his Ph.D. in 1987 from the University of Tokyo, Graduate School of Science. 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 the primordial mode of DNA replication, and the roles of unusual nucleic acid structures, including G-quadruplexes and RNA-DNA hybrids in shaping chromosomes, copying and reading genetic information, and causing detrimental diseases.

Genome Dynamics

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

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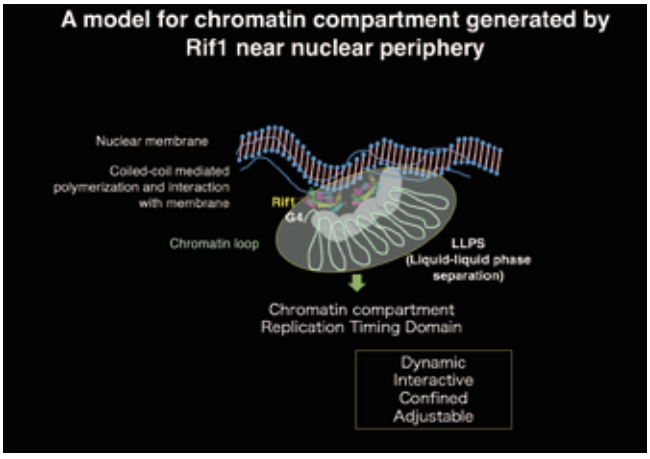
Trinh Thi To NGO
Shoha KINOSHITA
Ayaka ONUKI

Research Summary

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

1) How is the timing and location of DNA replication determined, and how are these coordinated with other chromosomal processes?
2) How do G-quadruplex structures regulate DNA regulation and chromosome architecture?
3) How do cells respond to replication stress, and how are these responses coordinated with other cellular stress response pathways?
4) What are the roles of replication factors in the development of individual organs and tissues? How do defects in these factors cause human diseases?
5) How have replication systems evolved and diversified in response to changing environments?
6) What are the roles of replication and checkpoint factors in developmental processes?



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

Selected Publications

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

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

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

Researchers
Kunie MATSUOKA
Shumpei YASUDA
Yuta SEKI

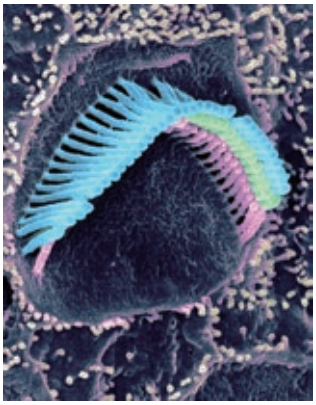
Students
Ikuo MIURA
Xuehan HOU

Research Summary

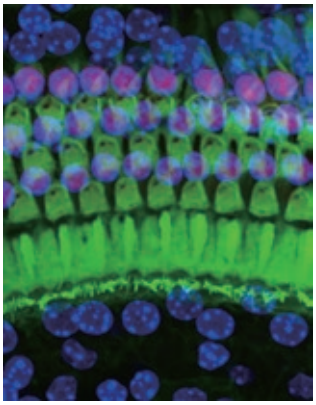
Hearing loss is a very common sensory disorder that severely affects human quality of life. In order to develop effective therapeutic strategies for deafness, it is critical to understand the mechanisms regulating its onset. Our aim is to discover novel genes associated with deafness. In particular,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

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

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

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

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
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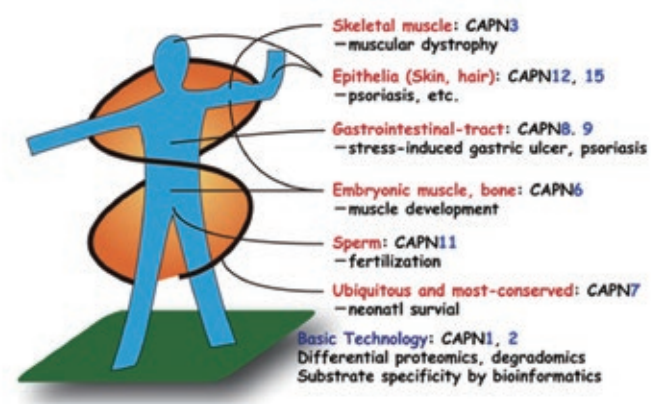
Fumiko SHINKAI-OUCHI
Aya NOGUCHI

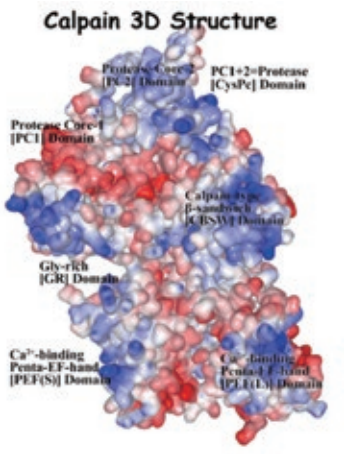
Research Assistants
Naoko DOI

Research Summary

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



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



Selected Publications

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

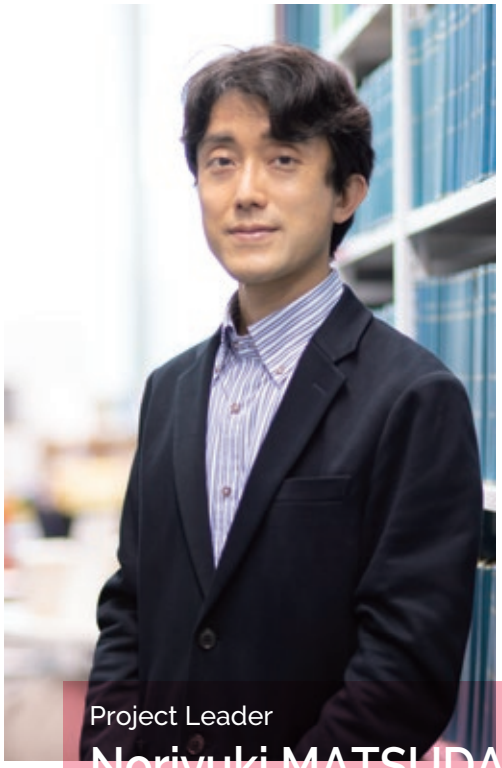
Hata S, et al. (2020) "A muscle-specific calpain, CAPN3, forms a homotrimer." ***Biochim. Biophys. Acta, Proteins Proteomics***, 7: 140411.

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

Ubiquitin

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

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.

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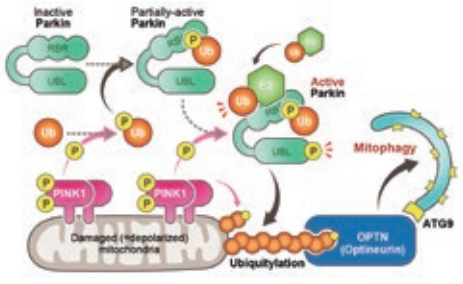
Rhota HAYASHIDA

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

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

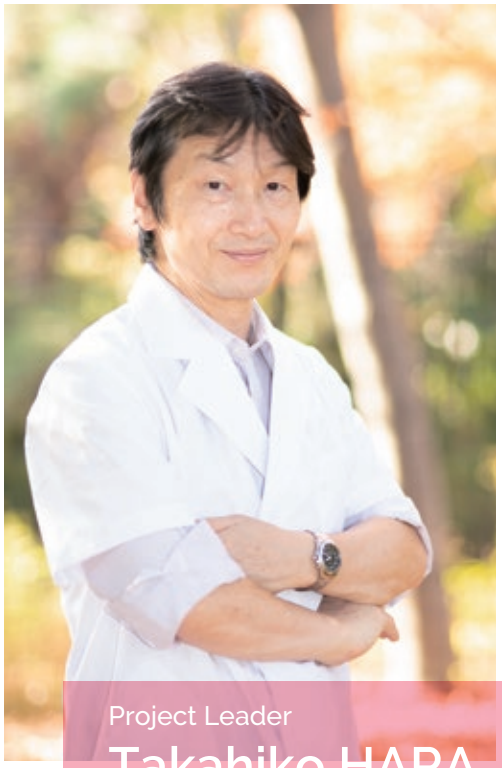
Kojima W, et al.(2021) "Mammalian BCAS3 and C16orf70 associate with the autophagosome formation site in response to selective and non-selective autophagy." ***Autophagy*** 17: 2011-2036.

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



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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Shoma YAMAGUCHI
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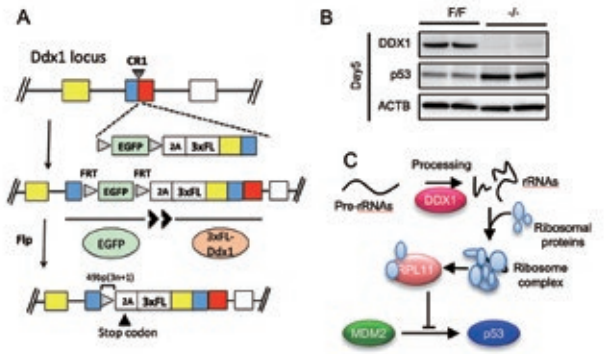
Shiho SASAKI
Minako SHINGAI
Fumiya SEKI
Hikaru ANDO

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

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

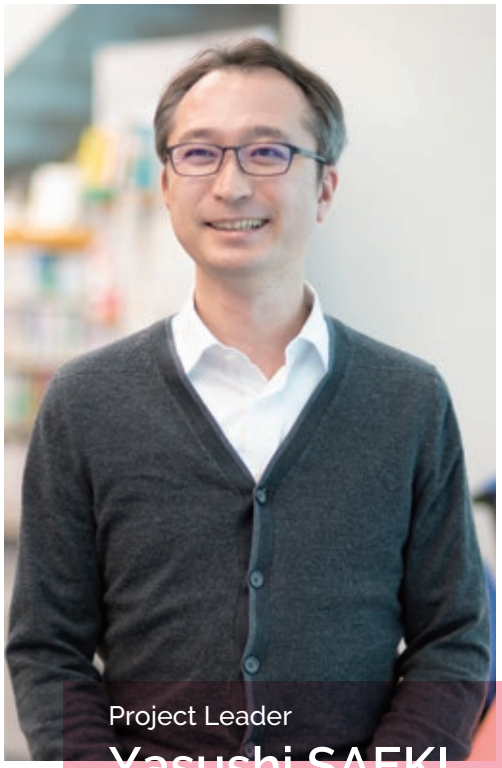
Suzuki, T. et al. (2021) "A novel all-in-one conditional knockout system uncovered an essential role of DDX1 in ribosomal RNA processing." ***Nucl. Acid Res.***, 49: e40.

