TMiMS

Annual Reports 2022

Contents

Message from the Chairperson

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.

From early 2020 to today, 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" three 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 2023.

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.

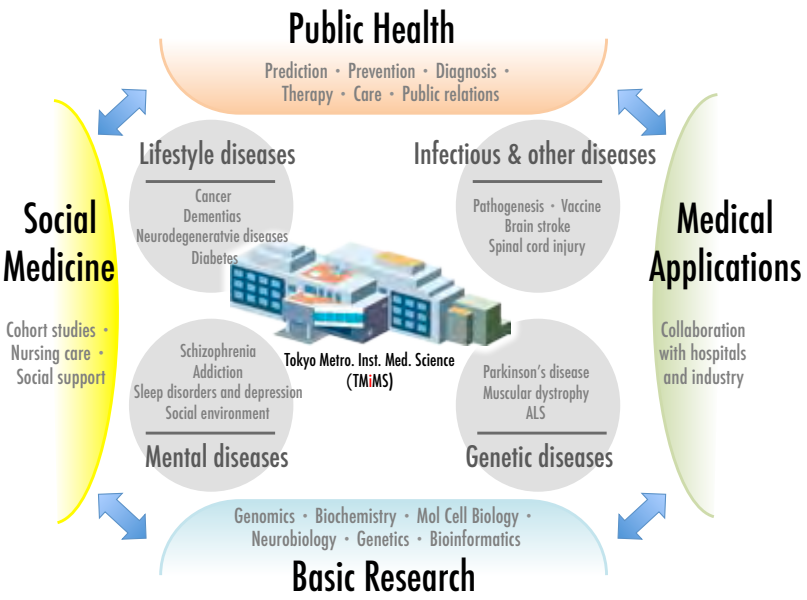
I am of the opinion that scientific research is a symbol of culture. A society cannot be considered cultured if it has no interest and knowledge of science and research. Accordingly, TMIMS aims to be acclaimed both academically and culturally for the knowledge and wisdom of its excellent researchers.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

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

We are working to make TMIMS the world's premiere research institute, and advancing and enriching its research power will create an institute capable of providing wide-ranging services to society. To this end, the entire staff of TMIMS strives to help pursue incomparable fundamental research, and pass the benefits of this research on to society. At the same time, we are continuing to recruit and educate talented people to increase our momentum. Thank you for your support, which is indispensable for the further development of TMIMS.

Our Mission

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



Message from the Director: TMIMS 2022

Director
Hisao MASAI

In 2022, we witnessed the tragedy that an unjustified war brought to people on this earth. Watching the tremendous loss of human lives in Ukraine and Russia simply has made us speechless. As scientists working to benefit humanity, we strongly oppose this senseless war and hope this tragedy will end soon. On the bright side, the COVID pandemic finally seems to be abating somewhat. After nearly three years, face-to-face meetings have finally resumed, and many have started to attend meetings abroad. Although life in Japan has not completely returned to normal, we hope to soon return to a way of life where we are not living in constant fear of infection.

TMIMS 2022

In September, we had very good news. Dr. Masato Hasegawa, the leader of the Dementia Research Project was selected as a 2022 Clarivate Citation Laureate. Clarivate Citation Laureates are candidates considered likely to win the Nobel Prize in their respective fields. His paper on TDP-43, a causative factor for neurodegenerative diseases and dementia published in 2006, was cited more than 2000 times and is in the top 0.1% of high-impact papers. We are very pleased that his long-term research on the pathology and molecular basis of neurodegenerative diseases has been recognized. Dr. Hasegawa continues to uncover basic mechanisms of disease development and expansion, and applies these findings to the development of novel drugs and therapies for treating people with dementias (see also page 16).

We are currently in the third year of the 4th project term, and we have started a "Frontier Research Laboratory" program in which young researchers in the institute can conduct independent research projects. Dr. Shinobu Hirai has been selected to head the first Frontier Research Laboratory with a new research team, and we are eager to expand this program in the coming years.

The Coronavirus pandemic has prevented many activities and forced many events to be on-line. Scientific interactions with other institutes were limited, and we had not been able to invite outside visitors. However, the situation improved much in 2022, and many seminars and public lectures were conducted in a hybrid manner, allowing both in-person and on-line interactions (see page 60).

On December 6, 2022, we were able to host the 23rd TMIMS International Symposium, "New Frontiers in the Ubiquitin Proteasome System" (organized by Dr. Yasushi Saeki of the Protein Metabolism Project). We invited 7 prominent scientists from abroad who are leaders in the field. During the one-day meeting, these scientists as well as 6 invited speakers from within Japan and 7 in-house speakers gave talks in the auditorium. There were heated questions and answers for every talk, and the meeting was followed by a reception with much further discussion. It had been three years since the last TMIMS international symposium, and we all thoroughly enjoyed face-to-face interactions.

Two years ago, we created a program for inviting prominent foreign scientists to visit and work at the institute for up to one year. However, we had not been able to put this program into action because of the pandemic. For the first time in 2022, we decided to invite three foreign scientists through this program, and Dr. Gemma Knowles (King's College London invited by Dr. Atsushi Nishida) visited our institute last year. Next year more scientists will visit us through this program.

We have continued to develop pan-vaccines against SARS-CoV-2 and conduct basic research to clarify mechanisms of

infection and develop new drugs against infections. We have also contributed to policy-making by the Tokyo Metropolitan Government by providing social dynamics data.

Research achievements from our institute in 2022

We had numerous notable findings from this institute in 2022. Dr. Taku Miyagawa in the Sleep Research Project discovered an association between a genetic variant of the orexin gene and idiopathic hypersomnia. This genetic variation occurs at the cleavage site on pre-pro orexin, and the variant showed a significantly reduced cleavage rate. The uncleaved polypeptide is less functional than the cleaved peptide, thus reducing the signal transduction efficiency through the orexin receptor. This is the first time that a significant risk factor for idiopathic hypersomnia has been identified, and this work provides a breakthrough in clarifying the mechanism of this disease. The finding was reported in npj Genomic Medicine (page 12). The Circadian Clock project (led by Dr. Hikari Yoshitane) identified a mechanism that stabilizes the circadian timekeeping system in mammals through rhythmic transcription of Bmal1. These results were published in Nature Communications and show how circadian clock regulation may be maintained robustly. Dr. Kosuke Tanegashima of the Stem cell project (led by Dr. Takahiko Hara), in collaboration with Dr. Hitoshi Okamura's group at Kyoto University, found that expression of CXCL14, a chemokine, is regulated in a circadian manner. They further found that CXCL14 regulates innate immunity and functions to protect animals from bacterial skin infections. Overall, their results demonstrate that CXCL14-controlled innate immune responses are more robust during circadian periods when animals are asleep or inactive compared to when they are awake and active. These findings were reported in the Proceedings of the National Academy of Science of the United States of America (PNAS), and are described in further detail in an interview article (page 14). Dr. Tsuyoshi Takahashi and Yuichiro Miyaoka in the Regenerative Medicine Project analyzed gene editing at a single-cell level. They found that gene editing either occurred in all alleles in a cell or in none. These findings revealed novel aspects of gene editing and were reported in iScience. Other interesting papers published this year are listed on our Home Page (https://www.igakuken.or.jp/topics/topics2022.html).

Science in 2022

The 2022 Nobel Prize in Physiology or Medicine was awarded to Swedish paleogeneticist Svante Paabo for his discoveries on the genomes of extinct hominins and in human evolution. Dr. Paabo sequenced the genome of Neanderthals, an extinct relative of Homo sapiens, and found that DNA sequences from Neanderthals were more related to sequences from present-day humans originating from Europe or Asia than to sequences from present-day humans from Africa. Dr. Paabo also discovered a previously unknown hominin, Denisova, from the Denisova cave in southern Siberia, whose genome is distinct from those of Neanderthals or Homo sapiens. He concluded that gene transfer took place from these now-extinct hominins to Homo sapiens. Homo sapiens are known to have first appeared in Africa around 300,000 years ago. They expanded out of Africa around 70,000 years ago, and coexisted with the Neanderthals in Eurasia for tens of thousands of years. During their millennia of coexistence, Homo sapiens interbred with both Neanderthals and Denisovans, and around 1% to 4% of the genome of present-day humans with European or Asian origins is derived from Neanderthals. How we, humans, have evolved on this planet earth is a mind-provoking question. With new technology, it has now become possible to experimentally examine the evolutional path of human beings.

Science in Japan

We hear much these days about the declining strength of scientific research in Japan. In 2000, Japan ranked 4th in countries with the most top 10% publications with 7.3%. In 2010, Japan ranked 7th with 5.5%, and in 2020, 12th with 4%. During this period, China moved from 13th to 3rd to first. In the last 20 years, government research support increased by 20-fold in China (60 trillion yen) and doubled in the USA (70 trillion yen), while it increased by only 20% in Japan (17 trillion yen). Besides problems with funding, it appears that in Japan, being a scientist is not a very attractive carrier choice. Many aspiring young scientists have a hard time getting by in temporary positions and are forced to give up their careers as researchers. Young graduate students in Japan cannot see much of a bright future in pursuing academic careers.

Japan has produced 27 Nobel laureates in the sciences and is ranked No.7 in the world. We've had 22 recipients since 2000 and are one of the top 3 countries in this regard. This achievement is mainly due to the strong support by the Japanese government for the basic sciences for last more than 40 years. The tree of science cannot grow without thick roots in the ground. The thick roots are the basic sciences that feed nutrients to the tree, which then produces ripe seeds. During hard times, the branches and leaves may be blown away, but the trunk will stay, as long as the roots are solid, and the tree will be able to yield seeds in the future. If the roots are fragile, the tree will not last, even though the seeds look ripe. We need to protect and expand the roots. Basic sciences need to be protected and grown even when seeds seem to be in the distant future. The current trend in Japanese science policy is to look for seeds instead of nurturing the basic sciences. Without watering the roots, the seeds will die, and the tree itself will wither away. I strongly urge the Japanese government to increase support for all aspects of the basic sciences. Only the basic sciences will uncover the mysteries of nature that will bring us solutions that will revolutionize our lives.

Outlook for 2023

In 2023, we will continue to strive for creative discovery in various biomedical fields including protein metabolism, genome maintenance, brain functions and neurodegenerative diseases, sleep disorders, circadian rhythms/aging, addiction, antibody therapy, gene editing, mental diseases, viral infections and so forth. Our findings should lead to improved prediction, diagnoses, and treatments for diseases.

With decreases in coronavirus severity and deaths, I hope our way of life will be more normal this year. That said, we will continue our efforts to develop more versatile vaccines that will respond even to new variants of COVID-19 and to other unpredictable emerging viruses/pathogens, and to establish a common platform for vaccine development. We will also continue to support the Tokyo Metropolitan Government by providing information and medical technology to aid in policy-making.

I hope that the atrocities and tragedies of 2022 will be mitigated in 2023 and we will be living on a more peaceful planet.

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 19th 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 18th 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 19th 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. Kohji Kasahara has found a clue for potential novel drugs targeting a glycolipid molecule his group found to be important for SARS-CoV-2 infection. 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).