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

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.



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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Hiromichi YONEKAWA

Visiting Scientists
Fumiaki OHTAKE
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Supervisor
Keiji TANAKA

Research Assistants
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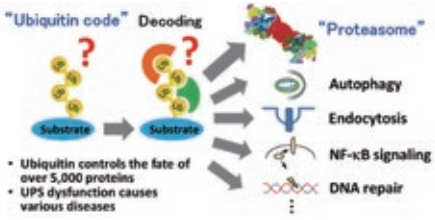
Sayaka ONO
Yasuko KAWASE
Harumi SETO
Kyoko UEDA
Students
Miho SAKUMA

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 (Nat Commun 2018, Mol Cell 2021). 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 2020). 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

Kaiho-Soma A, et al. (2021) "TRIP12 promotes small molecule-induced degradation through K29/K48 branched ubiquitin chains." ***Mol. Cell*** 81, 1411-1424.

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.

Project Leader
Hikari YOSHITANE

Circadian Clock

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

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

Staff

Researchers
Nobuhiro KURABAYASHI
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Research Assistants
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Students
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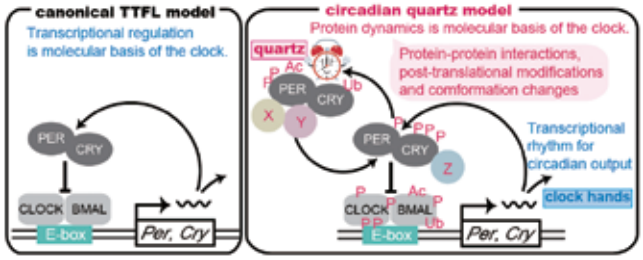
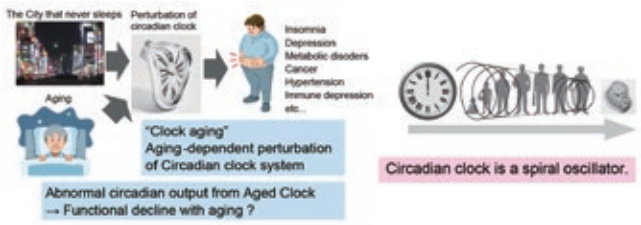
Satoshi KAWAKAMI
Shunsuke ITO
Taiki MORIMURA

Research Summary

<background>
Many organisms exhibit circadian rhythms, which are governed by a circadian clock. Clock genes and their encoded proteins form transcriptional/ translational feedback loops (TTFLs) that drive gene expression rhythms. Disruption of the circadian clock increases the risk of developing many diseases including insomnia, hypertension, metabolic disorders, and cancers.
<objective 1. circadian quartz>
How does the circadian clock autonomously oscillate with a period of about 24 hours? While the canonical TTFL model shown below is an essential component of the clock that regulates expression of downstream circadian genes, we believe that the critical timekeeping aspect of the clock is maintained by protein dynamics, where protein modifications and protein conformational changes regulate protein-protein interactions in an oscillatory manner. Thus, TTFL is required for clock read-out and is akin to the hands of the clock, while protein dynamics may be more similar to the quartz timekeeper in the clock. Currently we are studying TTFL-independent protein-based clock components to identify the quartz timing mechanism.
<objective 2. clock aging>
Disruption of the circadian clock causes dysregulation of gene expression rhythms. This leads to functional declines including aging-associated declines, which we refer to as “clock aging”. We are studying the molecular mechanisms of how aging disrupts the functional rhythms of the circadian clock and how clock perturbations cause aging-associated symptoms.





Selected Publications

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

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

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

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

Yoshitane et al., (2014) ***Molecular and Cellular Biology,*** 34(10): 1776-1787.

Yoshitane et al., (2012) ***EMBO Reports,*** 13(5): 455-461.

Yoshitane et al., (2009) ***Molecular and Cellular Biology,*** 29(13): 3675-3686.

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
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Tetsuya HIRABAYASHI
Keisuke KOMATSUYA
Norihito KIKUCHI

Students
Mai KAWAGUCHI
Jun KANBE

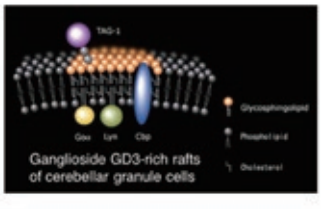
Research Summary

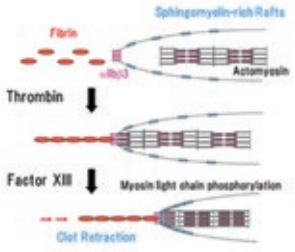
We are studying the function of lipid rafts. Lipid rafts are dynamic assemblies of glycosphingolipids, sphingomyelin, cholesterol, and proteins that can be stabilized in microdomains on cell surfaces. They are involved in the regulation of a number of cellular processes including axonal guidance, cellular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

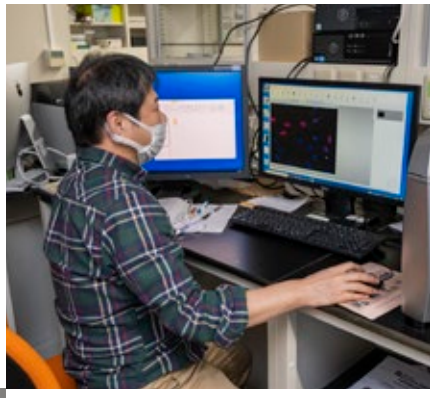
Kasahara K, et al. (2013) "Clot retraction is mediated by factor XIII-dependent fibrin-αIIbβ3-myosin axis in platelet sphingomyelin-rich membrane rafts." ***Blood*** 122, 3340-3348.

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.

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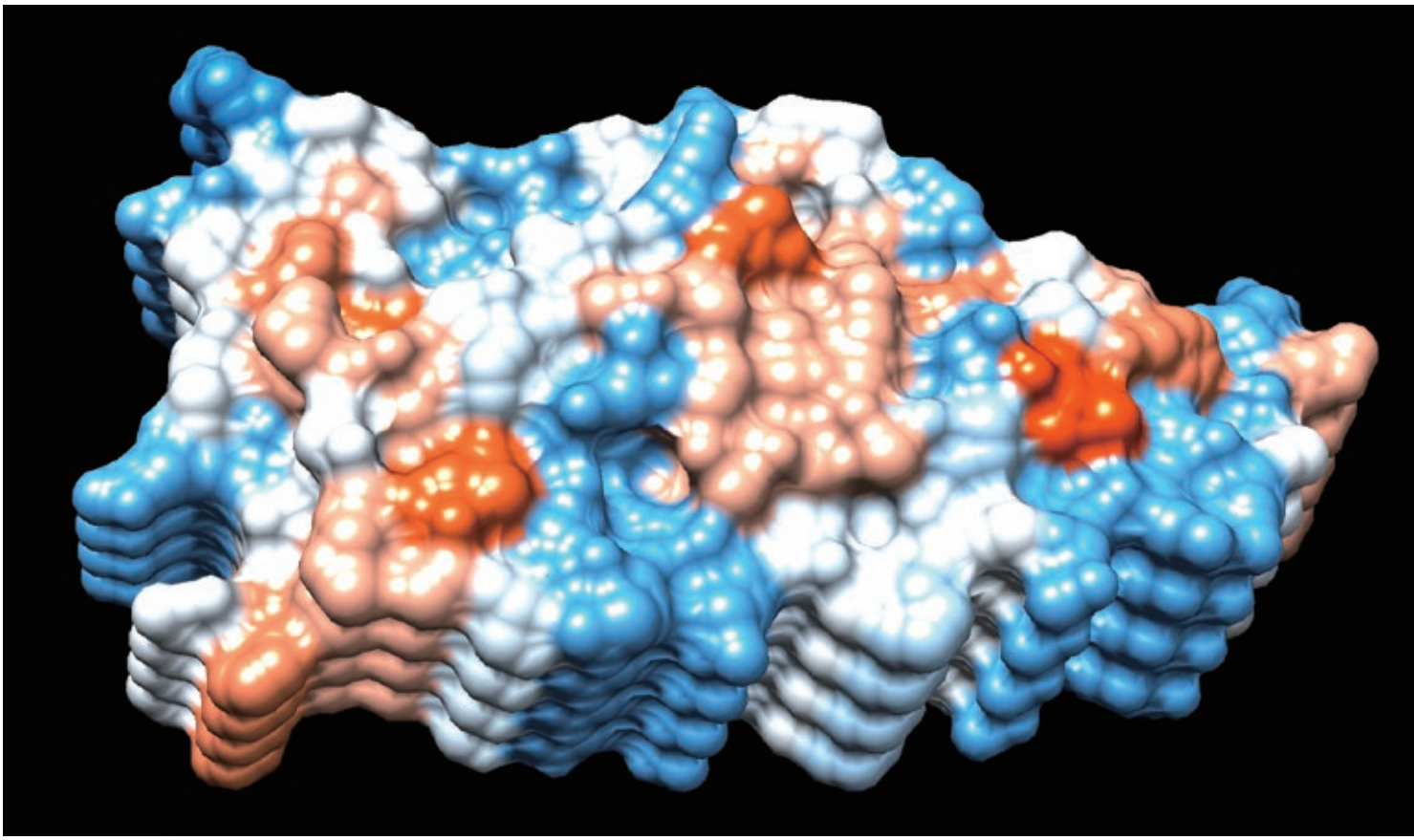
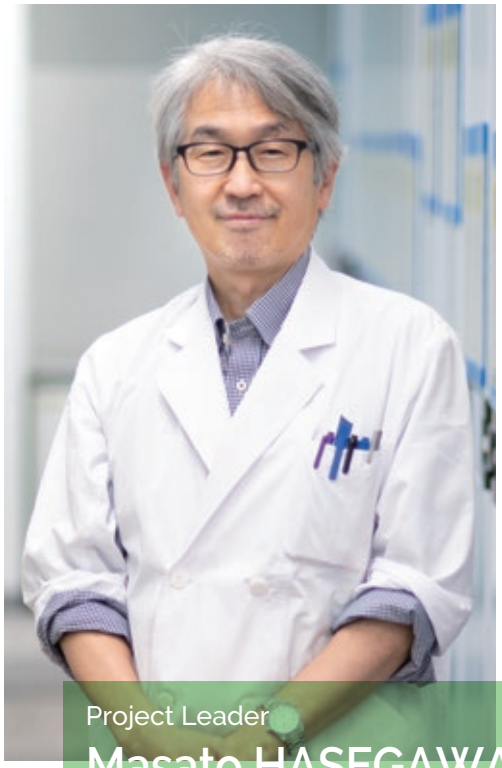