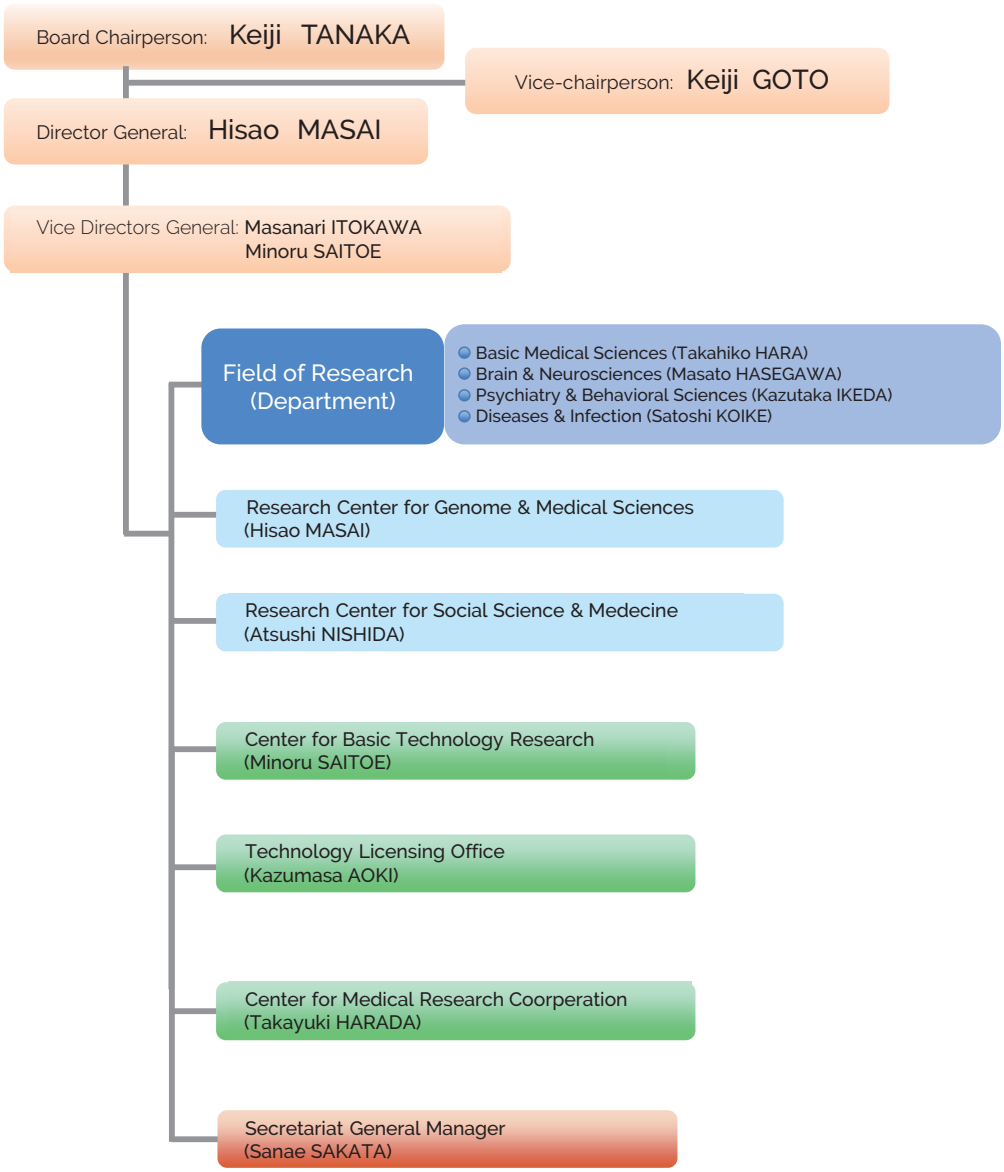
We, TMIMS COVID-19 team, are confronting against SARS-CoV-2 to protect the people's life and health in Tokyo by using scientific research and technologies as descendants of the Samurai-Scientists.

References

1. Sanada T, Honda T, Yasui F, 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* 2(2):105-111. 2022
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

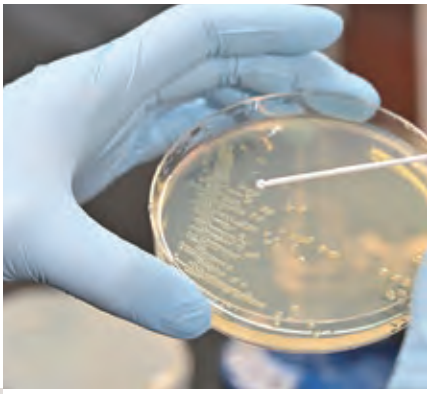


Our People at a Glance

Position	Number
Researchers	152
Postdoctoral Fellows	69
Students	157
Visiting Scientists	137
Guest Scientists	141
Administrative Staffs	33
Total	689

February 1, 2023

Meet our scientists!



Meet Our Scientists!

Inflammation is a critical immune response to attacks from bacteria, viruses, and other harmful substances. It functions to eliminate these harmful substances and clear out dead and damaged tissue. However, inflammation also has deleterious effects on the body. For example, neuroinflammation contributes to the severity of many neurodegenerative diseases. Thus, it is crucial to understand the molecular and cellular pathways causing inflammation. One of the goals of the Visual Research Project, led by Takayuki Harada, at TMIMS is to better understand diseases such as glaucoma or multiple sclerosis (MS) in order to develop more effective treatments. Previously, members from this project, including Xiaoli Guo, discovered that knocking out apoptosis signal-regulating kinase 1 (ASK1), a gene implicated in neuroinflammation, decreases the severity of a mouse model of MS. More recently, Guo and her colleagues identified the cell types and cellular and molecular interactions necessary for ASK1's role in inducing neuroinflammation in MS. This work, "ASK1 signaling regulates phase-specific glial interactions during neuroinflammation," was published in the Proceeding of the National Academy of Science, USA (Proc Natl Acad Sci U S A. 2022 Feb 8;119(6):e2103812119. doi: 10.1073/pnas.2103812119). We spoke to Dr. Guo about her work and her interest in science.

Xiaoli Guo

How did you become interested in science?
I was born in the countryside in China. We were very poor, so we had to be very self-sufficient. We grew our own crops and raised farm animals such as chickens and pigs for food. I think I naturally became interested in biology because I was exposed to animals and living things from such an early age.

Why did you decide to pursue research in Japan?
When I was a master's student in China, I came to Japan as an exchange student between universities. I enjoyed it so much that I applied for a scholarship from the Japanese government and came to Japan for my Ph.D. I later pursued post-doctoral work in the United States, but I missed my husband in Japan, so I returned here after my post-doc and joined Dr. Harada's lab at TMIMS, since I enjoy working on visual systems and neurodegenerative diseases.

Could you explain your latest publication on ASK1 and neuroinflammation?
In 2010, we published a paper on the role of ASK1 in experimental autoimmune encephalomyelitis (EAE), a mouse model for MS. MS is an inflammatory autoimmune disease characterized by demyelination of neurons. EAE is a classic model for MS that is generated by injecting a myelin basic protein peptide into mice to generate an autoimmune response to myelin. Similar to MS, EAE induces demyelination of neurons, severe neuroinflammation, and neuronal death. We found that knocking out ASK1 decreases EAE symptoms, but we didn't know exactly why this happened. We didn't know the cell types where ASK1 was activated, and we didn't know the pathway through which ASK1 affects the severity

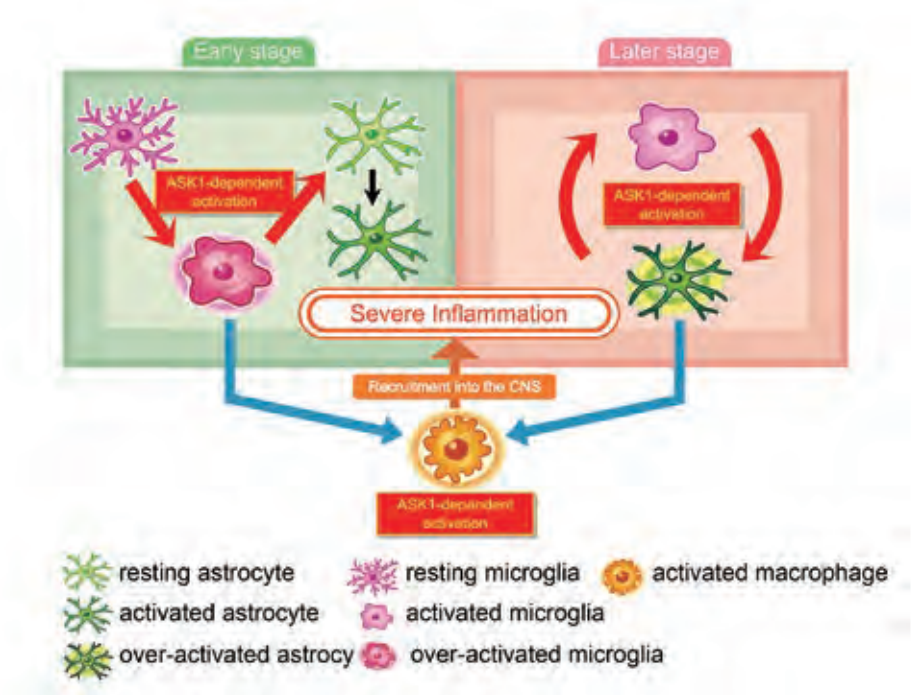
of EAE. ASK1 is also involved in other neurodegenerative diseases including glaucoma, amyotrophic lateral sclerosis, Alzheimer's disease, and Parkinson's disease, so understanding how ASK1 induces inflammation should be important for developing treatments for many diseases.

In our current paper, we worked to understand the cells and pathways that are activated by ASK1 to increase disease symptoms. Various types of immune cells are known to be involved in neuroinflammation, including T-cells, dendritic cells, microglia, macrophages, and astrocytes. We made conditional knockouts of ASK1 in each of these cell types to understand which cells need to express ASK1 to induce neuroinflammation. Altogether we found that ASK1 is needed in microglia early during EAE to start the inflammatory process, and then it's later needed in astrocytes to maintain inflammation. To start inflammation, many proinflammatory cytokine/chemokine signaling genes need to be expressed, and ASK1 in microglia is needed for this to occur. Activation of microglia in turn, activates astrocytes which are needed to maintain inflammation. We found that this interaction between microglia and astrocytes also requires ASK1 in both microglia and astrocytes. Without ASK1 in both cell types, activation of astrocytes doesn't occur. Altogether, we identified different cell interactions and molecular interactions through which ASK1 causes and maintains neuroinflammation. We hope to use this information to devise future strategies for treating neurodegenerative diseases.

What are your future plans?

We're interested in developing novel treatments for glaucoma and MS. To do this, we're pursuing three strategies. First, we're collaborating with a pharmaceutical company to evaluate the effects of ASK1 inhibitor treatments on MS and other diseases. Second, we're pursuing gene therapy approaches. In MS, myelin in oligodendrocytes is destroyed by autoimmune reactions. Using gene therapy, we plan to increase amounts of activated TrkB in oligodendrocytes to see if this induces remyelination. Third, we're examining cell replacement strategies using stem cells. I just came back from Kobe Eye Center, where I learned how to make retinal ganglion cells from stem cells. We plan on making retinal ganglion cells and oligodendrocytes from stem cells to determine whether addition of these cells may reduce disease symptoms. MS is an extremely painful disease for both patients and their families. My hope is to contribute to the development of new, good therapies to help these patients.

Interviewed by Jun Horiuchi



Schematic model of ASK1-mediated glial interaction during neuroinflammation.
Astrocytes and microglia activate each other in an ASK1-dependent manner. ASK1 signaling in microglia induces proinflammatory astrocytes in the early stage of EAE and ASK1 signaling in astrocytes induces proinflammatory microglia and recruit macrophages into the CNS in the late stage. ASK1-mediated activation of these glial cells causes sustained inflammation.

Meet Our Scientists!

Sleep is an essential part of our lives, but even now, we only have a limited understanding of why sleep is so important. What causes us to feel tired and fall asleep? Why do we feel so refreshed after waking? One way to understand sleep better is to identify biological pathways regulating sleep. Traditionally geneticists study mutants defective in a biological process and compare them to normal animals to identify mutations in genes important for that biological process. For example, narcolepsy type 1 is a neurological disease associated with defects in regulation of sleep-wake cycles. Narcolepsy has been shown to be caused by a defect in production of orexin-A, a neuropeptide that excites various brain nuclei to increase an animal's wakefulness. However, in contrast to narcolepsy, the causes of a different sleep disorder, idiopathic hypersomnia (IH), have been completely unknown. While narcolepsy patients tend to sleep for normal amounts of time and wake up refreshed after sleeping, IH patients suffer intolerable sleepiness in the daytime and tend to sleep much longer than normal. Taku Miyagawa, a staff scientist in the Sleep Disorders Project led by Makoto Honda, is interested in understanding the causes of IH. Interestingly, he found that a rare missense variant in the cleavage site of prepro-orexin is associated with IH. Thus, alterations in orexin signaling can be associated with two different sleep disorders, narcolepsy and IH. This work was published in a paper, "A rare genetic variant in the cleavage site of prepro-orexin is associated with idiopathic hypersomnia," (npj Genom.Med. 7, 29 (2022)). We spoke to him about his work.