Surface structures of the cross section of TDP-43 fibers isolated from brains of ALS patients. Red, hydrophobic amino acids; blue, hydrophilic amino acids

Brain & Neurosciences



Project Leader
Masato HASEGAWA

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

Dementia Research

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

Staff

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Fuyuki KAMETANI
Ito KAWAKAMI

Postdoctoral fellows
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Research Assistants
Reiko OOTANI

Students
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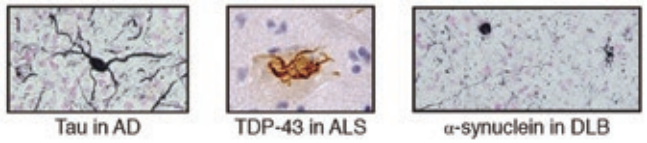
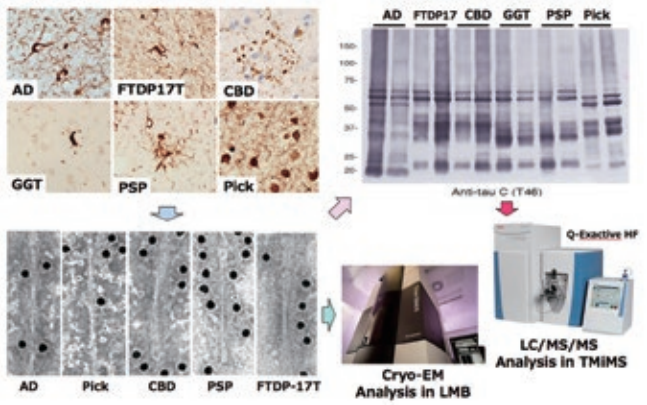
Mina TAKASE
Aiko ISAMI

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

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

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

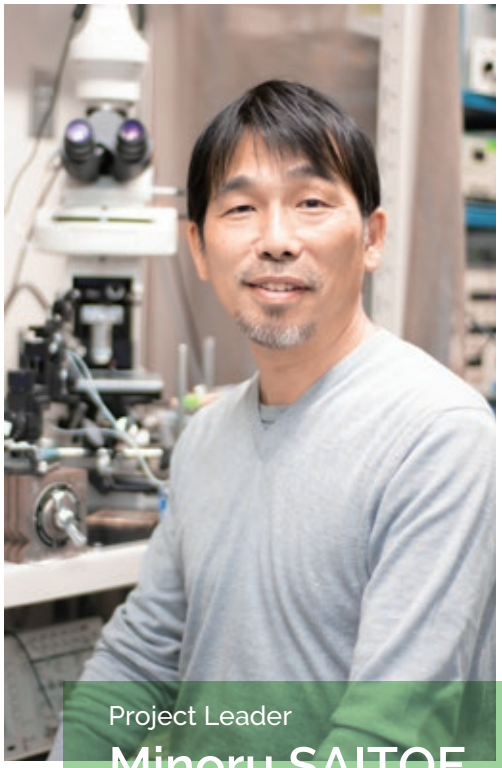
Shi Y, et al. (2021) "Structure-based classification of tauopathies." ***Nature.*** Sep 29. Online ahead of print. (Oct.14)

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

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

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

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



Project Leader
Minoru SAITOE

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

Learning and Memory

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

Staff

Researchers
Kohei UENO
Tomoyuki MIYASHITA
Motomi MATSUNO
Shintaro NAGANOS
Yoshinori SUZUKI

Postdoctoral fellows
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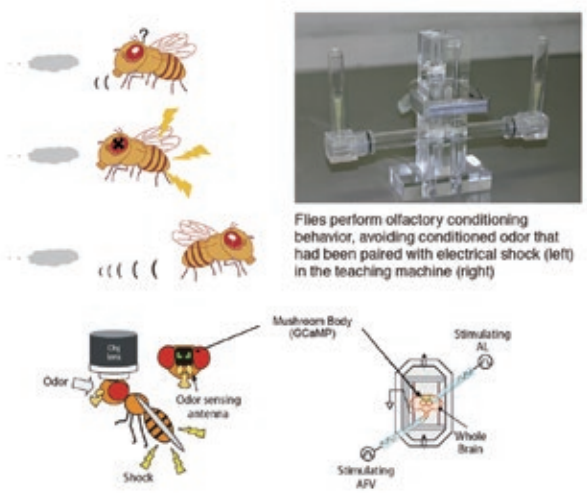
Research Assistants
Saki KOMIYA
Takae HASEGAWA
Tomoko TAKAMISAWA

Students
Maximiliano Martinez-Cordera

Research Summary

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

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



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

Selected Publications

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://neural-prosthetics.jp/

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Researchers
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Sho K. SUGAWARA
Michiaki SUZUKI

Postdoctoral fellows
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Noboru USUDA
Hikaru NAKAGAWA

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

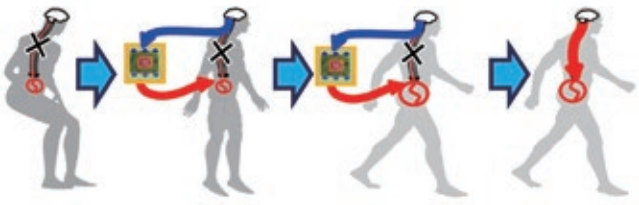
Students
Kei OBARA
Kouichi URAMARU
Kokoro KAWAMURA

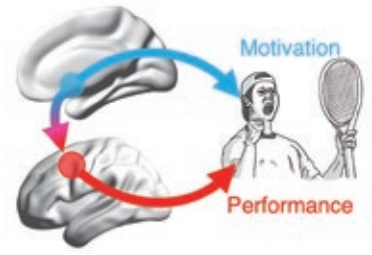
Research Summary

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
Tadayuki SHIMADA
Hiroko SUGIURA
Kuniko KOHYAMA

Visiting scientists
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Ai HOSHINO
Misato TSUBOI
Tomonori SUZUKI
Naoyuki TANUMA
Masaharu HAYASHI

Research Assistants
Mariko OZAKI

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

Research Summary

Our research focuses on 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

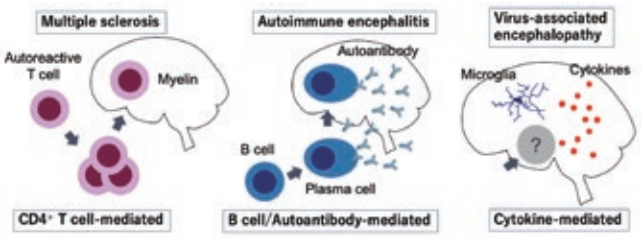


Figure Pathomechanisms of inflammatory and autoimmune neurological diseases
Multiple sclerosis has been regarded as a CD4 T-cell mediated disease in which autoreactive T cells are activated, proliferate, migrate to the brain, and cause myelin damage. Autoimmune encephalitis is caused by autoantibodies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

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

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

Mizuguchi M, et al. (2020) "Guidelines for the diagnosis and treatment of acute encephalopathy in childhood." ***Brain Dev.*** 43:2-31.

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

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

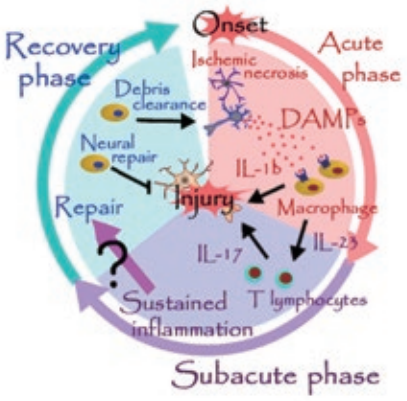
Researchers	Research Assistants	Students
Seiichiro SAKAI	Yoshiko YOGIASHI	Koutaro NAKAMURA
Jun TSUYAMA	Kumiko KURABAYASHI	Akari NAKAMURA
		Kento OTANI

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

Nakamura K, et al. (2021) "Extracellular DJ-1 induces sterile inflammation in the ischemic brain." ***PLOS. Biol.*** 19(5):e3000939.

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

Developmental Neuroscience

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

Staff

Researchers
Keisuke KAMIMURA
Takuma KUMAMOTO
Keiko MORIYA-ITO

Research Assistants
Kumiko HIRAI
Aiko ODAJIMA
Yoshiko TAKAHSAHI
Ayako MORITA

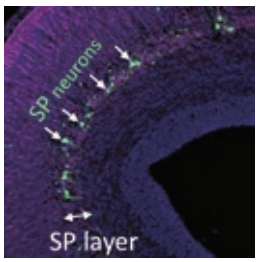
Students
Hitomi ACHIWA
Kyosuke WADA
Xiang SONG
Mayu OZAKI
Yusuke SUGITA
Yurika NOGUCHI

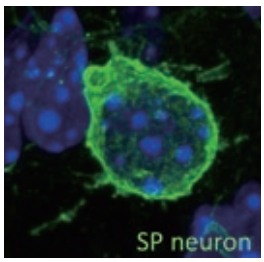
Research Summary

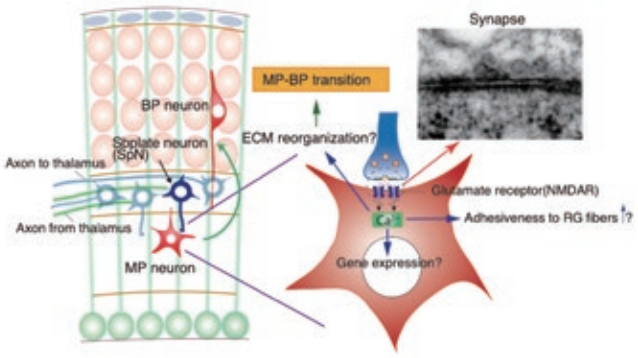
Mechanisms of Neural Network ormation: Neocortical development and synapse formation

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

"We are interested in the roles of the subplate later in the development of the cerebral cortex. It suggests that this transient cell population plays a crucial role as a symbolic "control tower" during neocortical formation and also adult cortical function."