Taku Miyagawa

How did you become interested in science?
When I was a child, I liked history rather than science. But in high school, most students picked physics or chemistry as their science class, so the biology class I picked was very small and comfortable. My high school biology teacher was fantastic and gave fascinating lectures which piqued my interest in human genetics, medicine, and disease. I thought about a career in medicine, but my mother, who was a nurse, discouraged me from becoming a doctor, so instead, I pursued my interest in genetic research.

Why did you start studying idiopathic hypersomnia (IH)?
I did my graduate work at Tokyo University, Department of Human Genetics, where I became interested in sleep disorders. Sleep is a big mystery. We spend roughly one-third of our lives sleeping, but no one really knows why. I performed genome-wide association studies to identify

narcolepsy-associated genes and I fortunately found one gene. However, many groups are studying narcolepsy, so I decided to change my target gene to IH, which few people are studying. Although narcolepsy and IH are both sleep disorders, they are different. Narcolepsy patients actually sleep for normal amounts of time. So, they might sleep for a total of about 7 hours per day and they wake up refreshed. On the other hand, IH patients sleep much more than normal, over 10 hours per day, but they're always tired. So the questions we have for each disease are different. For narcolepsy, we want to know why patients suddenly fall asleep. For IH, we want to know why patients have trouble sleeping even though they are tired, and why sleep doesn't cause patients to become refreshed. In many respects, IH may be a much more severe disease compared to narcolepsy.

Could you explain your 2022 Genomic Medicine paper?

In this paper, we found that orexin signaling is involved in IH. Reductions in orexin signaling are well-known to cause narcolepsy; narcolepsy in dogs can be caused by mutations in an orexin receptor, and narcolepsy in humans is caused by the death of orexin-producing cells. On the other hand, IH was thought to be caused by a different mechanism because amounts of orexin in the cerebrospinal fluid of IH patients are relatively normal, and because the two diseases have very different symptoms. However, when we sequenced the orexin and orexin receptor genes in IH patients and controls, we found that the frequency of a rare missense variant in the prepro-orexin gene was significantly higher in IH patients. Mature orexin is produced by cleavage of a longer prepro-orexin peptide, and we found that the cleavage efficiency of the rare variant was lower than that of wild-type. Further, we found that activation of orexin receptors by uncleaved prepro-orexin is decreased relative to activation by mature orexin peptides. Overall, our results demonstrate that at least some types of IH are associated with decreased orexin signaling.

Narcolepsy and IH have very different phenotypes. Why do you think two very different diseases can result from abnormalities in the same sleep pathway?

I think IH results from a partial reduction in orexin signaling, while narcolepsy is caused by a complete or almost complete reduction. 100% reductions lead to narcolepsy, while lesser 50% reductions may be associated with IH.

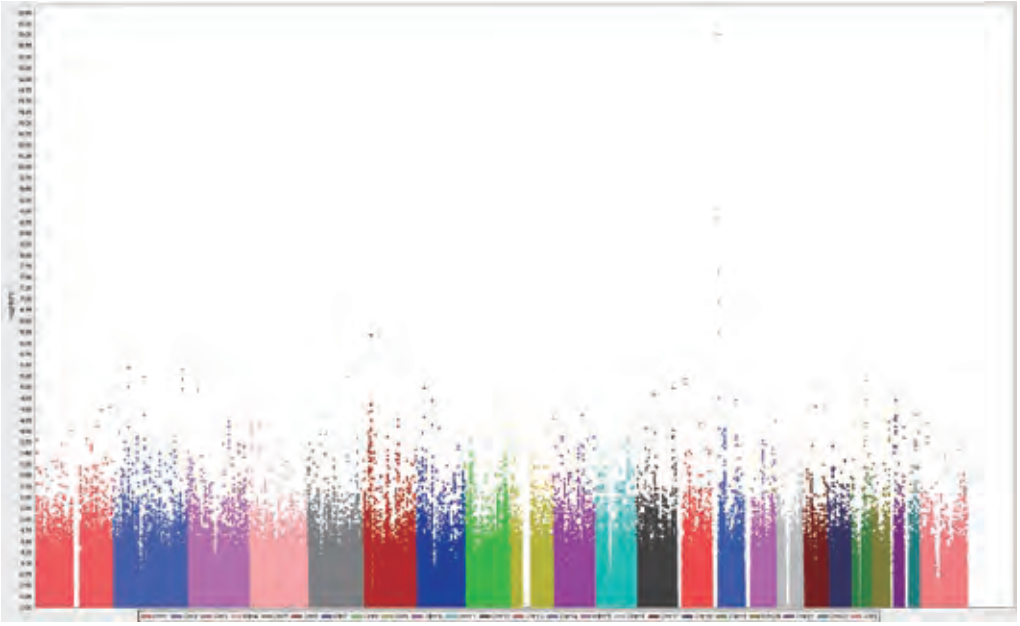
Do you think treating IH patients with orexin antagonists could make them more like narcolepsy patients and resolve their tiredness?

That's an interesting idea. I know that many pharmaceutical companies are trying the opposite idea. They are trying to produce orexin agonists that will increase wakefulness.

How do you plan to continue your experiments in the future?

In our previous paper, we looked for mutations and variants in the orexin pathway. In the future, I'd like to look for completely novel mutations associated with IH using genome-wide studies. From this, we should be able to identify new pathways involved in sleep disorders.

Interviewed by Jun Horiuchi



Manhattan plot of a genome-wide association study of narcolepsy

Meet Our Scientists!

A lot of research has focused on antibodies and adaptive immunity, especially recently because of the coronavirus pandemic. However, innate immune responses are also fascinating to study. They attack foreign invaders very quickly although they have less specificity than antibodies. Recently, Kosuke Tanegashima, a staff scientist in the Stem Cell Project, led by Takahiko Hara, identified a novel innate immunity mechanism that is regulated in a circadian manner. Immune responses are greater during an animal's subjective nighttime, when they are inactive, compared to their subjective daytime, when they are active. His work was published in a paper, "Circadian protection against bacterial skin infection by epidermal CXCL14-mediated innate immunity," in the Proceeding of the National Academy of Science, USA (Proc Natl Acad Sci U S A. 2022 Jun 21;119(25):e2116027119. doi: 10.1073/pnas.2116027119. Epub 2022 Jun 15). We spoke to him about his interest in science, his research, and why he thinks it makes sense for some immune responses to be regulated in a circadian manner.

Kosuke Tanegashima

How did you first become interested in science?

I've been interested in science for as long as I can remember. My father used to grow plants and crops in our backyard, and when I was a child, I dug up these plants to see their roots and flower bulbs. I wanted to see how plants grow and develop. I think this initial interest led me to pursue developmental biology using molecular biology in college and postdoctal study. I later switched to studying immunology since I thought molecular biology that I learned could be applied to the medical sciences. My current work on CXCL14 is particularly interesting to me since it has both medical implications and involves elucidating novel mechanisms of activation of innate immune responses.

Could you explain your recent work on innate immune responses?

In our paper, we describe a novel innate immunity mechanism that the epidermis uses to recognize proliferation of Staphylococcus aureus. S aureus is a bacterium that is normally found on the skin, but it can become pathogenic, causing infections and diseases under a certain circumstances. We were studying a chemokine called CXCL14. Chemokines are small, secreted proteins that cause inflammation by recruiting immune cells to sites of infection or injury. However, even though I tried for a long time, I just couldn't detect inflammatory responses when I added CXCL14 to cultured cells. So, I thought that there may be some cofactor that needs to bind to CXCL14 to induce inflammation. Since

CXCL14 is a highly basic protein, I thought this cofactor could be DNA, which is acidic. This idea turned out to be correct, and we found that CXCL14 collaborates to certain types of DNA, and this binding is needed to cause inflammation and activate innate immune responses. Interestingly, CXCL14 collaborates to S aureus DNA but not E coli DNA. S aureus is found mainly on the skin, while E coli is found mainly in the gut, so CXCL14 binding specificity could have evolved to predominantly recognize DNA from bacteria found on the skin.

How is this innate immune response regulated by circadian rhythms?

Dr. Hitoshi Okamura's group at Kyoto University independently found that CXCL14 is expressed in the skin in a rhythmic, circadian fashion, but he didn't know its function. When we found out about each other's work, we decided to collaborate, and we discovered that CXCL14 induces inflammation and immune responses to S aureus infections in a circadian manner. Mice are active during the night and sleep during the day, while marmosets are active during the day and sleep during the night. In mice, CXCL14 is high during the day when they are inactive and low during the night when they are active. Similarly, CXCL14 is high at night in diurnal marmosets when they are asleep and low during the daytime when they are active. We found that mice are more resistant to infection by S aureus during the day when CXCL14 is high compared to the nighttime when CXCL14 is low. Similarly, we'd predict that diurnal animals including human should be more resistant to S aureus infections at night compared to daytime.

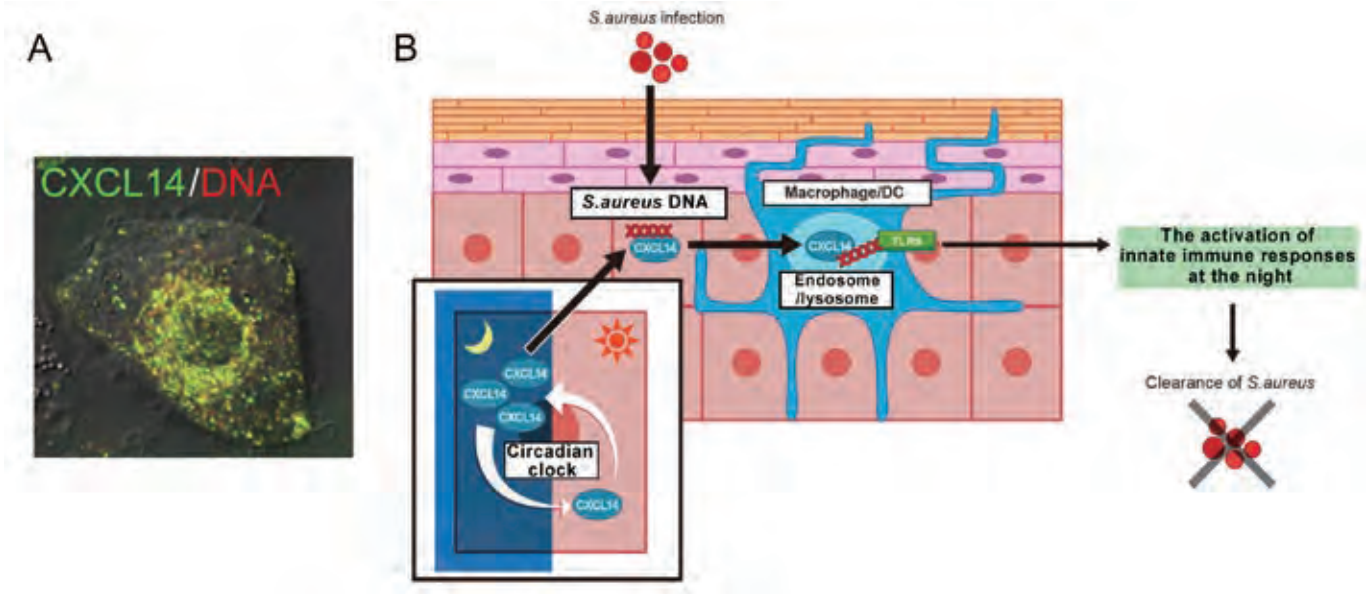
That's fascinating! Why do you think immune responses oscillate in a circadian manner?

We haven't proven this, but this is what I think. We have a limited amount of energy. When we are awake, we participate in many activities that require a lot of energy, such as running or thinking or digesting. Immune responses also require a lot of energy. When we are resting, we don't have to use energy for activities such as searching for food, eating, or running, so energy is available for immune responses. So, I think it's reasonable that during subjective nighttime, energy is directed toward activities such as tissue repair and immune responses. For really severe infections where you sleep during the day, maybe other mechanisms besides CXCL14 compensate to increase immune responses during normally active times.

What do you plan to do in the future?

I'm very interested in understanding how cells sense DNA. DNA is a very common substance, and represents the nature of living organisms. But we don't know how immune cells recognize and deal with DNA. It's a completely unknown field. So far, I've found that CXCL14 binds to S aureus DNA, and this CXCL14 DNA complex is somehow recognized by immune cells to induce immune responses. However, we don't know what receptor recognizes this CXCL14-DNA complex. I've been looking for this receptor by screening using expression cloning and I've found several candidates that I'm excited about studying.

Interviewed by Jun Horiuchi



(A) A fluorescent image that shows CXCL14/DNA complexes incorporated into dendritic cells. (B) A schematic model of circadian clock-mediated clearance of S. aureus by CXCL14. Expression of the Cxcl14 gene in epidermal keratinocytes is regulated by circadian rhythms. When S. aureus invades skin keratinocytes, CXCL14 binds to bacterial DNA and transports it into dendritic cells (DCs) and macrophages to activate innate immune defenses against the bacteria.

Meet Our Scientists!

Masato Hasegawa

This year, we were thrilled that Dr. Masato Hasegawa, the head of the Dementia Research Project, was selected as a Clarivate laureate. Clarivate laureates are chosen among scientists who publish highly cited, high-impact papers that strongly influence research in their respective fields, and laureates are leading candidates for being awarded the Nobel Prize. Dr. Hasegawa was chosen based on his 2006 paper, "TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis," as well as his continuing work on the propagation of neurodegerative diseases.

Neurodegenerative diseases can be separated into several different classes. For example, tauopathies including diseases such as Alzheimer's disease, Pick's disease, corticobasal degeneration, and progressive supranuclear palsy, are characterized by cytoplasmic inclusions containing insoluble tau aggregates, while synucleinopathies including diseases such as Parkinson's disease and dementia with Lewy bodies, are characterized by inclusions containing α-synuclein aggregates. In his landmark paper, Dr. Hasegawa and colleagues determined that insoluble aggregates of a protein known as TDP-43, compose a third class of neurodegenerative disease which include frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). Thus, three major pathogenic proteins, tau, α-synuclein, and TDP-43 are involved in major neurodegenerative diseases.

Dr. Hasegawa has studied these three proteins throughout his career in order to determine the difference between normal and abnormal versions, and elucidate how abnormal versions aggregate, accumulate in the brain, and spread to different regions of the brain. Early in his career, he characterized alterations in phosphorylation and ubiquitination in abnormal proteins and later helped propose the influential "prion-like propagation" hypothesis where abnormal proteins serve as seeds or templates that convert normal proteins to aberrant forms which then multiply and spread throughout the brain. To support this hypothesis, Dr. Hasegawa showed in multiple studies, both *in vitro* and *in vivo*, that normal proteins on their own very rarely convert to abnormal forms, while addition of a tiny amount of abnormal protein results in a much faster conversion to abnormal forms. The prion-like propagation hypothesis is currently the predominant theory for explaining disease progression. Dr. Hasegawa further

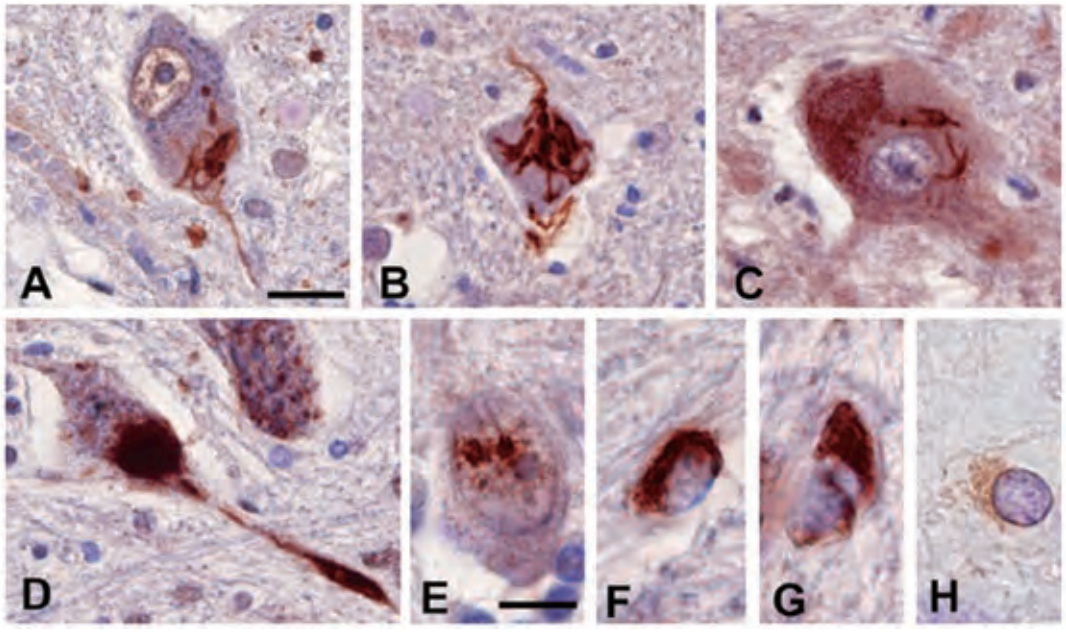
showed that abnormal proteins spread through neuronal connections during disease progression.

What causes the differences between individual neurodegenerative diseases? There are at least ten distinct diseases associated with abnormal tau. Dr. Hasegawa and colleagues determined that different tauopathies were associated with different morphological tau filaments, and inoculating mice with different filaments induced pathologies characteristic of different diseases. He further collaborated in elucidating the crystal structures of tau filaments from different tauopathies and determined that different diseases had completely distinct filamentous structures.

Dr. Hasegawa's work has contributed much to our understanding of the mechanisms that cause and propagate neurodegenerative diseases. While we do not yet have effective treatments to treat these diseases, elucidating mechanisms of disease progression is the first step in this process, and through his work and that of other scientists, we can hope for the development of effective treatments in the near future.

(Written by Jun Horiuchi)

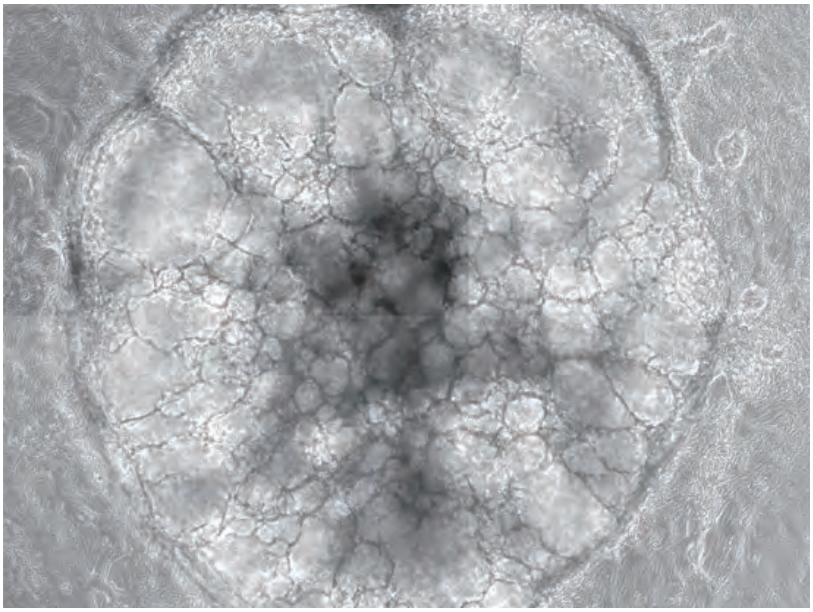
TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis

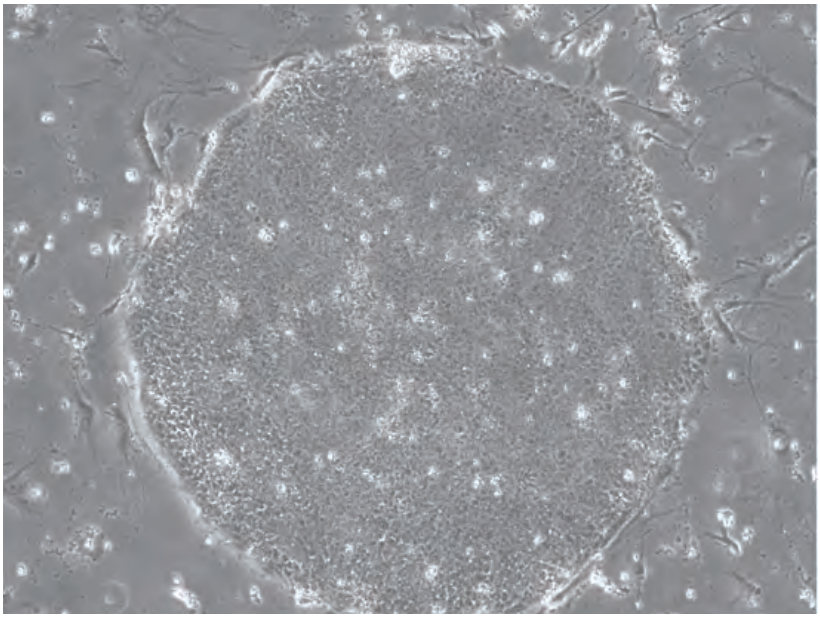


Our Goal

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





Pluripotent Human iPS cells (upper) and organoid derived from differentiated iPS cells (lower)

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 enviroment-adaptive mode of DNA replication, how various stresses arrest DNA replication causes cancer, how replication is coordinated with developmental processes, and how unusual nucleic acid structures and their interactions with specific proteins and membranes shape chromosomes, copy and read genetic information, and how failures of these processes cause detrimental diseases.

Genome Dynamics

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

Staff

Senior Researcher
Hiroyuki SASANUMA

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

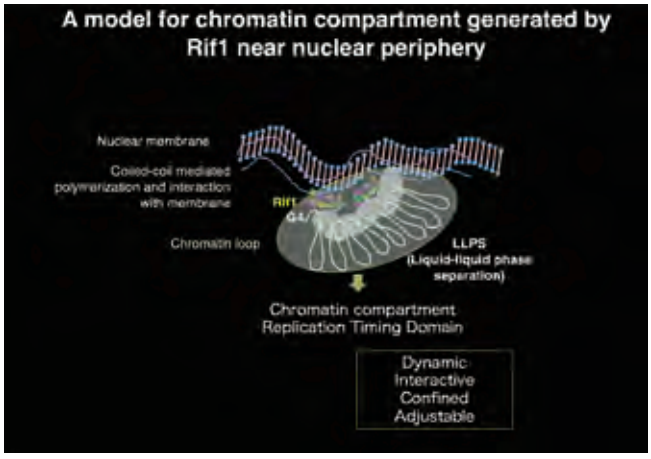
Research Assistants
Naoko KAKUSHO
Rino FUKATSU
Akiko MINAGAWA

Students
Karin HORI
Tomoko SAGI
Hao-Wen HSIAO
Trinh Thi To NGO
Maho SASHIDA
Zheng WENXIN
Bayrak MELIH
Ayaka ONUKI
Kosuke YAMAZAKI
Kanna HOTTA
Tatsuki FUKUSHIMA
Keisuke KATSUKI

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 various biological stresses induce replication checkpoint and how does it affect genome stability and potentially cause cancer?
4) What are the roles of replication and checkpoint factors in developmental processes?
5) How have replication systems evolved and diversified in response to changing environments?
6) How can we develop effective cancer therapies targeting replication/ checkpoint factors?



A model for chromatin compartmentalization generated by Rif1 near nuclear periphery. Rif1 protein binds to G4 structures in chromatin and promotes chromatin loop formation through oligomerization. Rif1 also binds to nuclear membranes 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

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

Yang and Masai (2023) "Claspin is required for growth recovery from serum starvation through regulating the PI3K-PDK1-mTOR pathway in mammalian cells." ***Mol. Cell. Biol.*** 43(1): 1-21.