Selected Publications

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

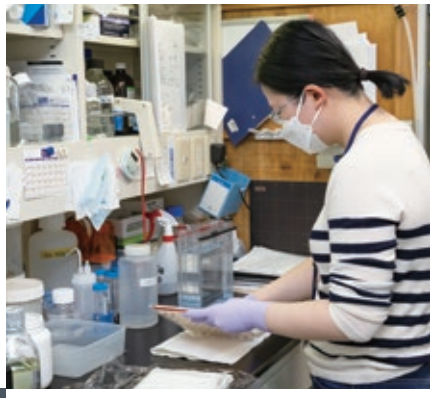
Nomura T, et al. (2020) "Changes in Wnt-dependent neuronal morphology underlie the anatomical diversification of neocortical homologs in amniotes." ***Cell Reports, 31***,107592.

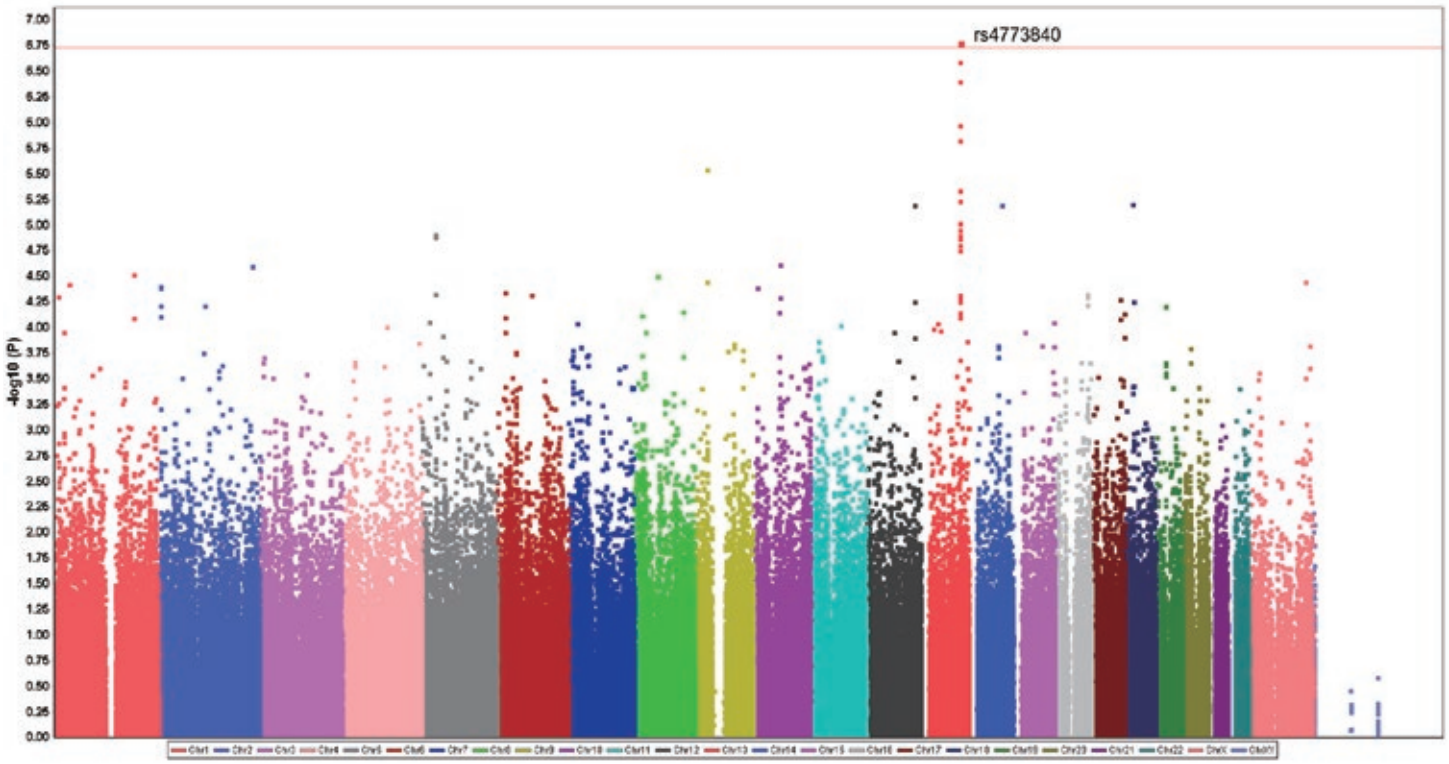
Kamimura K et al. (2019) "The HSPG Glypican Regulates Experience-Dependent Synaptic and Behavioral Plasticity by Modulating the Non-Canonical BMP Pathway." ***Cell Reports, 28***, 3144-3156.

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.





Genome-wide association study (GWAS) on postherpetic neuralgia. Genetic polymorphisms in the region of the ABCC4 gene that encodes ATP binding cassette subfamily C member 4 are associated with postherpetic neuralgia.

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
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Mitsuhiro MIYASHITA
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Izumi NOHARA
Mai HATAKENAKA
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Tomoko INOUE

Students
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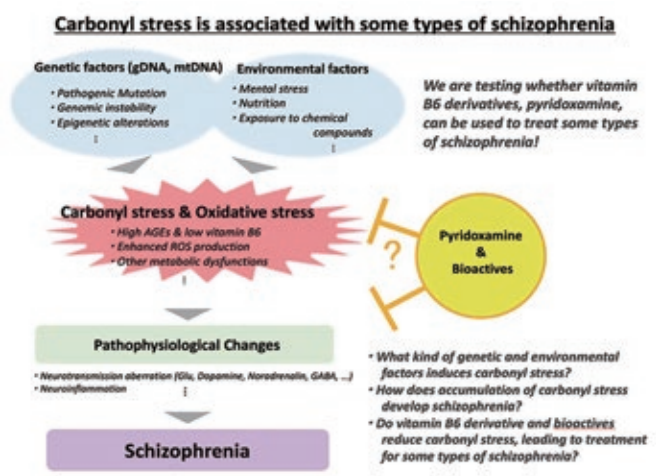
Kyoka IINO
Mayuko MASADA
Azuna OZAWA
Chinatsu SUGIMURA
Yasufumi TOMITA

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

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

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

Yoshikawa A, et al. (2021) "Dysregulation of post-transcriptional modification by copy number variable microRNAs in schizophrenia with enhanced glycation stress." ***Transl Psychiatry.*** 11:331.

Kobori A, et al. (2021) "Advanced glycation end products and cognitive impairment in schizophrenia." ***PLoS One.*** 16: e0251283.

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

Koike S, et al. (2021) "Analysis of carbonyl proteins accumulated in the brain of mouse model for methylglyoxal detoxification deficits by feeding Glo1 knockout mice with VB6-lacking diets." ***Antioxidants.*** 10: 574.

Mizutani R, et al. (2021) "Structural diverseness of neurons between brain areas and between cases." ***Transl Psychiatry.*** 11: 49.

Saiga R, et al. (2021) "Brain capillary structures of schizophrenia cases and controls show a correlation with their neuron structures." ***Sci Rep.*** 11:11768

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

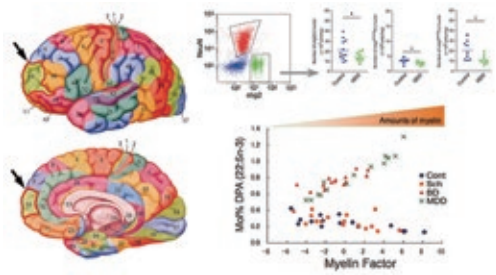
Staff

Researchers

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

Research Summary

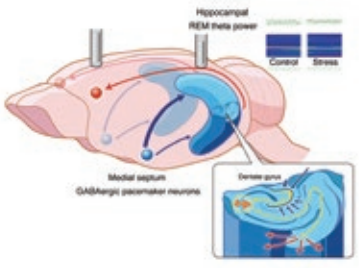
Major depressive disorder (MDD) and bipolar disorder (BD), collectively known as affective disorders, are relapsing and remitting disorders of affect with nearly full recovery between episodes. We use human postmortem brains and animal and cell culture models to identify the processes in which stress 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
Tohru KODAMA
Haruo OKADO
Taku MIYAGAWA
Akiyo NATSUBORI
Shinobu HIRAI

Research Assistants
Takashi KOJIMA
Yasuko SEKI
Yoshiko HONDA
Hiroko SHIMBO
Katsuko TAKASAWA

Visiting Scientist
Mihoko SHIMADA

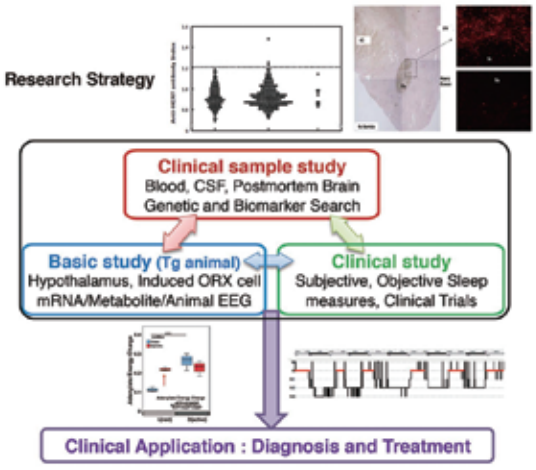
Students
Momoka MIYAZAWA

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

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

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

Shimada M et al (2020) 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.

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	Research Assistants	Students
Soichiro IDE	Yoko HAGINO	Yukiko OCHIAI
Shinya KASAI	Junko HASEGAWA	Yoshihisa KATO
Daisuke NISHIZAWA	Etsuko KAMEGAYA	Aimi YAMAGISHI
Masayo FUJITA	Yuiko IKEKUBO	Masako MORII
Seii OHKA	Yuki SERITA	Yasuharu YAMAGUCHI
Hiroko KOTAJIMA	Yuko EBATA	Masato Okitsu
Yuki MORIYA	Kyoko NAKAYAMA	Joei Zou

Research Summary

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

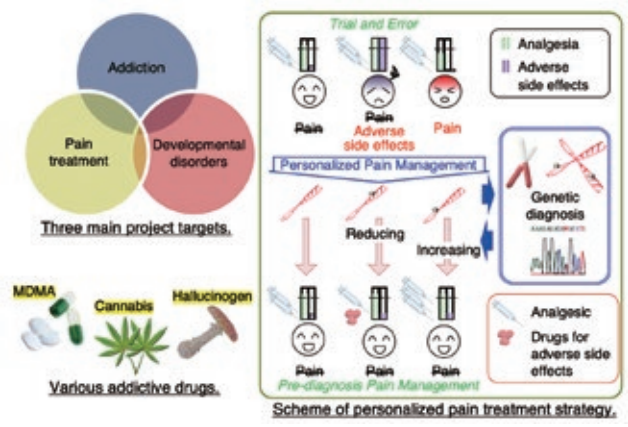
Some addictive drugs are also widely used as analgesics and for the treatment of developmental disorders. Some molecules that are involved in the actions of addictive drugs may be shared between analgesia and developmental disorders. The goals of our project are the following:

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

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

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

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



Selected Publications

Kotajima-Murakami H, et al. (2021) "Ifenprodil for the treatment of methamphetamine use disorder: An exploratory, randomized, double-blind, placebo-controlled trial." ***Neuropsychopharmacol Rep***. in press.