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): 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
Shumpei YASUDA
Yuta SEKI

Research Assistants
Ai TAKAHASHI
Ting MAO
Ornjira PRAKHONGCHEEP

Students
Xuehan HOU

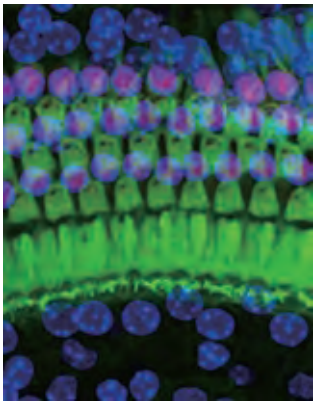
Research Summary

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

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

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

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

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

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

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

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

Project Leader
Yasuko ONO

Calpain

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

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

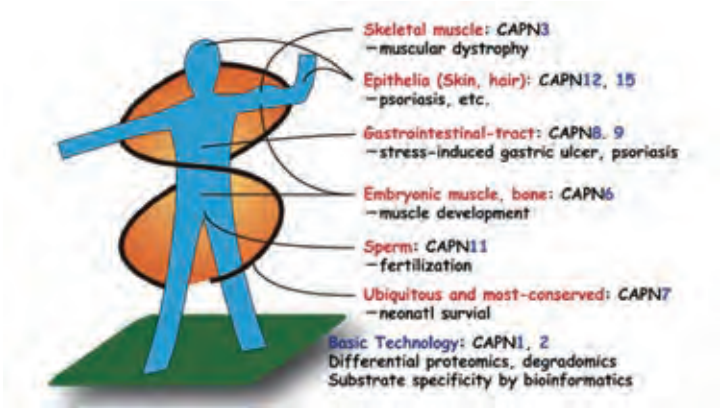
Staff

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

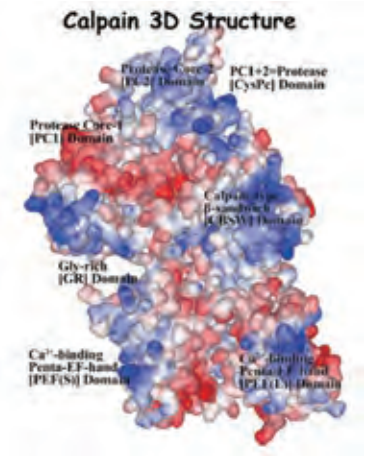
Research Assistants
Naoko DOI

Research Summary

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



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



Selected Publications

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

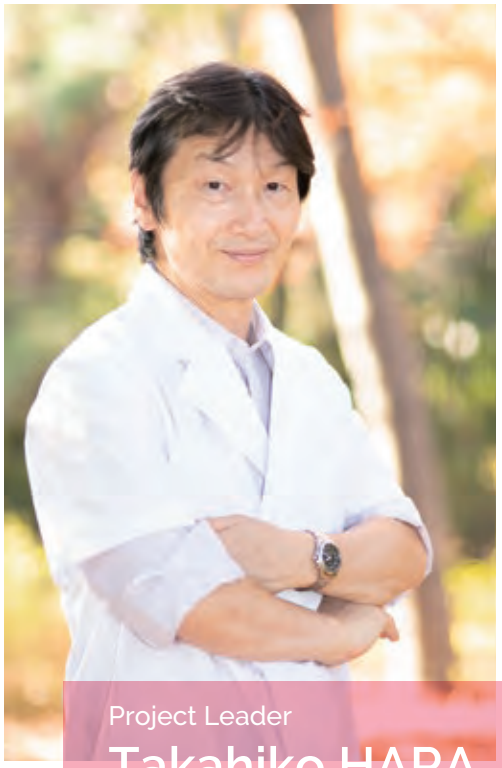
Hata S, et al. (2020) "A muscle-specific calpain, CAPN3, forms a homotrimer." ***Biochim. Biophys. Acta, Proteins Proteomics***, 7: 140411.

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

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

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

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



Project Leader
Takahiko HARA

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

Stem Cell

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

Staff

Researchers
Kenji KITAJIMA
Kosuke TANEGASHIMA
Teruhiko SUZUKI
Masatoshi MURAOKA

Research Assistants
Tsuruyo TANIGUCHI

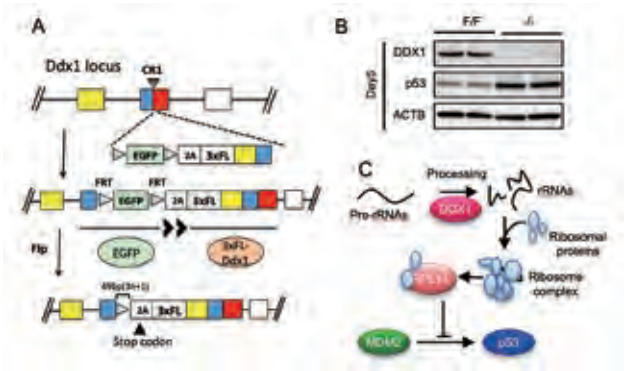
Students
Satoko TAKAGI
Shota HOYANO
Risa SAITO
Shiho SASAKI
Minako SHINGAI
Fumiya SEKI
Hikaru ANDO
Riku TAKAHASHI

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

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

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

Researchers
Yukiko YOSHIDA
Akinori ENDO
Hikaru TSUCHIYA
Takuya TOMITA
Daiki KINOSHITA
Emeritus Researcher
Hiromichi YONEKAWA
Visiting Scientists
Fumiaki OHTAKE
Sayaka YASUDA
Yosuke DEMIZU
Gosuke HAYASHI

Supervisor
Keiji TANAKA
Research Assistants
Naoko ARAI
Sayaka ONO
Chikage TAKAHASHI
Chikara ANDO
Meari YOSHIDA-OKADA
Harumi SETO
Kyoko UEDA

Students
Kota NAKADAI
Liu DONGQI
Takuro SUGIMOTO

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

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.

Circadian Clock

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

Staff

Researchers
Nobuhiro KURABAYASHI
Naomi NIHONMATSU
Tomoko TANAKA
Shingo HIROKI
Yuki KATO
Kyohei UEMOTO

Research Assistants
Arisa KURABAYASHI

Visiting Scientist
Yoshitaka FUKADA
Miho YOSHIMURA

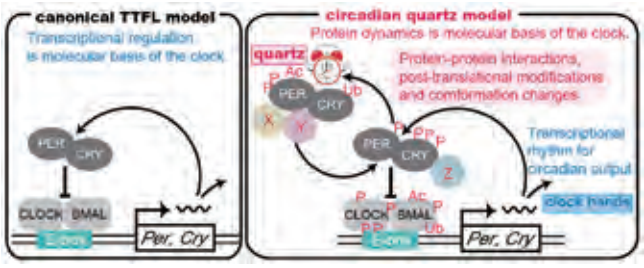
Students
Yuta OTOBE
Satoshi KAWAKAMI
Etsuko MITSUYOSHI
Shunsuke ITO
Taiki MORIMURA
Suzune ANDO

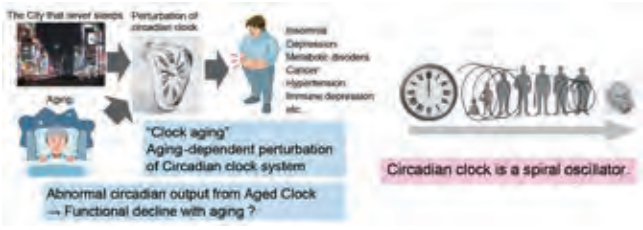
Research Summary

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

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

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





Selected Publications

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

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

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

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

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

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

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

Laboratory Head
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
Kiyoshi OGURA
Tetsuya HIRABAYASHI
Keisuke KOMATSUYA
Norihito KIKUCHI

Students
Mai KAWAGUCHI
Tatsuki ANJO

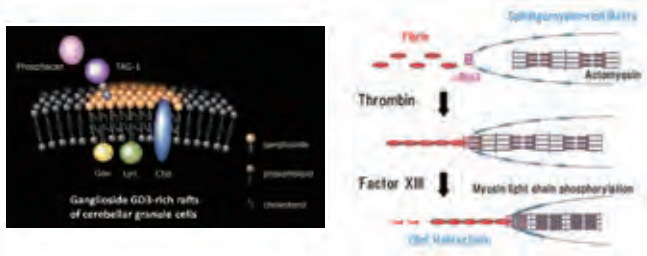
Research Summary

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 (CGC) 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 CGC. 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 CGC. Phosphacan, a chondroitin sulfate proteoglycan, acts as a barrier to migration of TAG-1-expressing CGC.

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 α IIbβ3-myosin axis in sphingomyelin-rich membrane rafts that is important in clot retraction.



Selected Publications

Komatsuya K et al. (2022) "Phosphacan acts as a repulsive cue in murine and rat cerebellar granule cells in a TAG-1/GD3 raft-dependent manner" ***J Neurochem*** 163(5) 375-390.

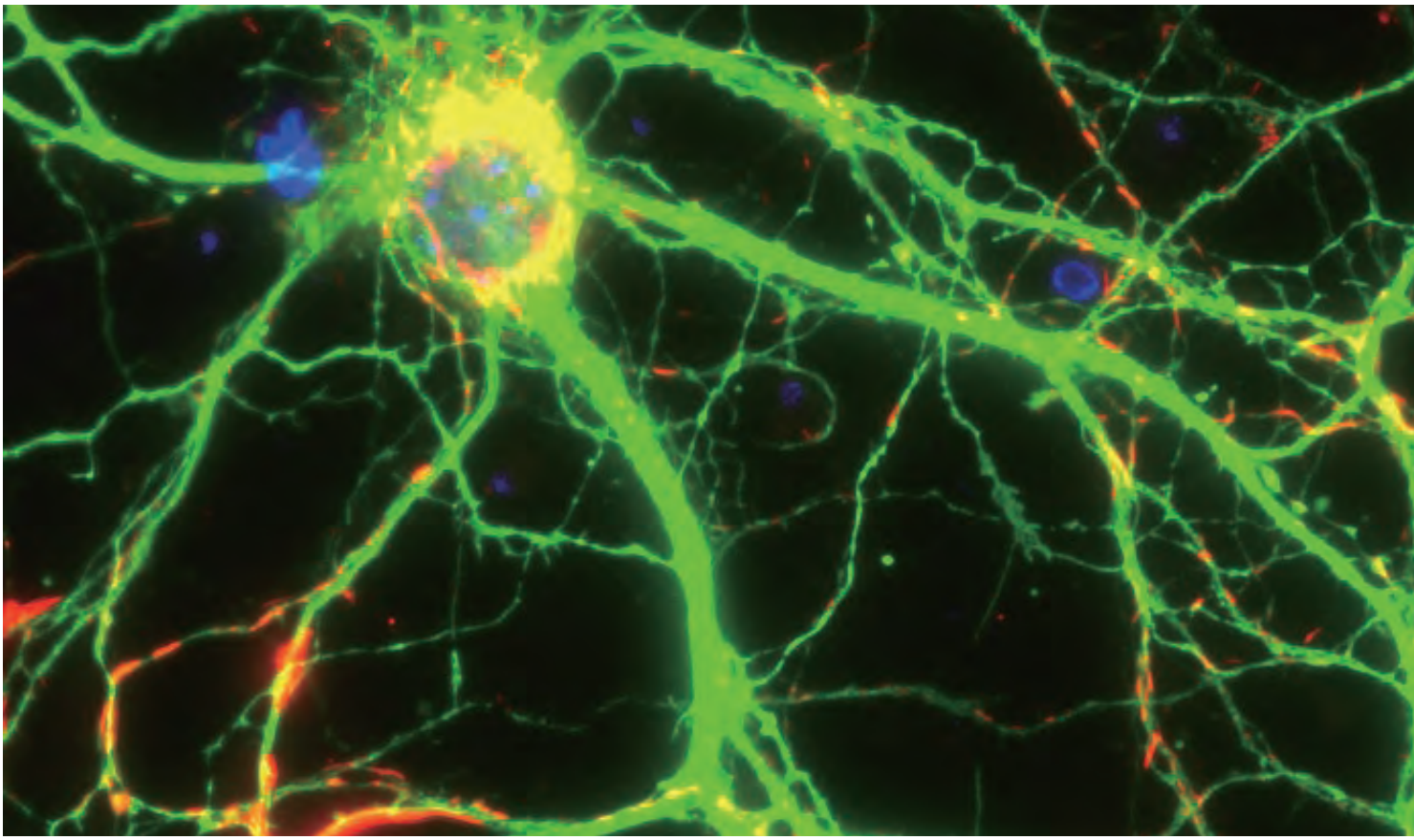
Komatsuya K et al.(2020) "Function of Platelet Glycosphingolipid Microdomains/Lipid Rafts." ***Int. J. Mol. Sci.*** 21(15) :5539.