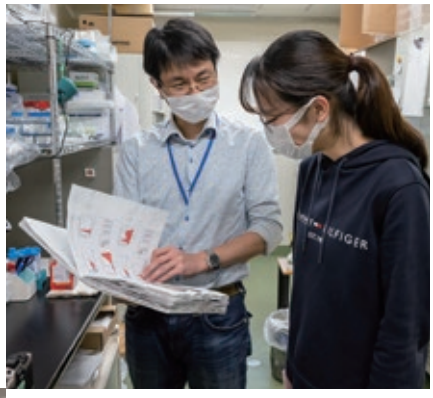
Sato A and Ikeda K. (2021) "Genetic and environmental contributions to autism spectrum disorder through mechanistic target of rapamycin." ***Biol. Psychiatry: Glob. Open Sci.*** in press.

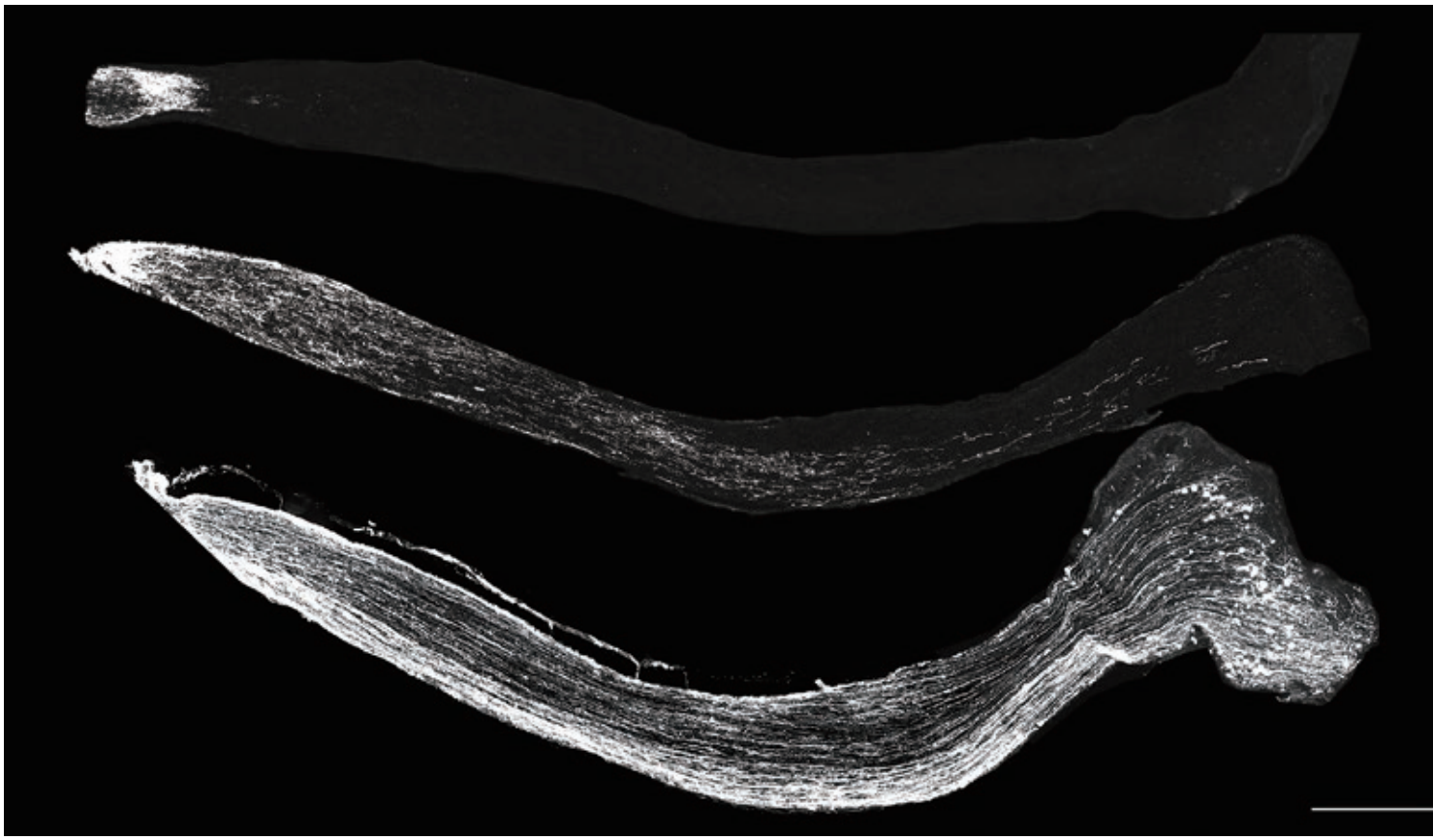
Ide S, et al. (2021) Caenorhabditis elegans exhibits morphine addiction-like behavior via the opioid-like receptor NPR-17. ***Frontiers in Pharmacology***, 12:802701

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

Nishizawa D, et al. (2021) "Genome-wide association study identifies candidate loci associated with chronic pain and postherpetic neuralgia." ***Mol Pain*** 17:1744806921999924

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





Regeneration of optic nerves after gene therapy. From top to bottom, one, two and four weeks after treatment

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
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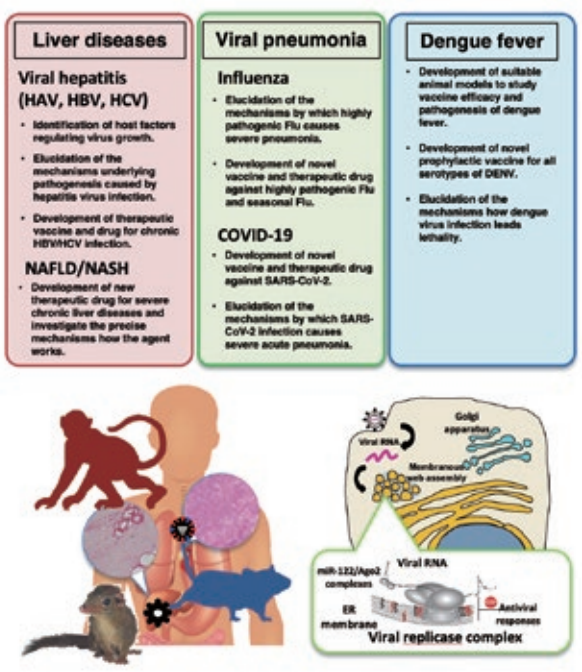
Kenzaburo YAMAJI
Yuko TOKUNAGA
Naoki YAMAMOTO
Takahiro SANADA
Yusuke MATSUMOTO
Tomoko HONDA

Research Assistants
Asako TAKAGI
Risa KONO
Masahiko HIGA
Sakiko TOYAMA
Aya KOSEKI

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

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

Saito M, et al. (2021) "Macrocyclic peptides exhibit antiviral effects against influenza virus HA and prevent pneumonia in animal models." ***Nat Commun***. 12(1):2654.

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.

Project Leader
Satoshi KOIKE

Neurovirology

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

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.

Staff

Researchers
Kyousuke KOBAYASHI
Naoki KAJIWARA

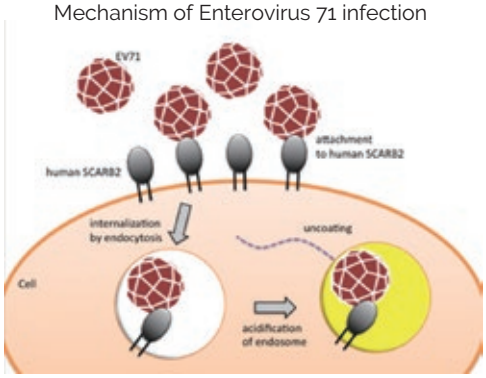
Research Assistants
Ayako TAKASHINO
Masako UKAJI
Namiko NOMURA
Tomoha NISHIZAWA
Wakako MIWATASHI
Minori ISHIDA
Sayaka ESAKI

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.

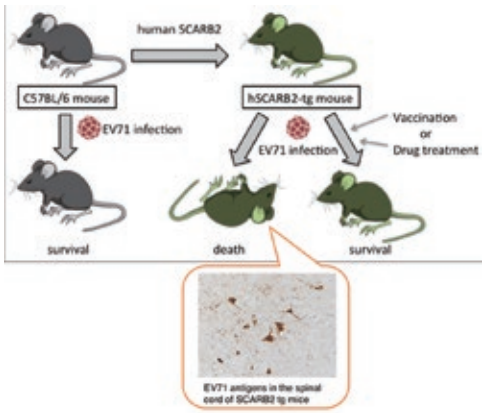
Research Topics

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

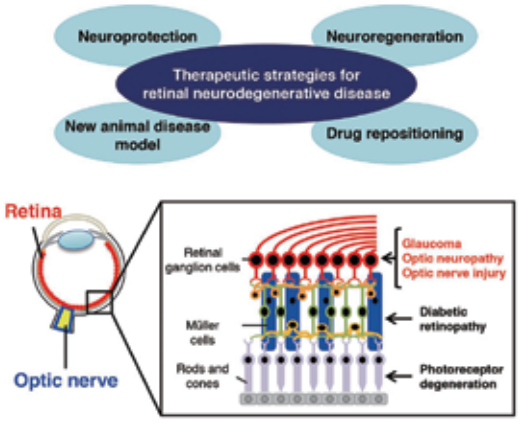
Researchers
Kazuhiko NAMEKATA
Xiaoli GUO
Atsuko KIMURA
Chikako HARADA
Takahiko NORO
Euido NISHIJIMA
Yuta KITAMURA
Naoki KIYOTA
Akiko SOTOZONO

Research Assistants
Mayumi KUNITOMO
Tomoko HARA

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.



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

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

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

Selected Publications

Guo, X., Kimura, A., Namekata, K., Harada, C., Arai, N., Takeda, K., Ichijo, H. and Harada,T(2022) "ASK1 signaling regulates phase-specific glial interactions during neuroinflammation."*Proceedings of the National Academy of Science of the United States of America (PNAS)*119(6), e2103812119,

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

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

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

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

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
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Hitoshi KAWANO
Ken MURAMATSU
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Tomoyo AKAMINE
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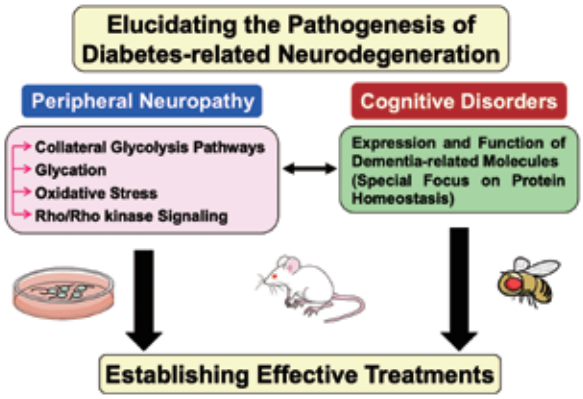
Students
Masaki OBA
Nozomi SAKATA
Takuma HARA
Mari KIMURA
Shoya WATANABE

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

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

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

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

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.

Project Leader
Yuichiro MIYAOKA

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

Regenerative Medicine

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

Staff

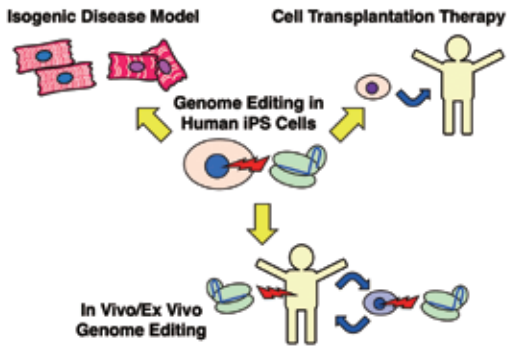
Researchers
Tomoko KATO-INUI
Gou TAKAHASHI

Students
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

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

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

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

Miyaoka Y, et al. (2016) "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.

Project Leader
Hidetaka TANNO

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

Cancer Immunology

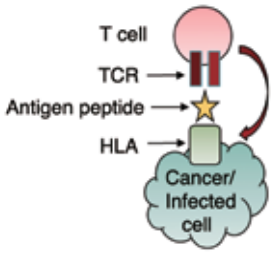
Laboratory HP: https://www.igakuken.or.jp/cancer_immunology/

Staff

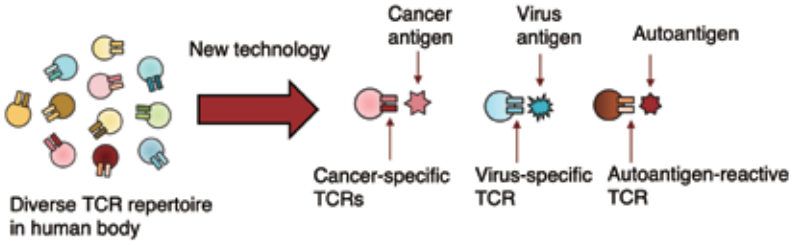
Research Assistants
Yuri Tanno

Research Summary

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



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



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

Selected Publications

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

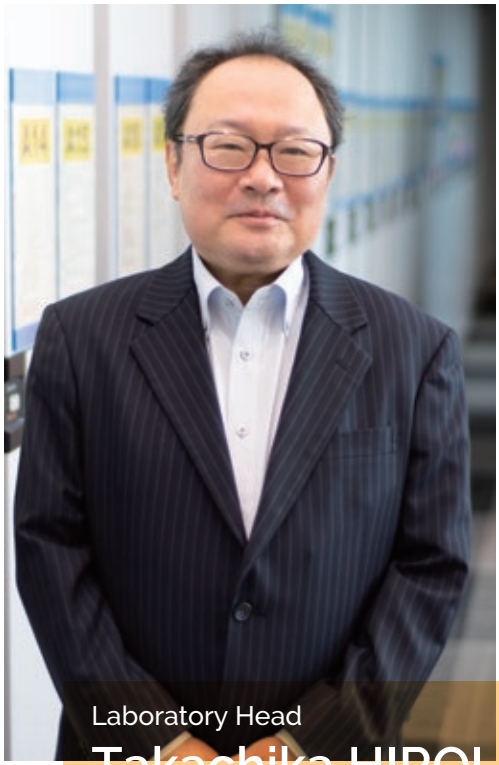
H Tanno et al. (2020) "A Facile Technology for the High Throughput Sequencing of the Paired VH:VL and TCRβ:TCRα Repertoires." ***Science Advances.***

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

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

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

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



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
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Tomoe NISHIMURA

Research Assistants
Noriko KITAMURA

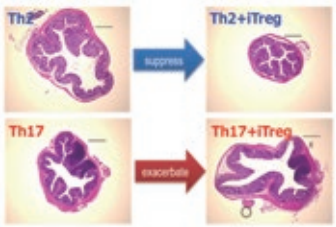
Students
Kohei FUSANO
Maho TAMURA
Masato TAMAI
Shotaro NAKAMURA

Research Summary

Recent Topics of Mucosal Immunology

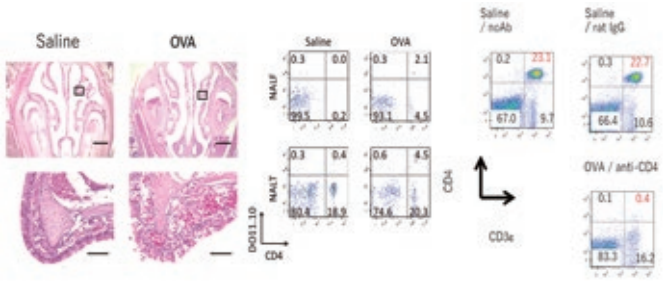
1. Antigen-specific iTreg cells stimulate Th17-mediated colon inflammation

$CD4^+$ 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

Koyama T, et al. (2021). "Suppressive effect of dexamethasone on murine Th9 cell-mediated nasal eosinophilic inflammation. "***Asia Pac Allergy***. 11(3):e25. doi: 10.5415/apallergy.2021.11.e25. eCollection

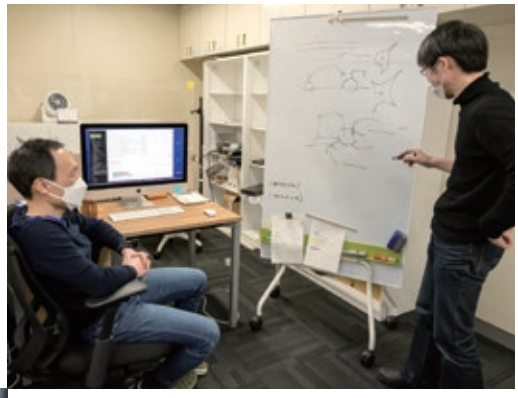
Tachibana M, et al. (2020). "Ablation of IL-17A leads to severe colitis in IL-10-deficient mice: implications of myeloid-derived suppressor cells and NO production." ***Int Immunol.*** 32: 187-201.

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

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

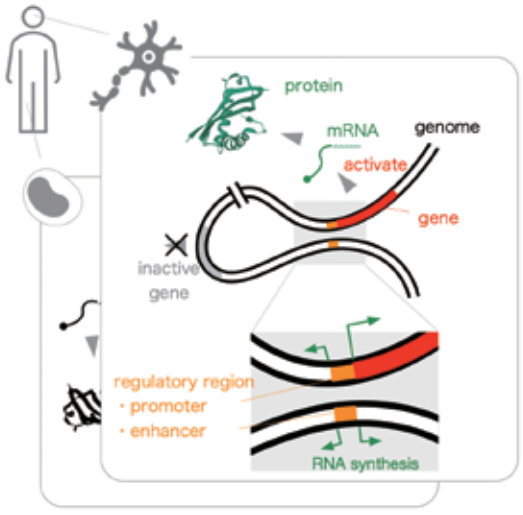
Director
Hisao MASAI
Senior Researcher
Keisuke OBOKI

Researcher
Naoko YOSHIZAWA
Toyoaki NATSUME
Yuichiro HARA
Saki SAITO

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

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

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

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

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

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

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

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

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

Director Unit Leader
Atsushi NISHIDA

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

Mental Health Promotion

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

Staff

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

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

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

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

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

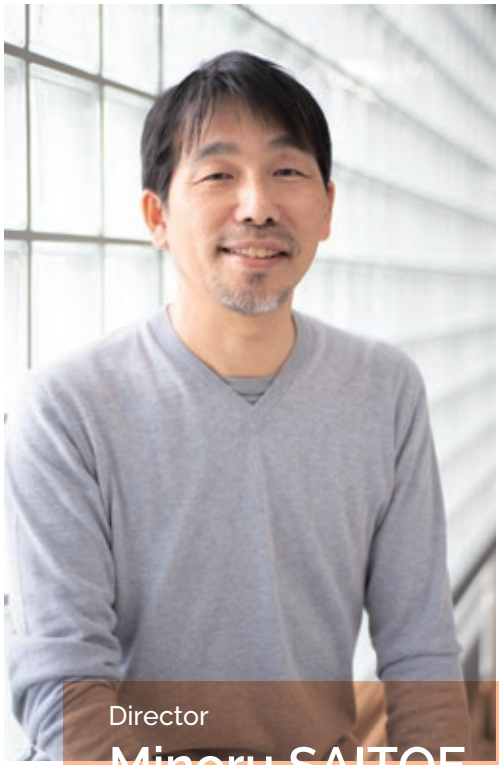
Matsuda C, Shimizu T, Nakayama Y, Haraguchi M. (2019) "Cough peak flow decline rate predicts survival in patients with amyotorophic lateral sclerosis" ***Muscle & Nerve***. 59(2) 168-173.