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.



Primary-cultured cells treated with α-synuclein pre-formed fibrils were stained with anti-tau (green) and anti-phosphorylated α-synuclein (red). Nuclei were stained with DAPI (blue).

Brain & Neurosciences

Project Leader
Masato HASEGAWA

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

Dementia Research

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

Staff

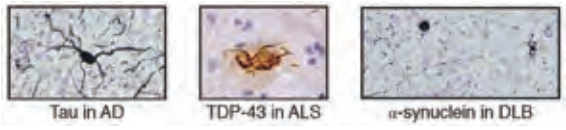
Researchers
Takashi NONAKA
Genjiro SUZUKI
Yoshiki TAKAMATSU
Masami SUZUKAKE
Fuyuki KAMETANI
Ito KAWAKAMI

Research Assistants
Reiko OOTANI
Marina TAHIRA

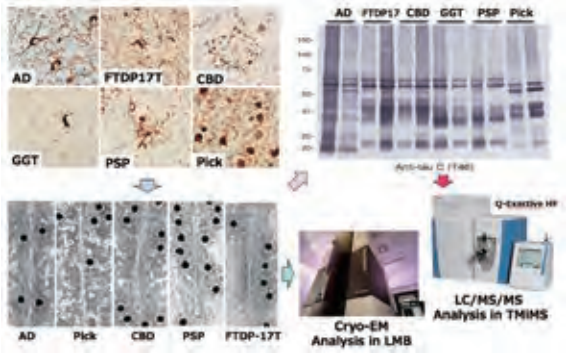
Students
Mina TAKASE
Shohei TAKAKI
Yuta SATO
Syunsuke KANNO

Research Summary

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



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



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

Selected Publications

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

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

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

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

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

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

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

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

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

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

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

Project Leader

Minoru SAITOE

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

Learning and Memory

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

Staff

Researchers
Kohei UENO
Tomoyuki MIYASHITA
Motomi MATSUNO
Shintaro NAGANOS
Yoshinori SUZUKI
Takahiro ISHIKAWA

Postdoctoral fellows
Hiroshi KUROMI

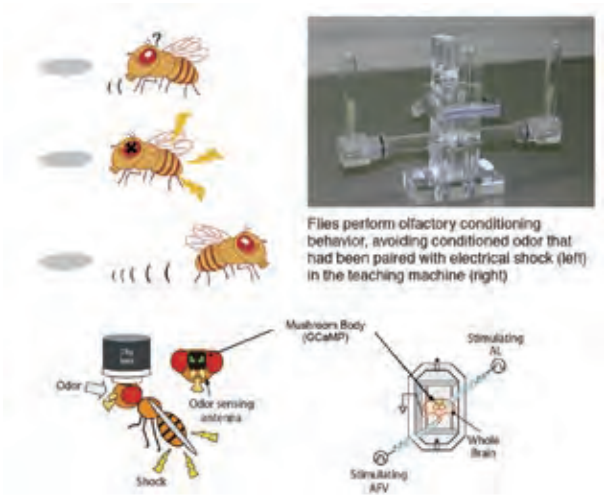
Research Assistants
Saki KOMIYA
Takae HASEGAWA
Tomoko TAKAMISAWA
Kayoko GOTO
Yayoi ONODERA

Students
Maximiliano Martinez-Cordera
Hinako MURATANI

Research Summary

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

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



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

Selected Publications

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/

Staff

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

Postdoctoral fellows
Noboru USUDA
Hikaru NAKAGAWA

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

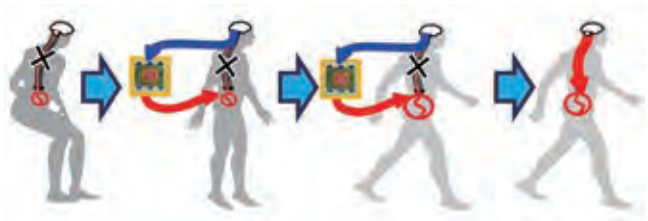
Students
Kei OBARA
Kouichi URAMARU
Kokoro KAWAMURA

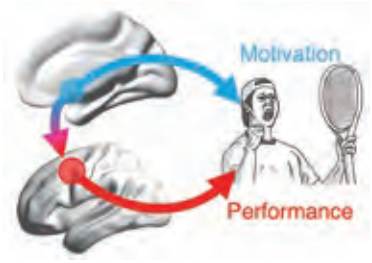
Research Summary

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

Child Brain

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

Staff

Researchers
Tadayuki SHIMADA
Kuniko KOHYAMA

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

Research Assistants
Mariko OZAKI

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

Research Summary

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

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

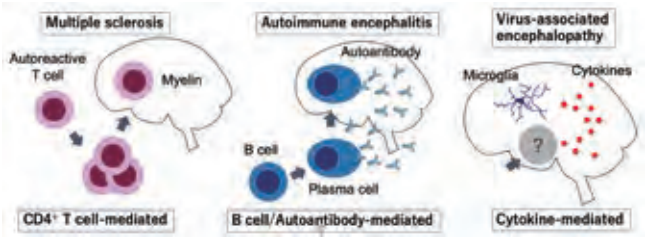


Figure Pathomechanisms of inflammatory and autoimmune neurological diseases
Multiple sclerosis has been regarded as CD4 T-cell mediated disease, in which autoreactive T cells are activated, proliferate, migrate into brain, and cause myelin damage. Autoimmune encephalitis is caused by autoantibodies against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

Selected Publications

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

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

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

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

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

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

Project Leader
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
Yumiko HATANAKA
Keiko MORIYA-ITO
Yasuhiro MATSUMURA

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

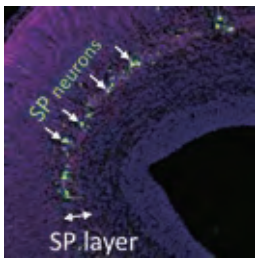
Students
Hitomi ACHIWA
Ayumu MORIOKA
Kyosuke WADA
Haruka NOMURA
Yusuke SUGITSA
Mayu OZAKI
Ryoka KATAYAMA
Xianghe SONG
Yurika NOGUCHI

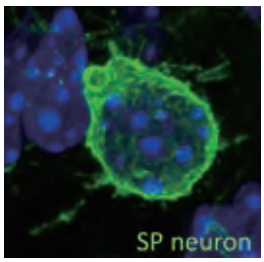
Research Summary

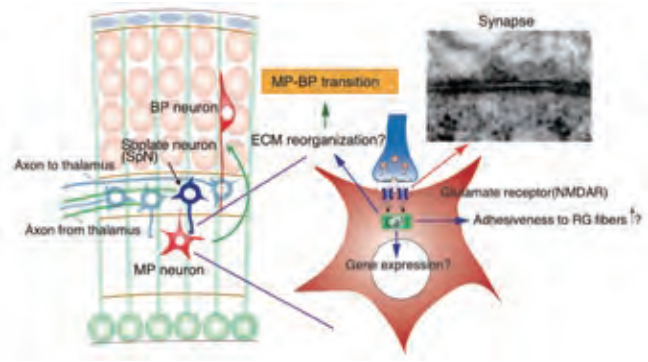
Mechanisms of Neural Network ormation: Neocortical development and synapse formation

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

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

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

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

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

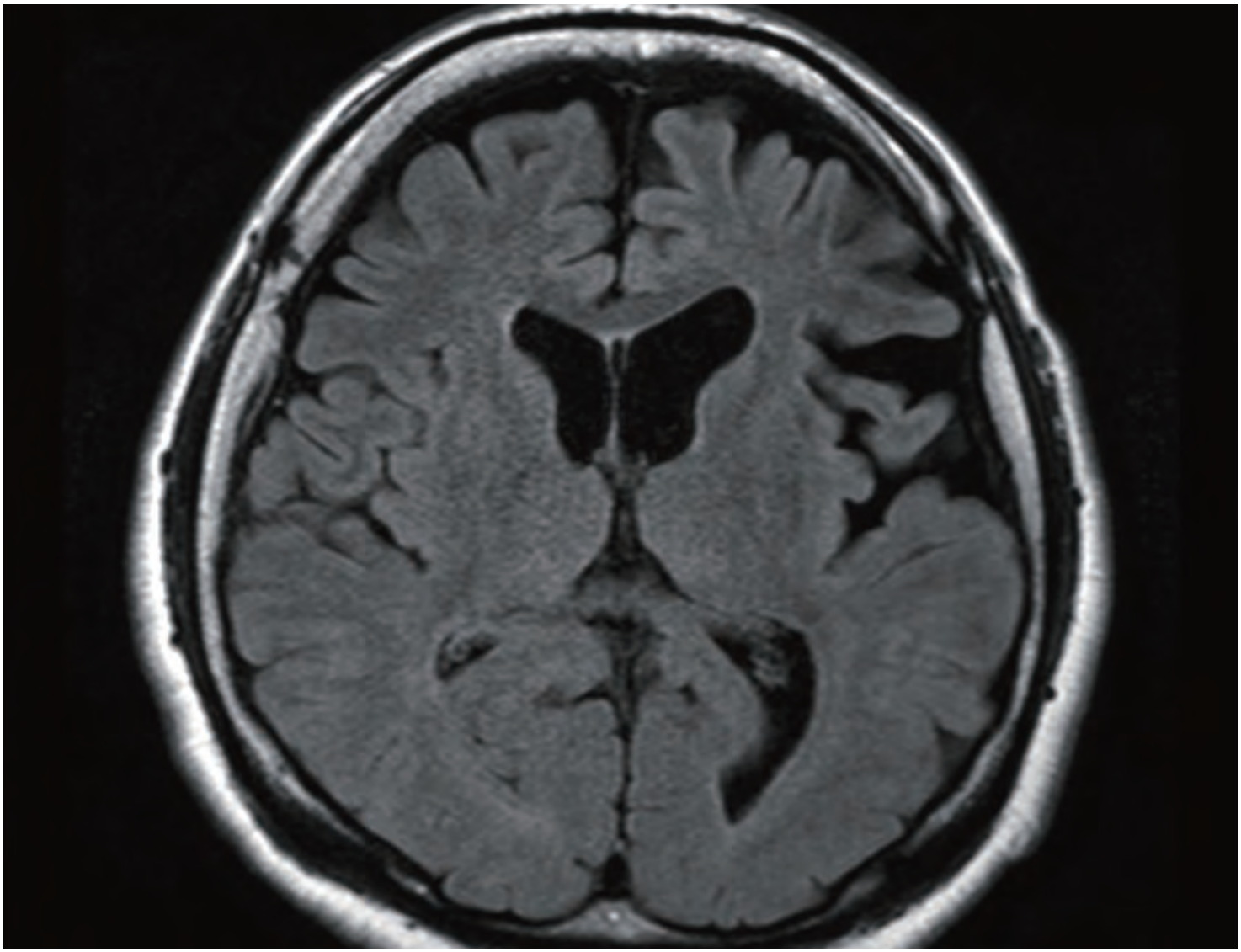
Kamimura K et al. (2019) "The HSPG Glypican Regulates Experience-Dependent Synaptic and Behavioral Plasticity by Modulating the Non-Canonical BMP Pathway." ***Cell Reports, 28***, 3144-3156.

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

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

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


128



MR image of the brain. In this instance, slight atrophy was detected in the left frontal lobe and around the gutter.

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
Masanari ITOKAWA
Yasue HORIUCHI
Kazuya TORIUMI
Hiroaki ISHIDA

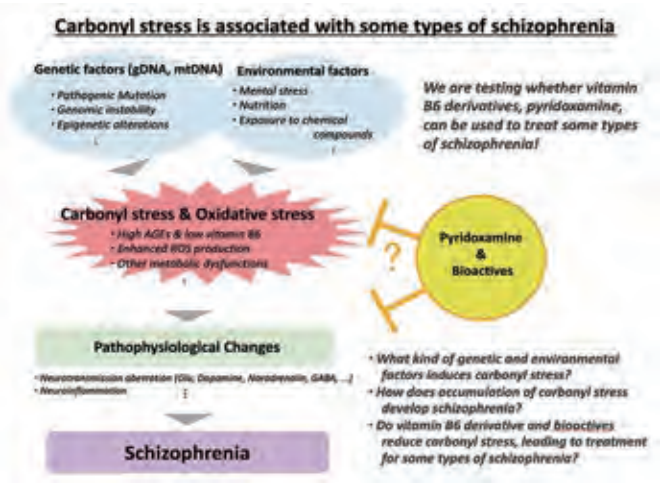
Research Assistants
Ikuyo KITO
Nanako OBATA
Izumi NOHARA
Mai HATAKENAKA
Tomoko INOUE

Students
Yasuhiro MIYANO
Koichi TABATA
Mai ASAKURA
Tianran WANG
Kyoka IINO
Mayuko MASADA
Azuna OZAWA
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

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

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

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

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

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

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.

Project Leader
Makoto HONDA

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

Sleep Disorders

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

Staff

Researchers
Taku MIYAGAWA
Akiyo NATSUBORI
Yoshiki MATSUDA
Tohru KODAMA
Haruo OKADO

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

Visiting Scientist
Mihoko SHIMADA

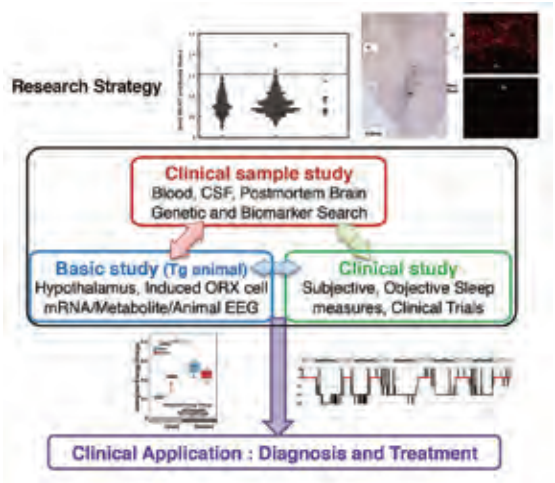
Students
Momoka MIYAZAWA

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

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

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

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

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

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

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

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

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

Project Leader
Kazutaka IKEDA

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

Addictive Substance

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

Staff

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

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

Students
Yoshihisa KATO
Aimi YAMAGISHI
Masako MORII
Yasuharu YAMAGUCHI
Masato OKITSU
Joei ZOU
Ryunosuke MARUYAMA
Jun ARAIDA
Yuna KANG
Ririka MORIMOTO
Futaba UMEMURA

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.

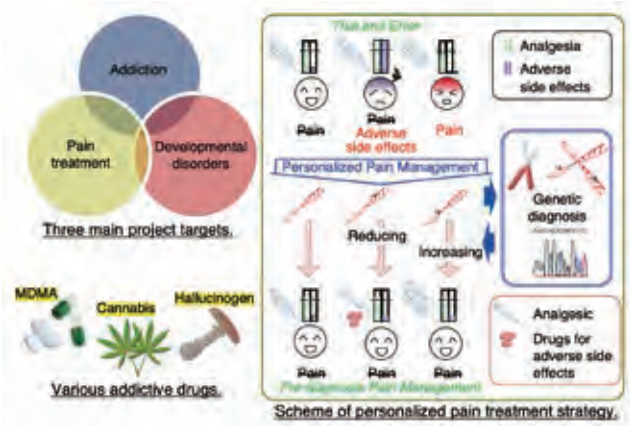
Some addictive drugs are also widely used as analgesics and for the treatment of developmental disorders. Some molecules that are involved in the actions of addictive drugs may be shared between analgesia and developmental disorders. The goals of our project are the following:

(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. (2022). "Exposure to GABAA receptor antagonist picrotoxin in pregnant mice causes autism-like behaviors and aberrant gene expression in offspring." ***Front Psychiatry*** 13:821354.

Nishizawa D, et al. (2022) "Genome-wide association study identifies candidate loci associated with opioid analgesic requirements in the treatment of cancer pain." ***Cansers*** 14:4692.

Sato A and Ikeda K. (2022) "Genetic and environmental contributions to autism spectrum disorder through mechanistic target of rapamycin." ***Biol Psychiatry: Glob Open Sci*** 2:95-105.

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

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

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

Frontier Research Laboratory

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

Head researcher,
independent research group
Shinobu HIRAI

Staff

Atsushi SAKUMA
Hiroko SHIMBO
Yayoi ONODERA
Keiko OOFUSA
Serina UCHIDA
Rei SHIRAKAWA
Nobuyuki ARUGA

Research Summary

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

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

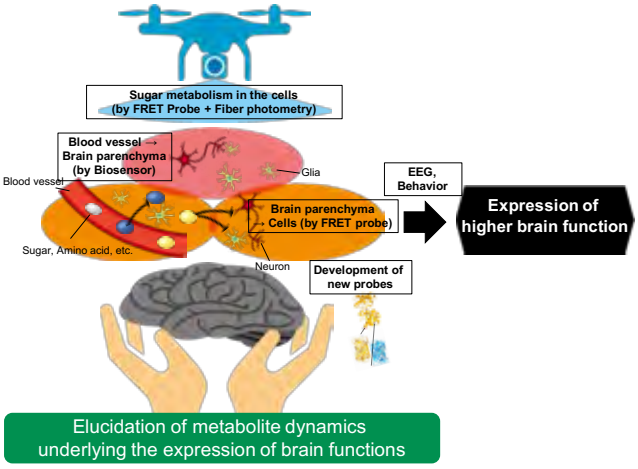


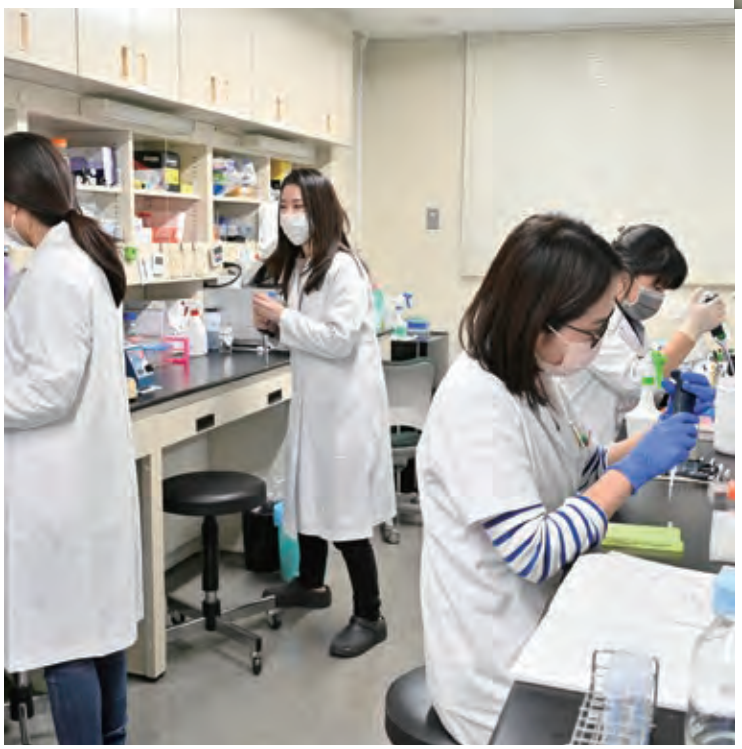
Figure 1. Conceptual diagram of our research. To understand the effects sugar dynamics have on higher brain functions by identification of cells contributing to sugar transport to the brain (construction and behavioral analyses of conditional knock-out mice) and analyses of intra- and extracellular sugar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

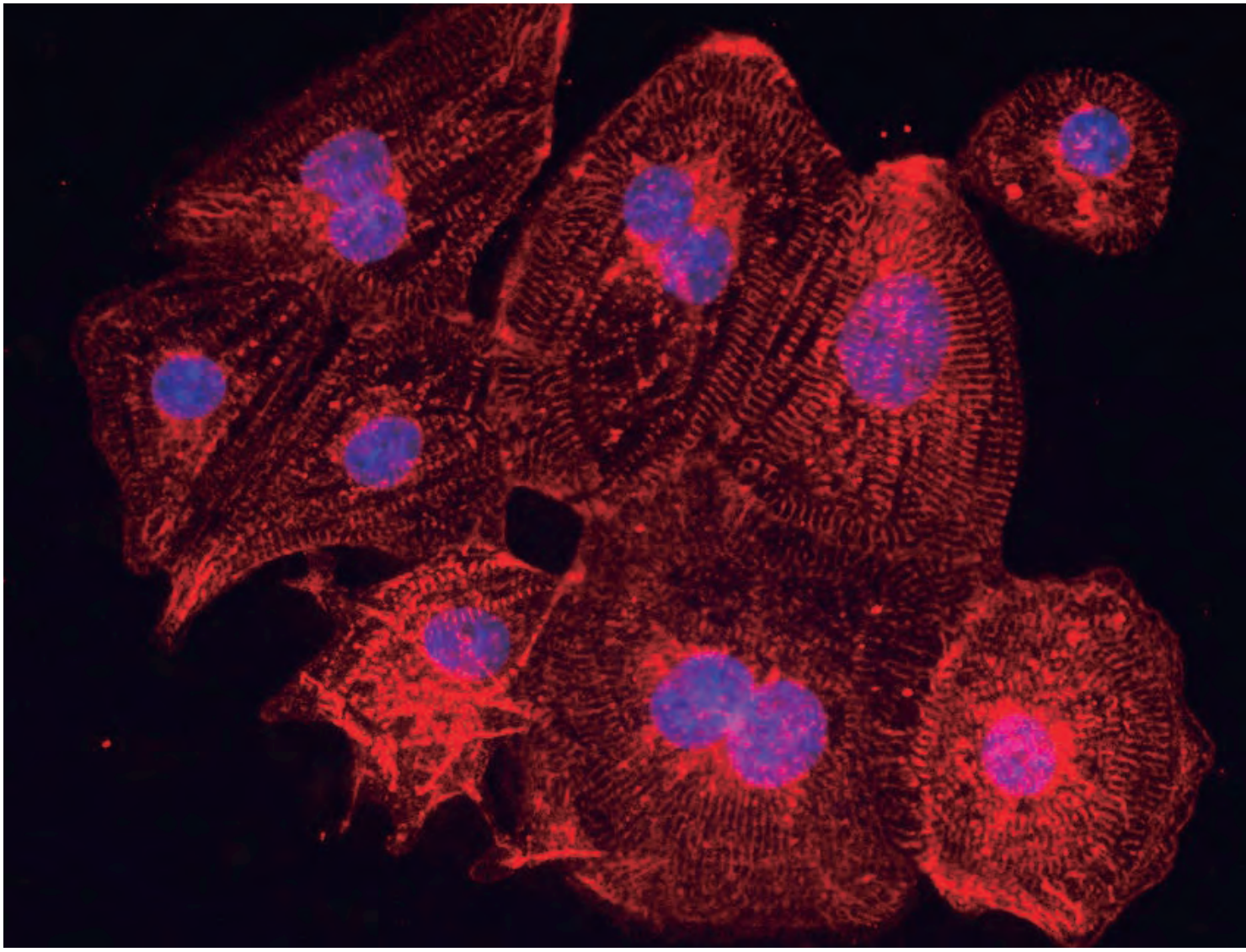
Selected Publications

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

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

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





Cardiomyocytes differentiated from human iPS cells: Sarcomeres (red; stained by ACTININ), functional units for contraction, and the nuclei (blue) are visualized.