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

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

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

Research Supports



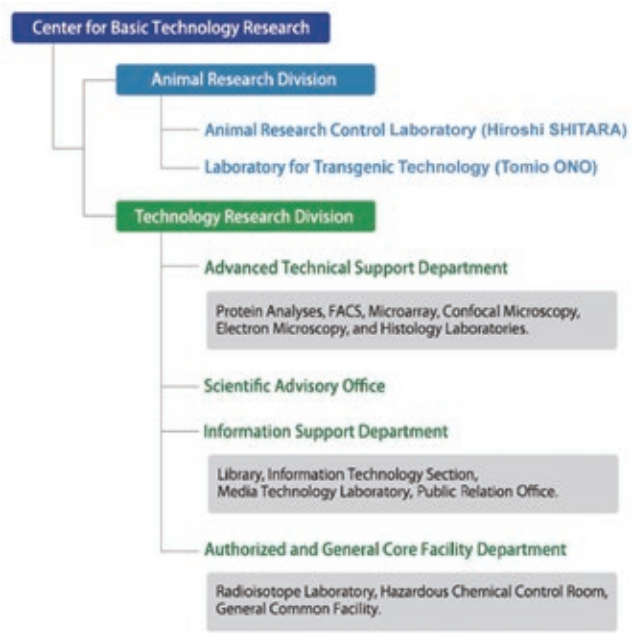
Basic Technology Research

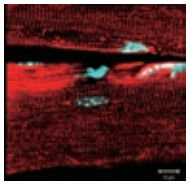
Laboratory HP: https://www.igakuken.or.jp/english/center/basic/basictech.html

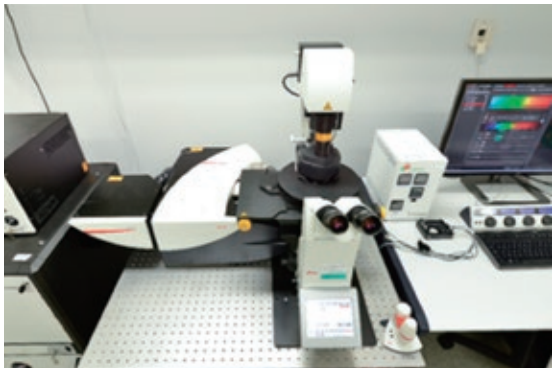
Director
Minoru SAITOE

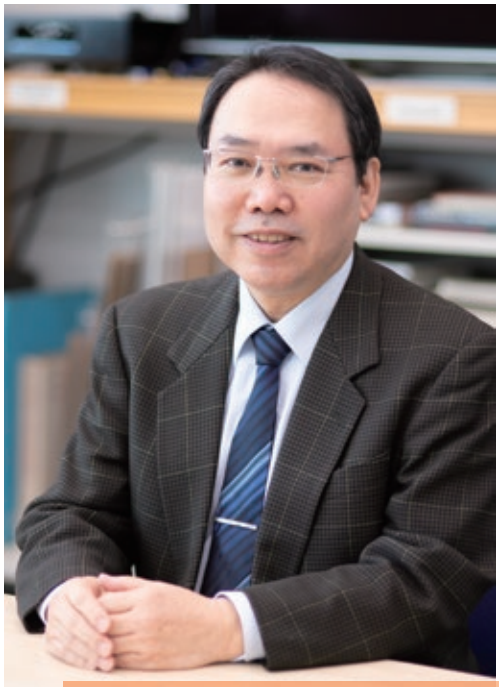
The Basic Technology Research Center provides resources to assist scientists to conduct their research efficiently. We provide state-of-the-art technologies required for biomedical and life science research and maintain various facilities used by researchers.

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









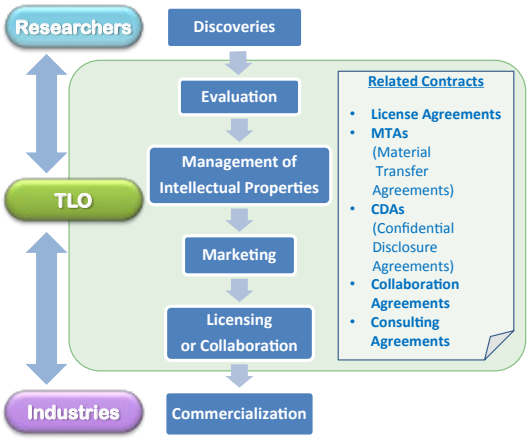
Technology Licensing Office

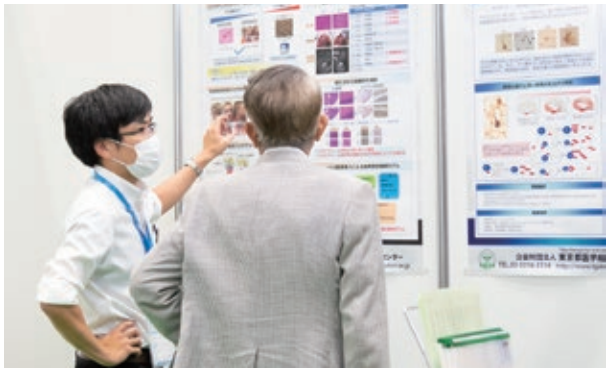
TLO HP: https://www.igakuken.or.jp/english/center/tlo/tlo.html

General Manager
Kazumasa AOKI

Who we are

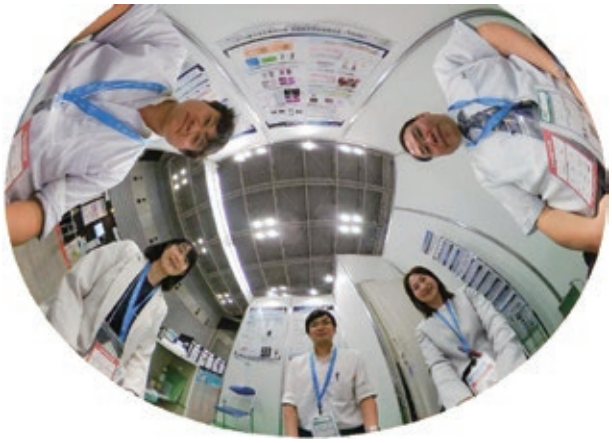
- The Technology Licensing Office (TLO) facilitates the conversion of scientific discoveries to innovative technologies with the ultimate goal of improving public health and welfare.
- We evaluate basic research findings (seeds) as intellectual property assets, and license promising candidates to industries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





What we do

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



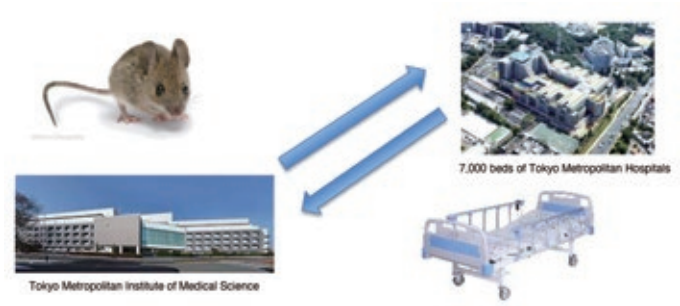
Director
Takayuki HARADA

Medical Research Cooperation

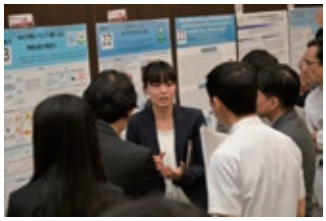
Laboratory HP: https://www.igakuken.or.jp/english/center/tr/tr.html

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

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



Conference with researchers and medical doctors



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

Neuropathology

The Laboratory of Neuropathology conducts neuropathological research using specimens of human origin. The laboratory features fixed asset management and research use of approximately 5,000 human neuropathology specimens and samples, one of the largest in Japan and abroad; research and educational use of a neuropathology image database using virtual slides from a high-precision digital scanner; and dissemination and use of specialized techniques by faculty members specializing in neuropathology.

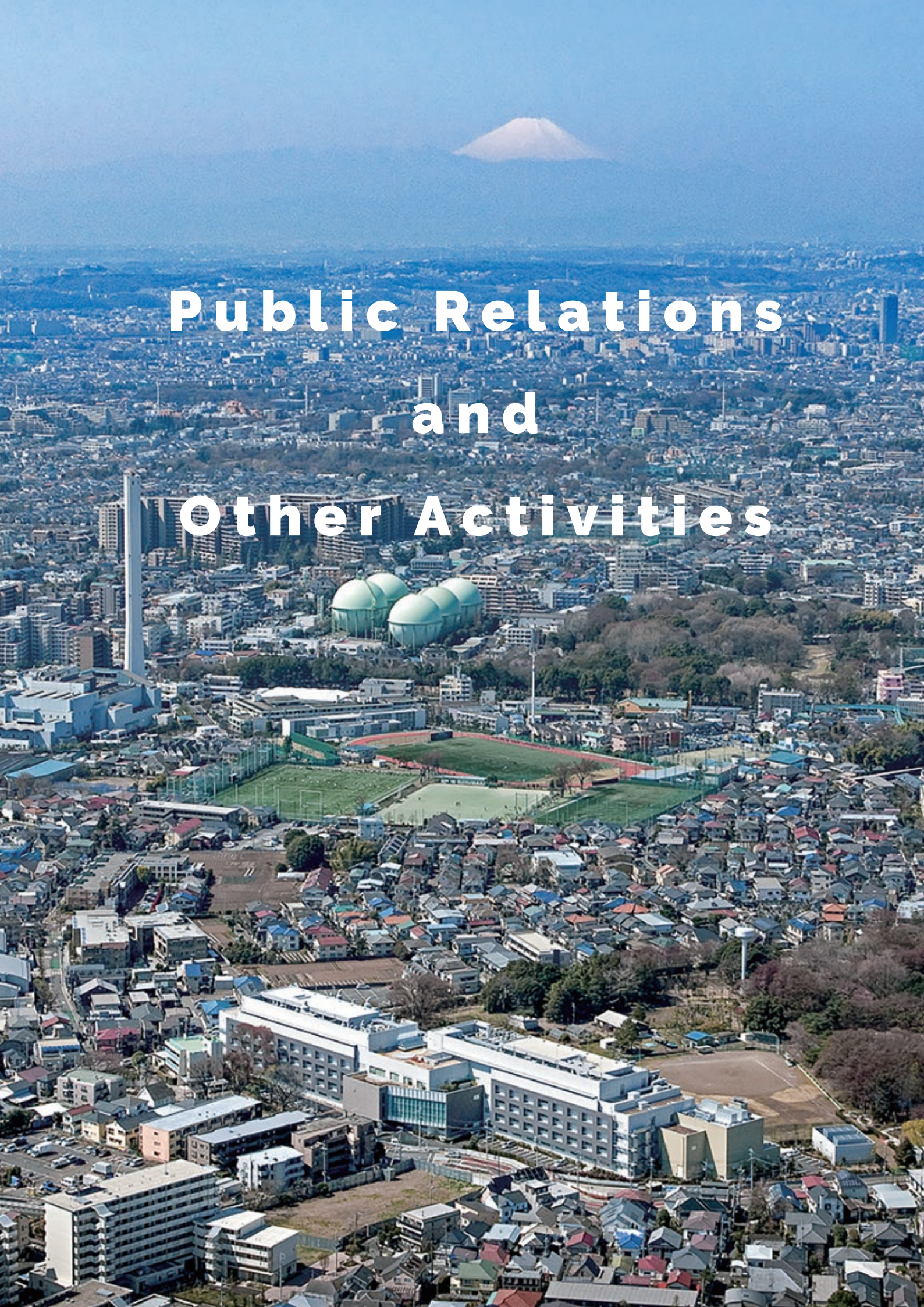
Laboratory HP: https://pathologycenter.jp/english/en_index.html

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

Staff

Masanari ITOKAWA
Kenichi OSHIMA
Erika SEKI
Rika KOJIMA
Nobuko UEKI
Tomoko YAGI
Tsunemi YAMANISHI
Keiko AKAMATSU

We are one of the rare laboratories preparing large brain sections in Japan. The large brain section allows us to detect the distribution patterns of lesions in brain diseases.



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 2021, we conducted all the lectures on line.
Lecture topics included Dementia, cancer treatment, brain functions and infectious diseases.

Dementia: Prevention and Early Diagnosis
.....Masato HASEGAWA (TMIMS, Dementia Research Project)
.....Tetsuaki ARAI (University of Tsukuba)

A challenge for treating cancer: Targeting cancer-causing proteins for degradation
.....Yasushi SAEKI (TMIMS, Protein Metabolism Project)
.....Mikihiko NAITO (The University of Tokyo)

A new era for genome-based cancer medicine
.....Hisao MASAI (TMIMS, Genome Dynamics Project)
.....Hiroyuki SASANUMA (TMIMS, Genome Dynamics Project)
.....Masatoshi FUJITA (Kyushu University)

Break-through technologies to open new frontier in brain functions
.....Yukio NISHIMURA (TMIMS, Neural Prosthetics Project)
.....Toshiki TAZOE (TMIMS, Neural Prosthetics Project)
.....Shinichi FURUYA (Sony CSL)

Can human win battles with viruese?: a case of Polio virus
.....Satoshi KOIKE (TMIMS, Neurovirology Project)
.....Hiroyuki SHIMIZU (NIID)

Cancer treatment without pain
.....Kazutaka IKEDA (TMIMS, Addictive Substance Project)
.....Masahiko SUMITANI (The University of Tokyo Hospital)

How infection occurs: case studies with Coronavirus and Chlamydia
.....Kouji KASAHARA (TMIMS, Cell Membrane Laboratory)
.....Kentaro HANADA (NIID)

Brain, mind and body of senior citizens: lessons from Lewy Body Dementias
.....Masato HASEGAWA (TMIMS, Dementia Research Project)
.....Yoshiyuki NISHIO (Tokyo Metropolitan Matsuzawa Hospital)






Science café

In the past ten years we have had 35 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 2021, we had three online science cafes on human body operation and genomes. The participants enjoyed our online quizzes in these events.

How the human body works; a pediatrician's view
.....Hiroshi SAKUMA (TMIMS,Child Brain Project)

Seeing and playing with the genome sequences
.....Hideya KAWAJI
(TMIMS,Research Center for Genome & Medical Sciences)

What is the circadian clock? Wonders of a 24-hour rhythm
.....Hikari YOSHITANE
(TMIMS,Circadian Clock Project)


Institutional seminars (Igakuken Seminars)

We have institutional seminars on a regular basis. In 2021, despite the continued coronavirus pandemic we had 18 on line seminars by both domestic and international scientists including those from Yale and Johns Hopkins Universities in USA. We were particularly excited to be able to invite world-prominent scientists to the Igakuken Seminars by taking advantage of the use of the on line presentation.

Sleep-based treatment of neurodegenerative diseases
.....Eiko N MINAKAWA (NCNP)

Optical functional neuroimaging in human infant brains
.....Gentaro TAGA (The University of Tokyo)

Immune responses to SARS-CoV-2
.....Akiko IWASAKI
(Yale University School of Medicine & Howard Hughes Medical Institute)

Medical research and intellectual property: a case study with regenerative medicine
.....Masaho ISHINO (Sapporo Medical University)

Development and maintenance of brain: from ascidian to mouse
.....Haruo OKADO
(TMIMS, Laboratory of Neural Development)

Neural activity-dependent gene expression in brain functions
.....Kanato YAMAGATA
(TMIMS, Laboratory of Synaptic Plasticity)

Rules for distributing synaptic weights in hippocampal neurons
.....Yukiko GODA (RIKEN)

How scietists publish and advertize scientific papers: Open Access and self-promotion of your paper
.....Mami YAMADA (Wiley Japan)

Molecular Genetic Studies of CNS Vascular Development and Disease
.....Jeremy NATHANS
(Johns Hopkins Medical School)

Combat with COVID-19, a large-scale antibody testing and vaccine development: a virologist's reflection
.....Michinori KOHARA
(TMIMS, Viral Infection Control Project)

Human systems biology approach to validate "sleep phosphorylation" hypothesis
.....Hiroki UEDA (The University of Tokyo)

About the outline of "Ethical Guidelines for Life Science and Medical Research targeting Humans"
.....Kaori MUTO (The University of Tokyo)

Introducion of the National Center of Neurology and Psychiatry (NCNP): Aiming to overcome mental, neural, muscular diseases and developmental disorders
.....Kazuyuki NAKAGOME (NCNP)

Roles of glucose metabolism in brain aging and neurodegenerative diseases
.....Mikiko OKA (Tokyo Metropolitan University)

Epigenome changes and SASP associated with cellular senescence
.....Akiko TAKAHASHI (The Cancer Institute Of JFCR)

Viewing and Understanding Representation of Information in the Cerebellum: What Do Complex-spikes Represent?
.....Takayuki MICHIKAWA (RIKEN)

Diversity of dopamine signals and their functional significance
.....Masayuki MATSUMOTO (University of Tsukuba)

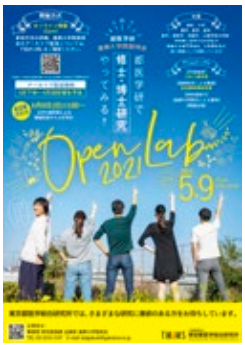
Mechanism of switching from mitotic to meiotic cell cycle
.....Kei-ichiro ISHIGURO (Kumamoto University)

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 Takashi SHICHITA on stroke, and the other by Kohei UENO on brain memory.

Joint programs with universities

Many scientists at TMIMS have joint appointments as visiting professors or lecturers at various universities. In 2021, we held our annual "open institute" events for prospective graduate students on line with close to 100 attendants. We currently have 149 students from affiliated universities and other schools, who conduct their research here.



Support for students and young scientists

Research Associate Fellowships

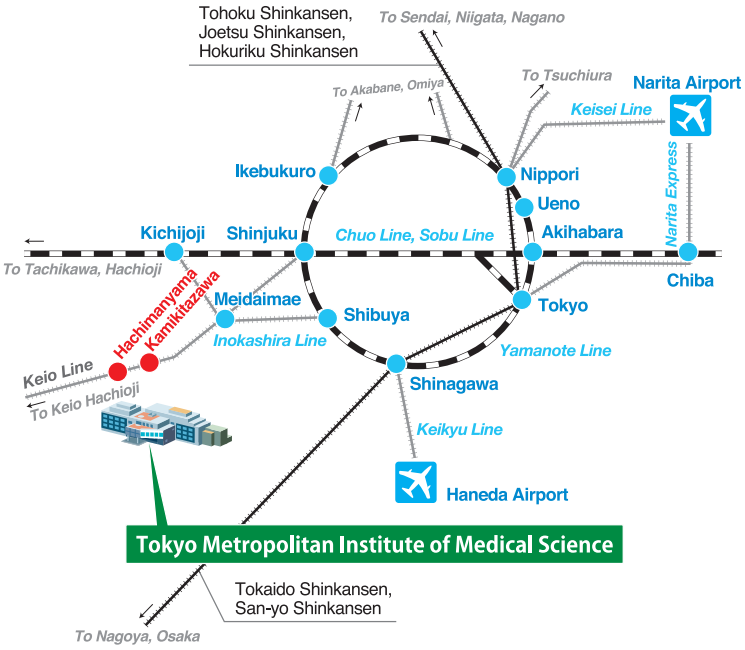
We provide graduate students who conduct their masters/Ph.D. research at TMIMS with research associate fellowships that provide them with financial support, and allow them to concentrate on their studies and research.

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

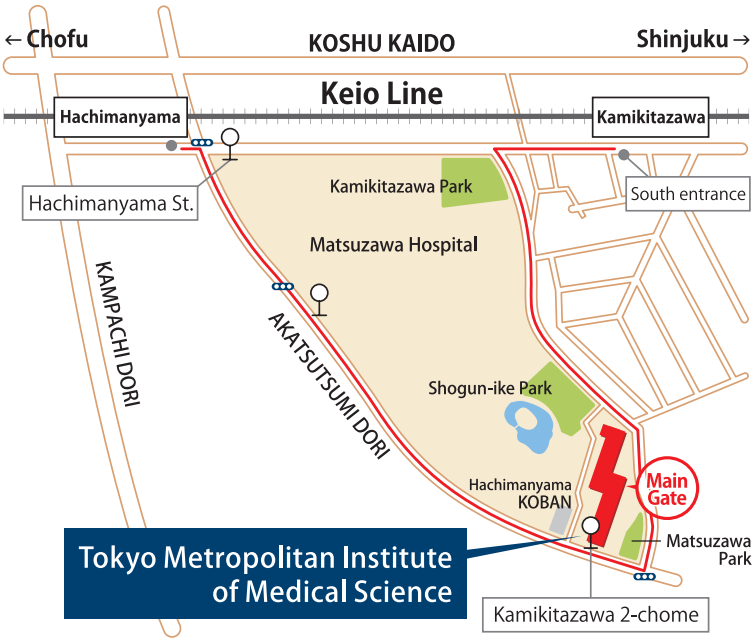
Tokyo Metropolitan Institute of Medical Science	
Address	2-1-6 Kamikitazawa, Setagaya-ku, Tokyo, 156-8506, Japan
Tel	+81-3-5316-3100
Fax	+81-3-5316-3150



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

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

As of March 1, 2022