Diseases & Infection

Project Leader
Fumihiko YASUI

Viral Infection Control

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

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

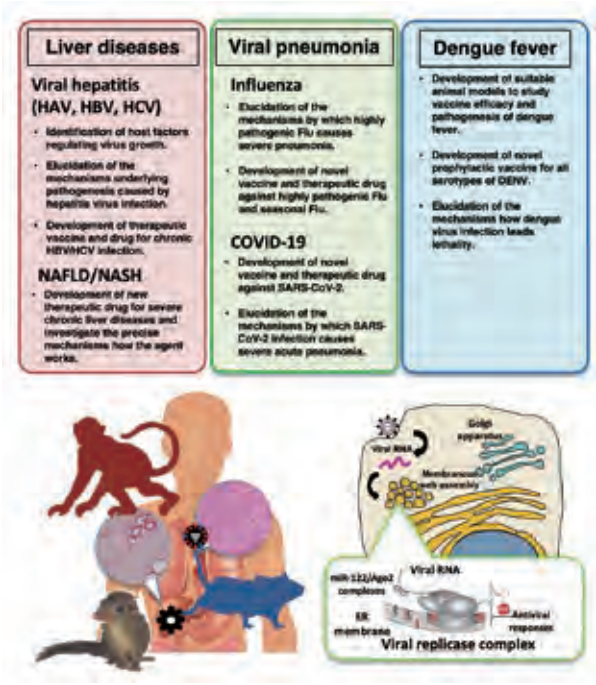
Staff

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

Research Assistants
Asako TAKAGI
Risa KONO
Masahiko HIGA
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

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

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

Sanada T, et al. (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." ***Journalof 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.

Honda T., et al. (2021) "Development and Characterization of a Highly Sensitive NanoLuciferase-Based Immunoprecipitation System for the Detection of Anti-Influenza Virus HA Antibodies." ***mSphere*** 6(3): e01342-2

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

Project Leader
Satoshi KOIKE

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

Neurovirology

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

Staff

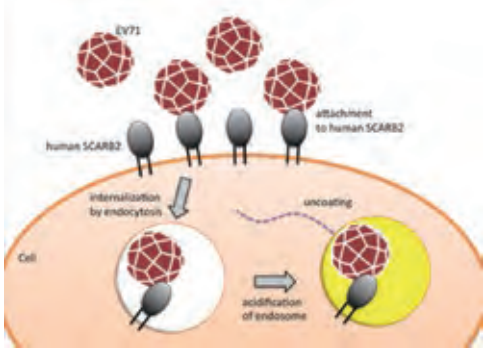
Researchers
Kyousuke KOBAYASHI

Research Assistants
Ayako OKUBO
Masako UKAJI
Namiko NOMURA
Tomoha NISHIZAWA
Minori ISHIDA
Sayaka ESAKI

Research Summary

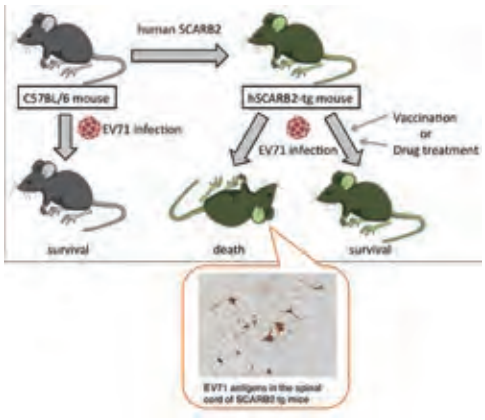
Enterovirus 71 (EV71), a human enterovirus species A of the genus Enterovirus within the Picornaviridae family, is known to be one of the causative agents of hand-foot-and-mouth disease (HFMD). HFMD is generally a mild and self-limiting disease. However, in some infants and young children, HFMD caused 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

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

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

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

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

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

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

Project Leader
Takayuki HARADA

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

Visual Research

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

Staff

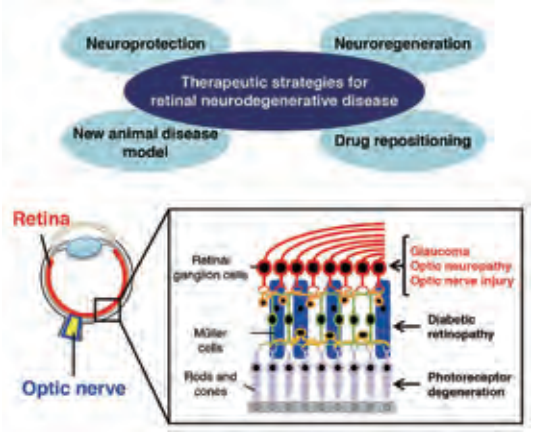
Researchers
Kazuhiko NAMEKATA
Xiaoli GUO
Chikako HARADA
Takahiko NORO
Euido NISHIJIMA
Yuta KITAMURA
Naoki KIYOTA
Akiko SOTOZONO

Research Assistants
Mayumi KUNITOMO
Tomoko HARA

Students
Shuri SANADA

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

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

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

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

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

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

Ohashi T, Namekata K, Guo X, Kimura A, Harada C, Harada T (2022) "Effects of lighting environment on the degeneration of retinal ganglion cells in glutamate/aspartate transporter deficient mice, a mouse model of normal tension glaucoma." ***Biochemistry and Biophysics Reports*** 29, 101197.

Sano H, Namekata K, Niki M, Semba K, Murao F, Harada T, Mitamura Y (2022) "Ocular expression of cyclin-dependent kinase 5 in patients with proliferative diabetic retinopathy." ***Journal of Diabetes Investigation*** 13(4), 628-637.

Project Leader
Kazunori SANGO

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

Diabetic Neuropathy

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

Staff

Researchers
Mari SUZUKI
Hideji YAKO
Naoko NIIMI
Shizuka TAKAKU

Research Assistants
Kumi SUMIDA

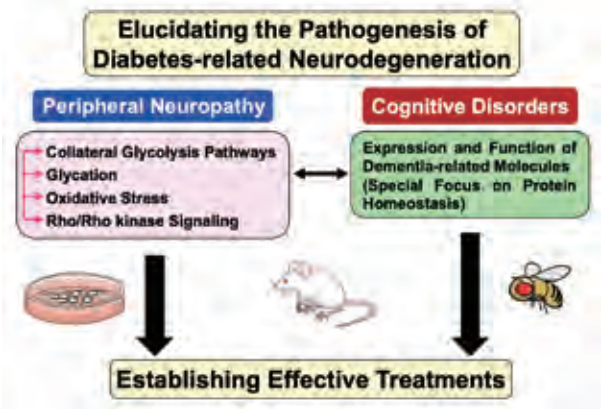
Visiting Scientists
Koichi KATO
Tatsufumi MURAKAMI
Junji YAMAUCHI
Hitoshi KAWANO
Ken MURAMATSU
Keiichiro MATOBA
Tomoyo AKAMINE
Tomoko ISHIBASHI
Ryosuke SHINOUCHI

Students
Masaki OBA
Nozomi SAKATA
Yuki TAKEZAWA

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

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

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

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

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

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

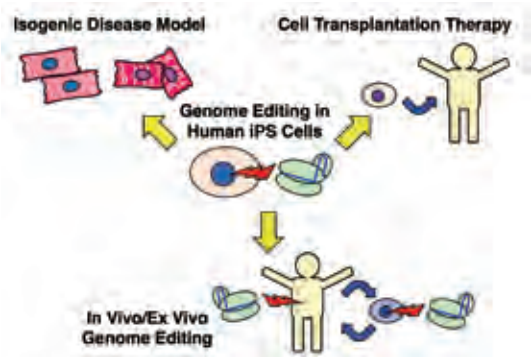
Researchers
Tomoko KATO-INUI
Gou TAKAHASHI

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

Research Summary

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

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



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

Selected Publications

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

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

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

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

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

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

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

Project Leader
Hidetaka TANNO

Cancer Immunology

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

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

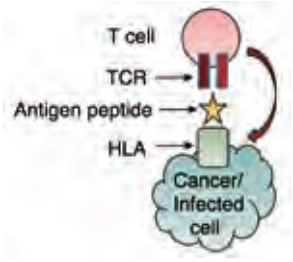
Staff

Researchers
Mayumi SAEKI
Kazuhisa AOKI

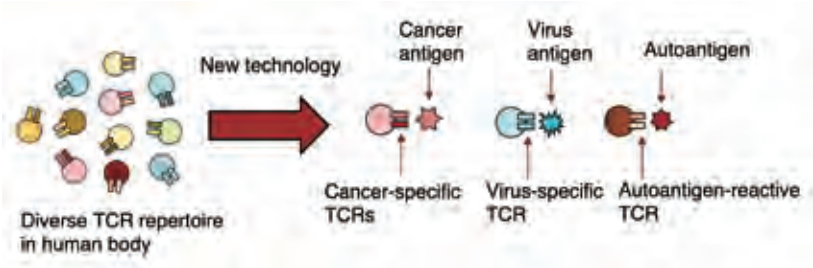
Research Assistants
Noriko KITAMURA
Yuri TANNO

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

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

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

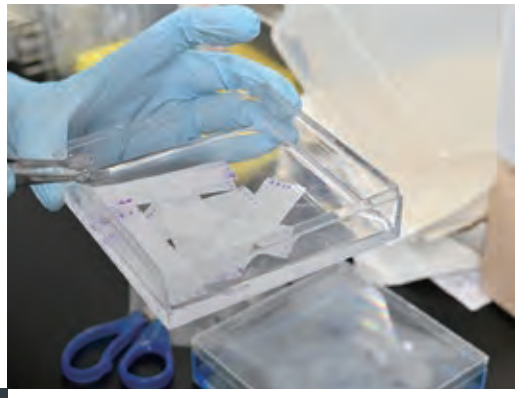
H Tanno et al. (2020) "A Facile Technology for the High Throughput Sequencing of the Paired VH:VL and TCRβ:TCRα Repertoires." ***Science Advances.***

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.***




Template: AmpliTaq
Cover: 105.0°C
Volume: 50 µL
Stage 2
Stage 3
95.0°C
55.0°C
72.0°C
72.0°C
4.0°C
0:00:15
0:00:15
0:00:30
0:07:00
35x
1x
1x
Cancel
Edit

Research Centers

Vice Director
Hideya KAWAJI

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

Genome & Medical Sciences

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

Staff

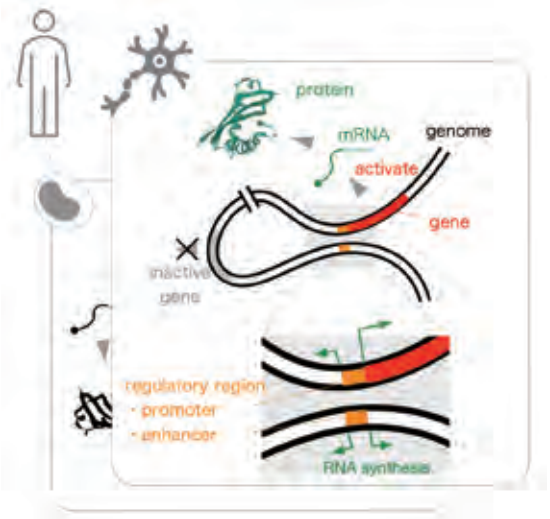
Director
Hisao MASAI
Senior Researcher
Keisuke OBOKI

Researcher
Nobumasa WATANABE
Naoko YOSHIZAWA
Toyoaki NATSUME
Yuichiro HARA
Saki SAITO
Nilmini HETTIARACHCHI

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.htmll

Staff

Researchers

Syudo YAMASAKI
Mitsuhiro MIYASHITA
Kaori BABA
Junko NIIMURA
Kaori ENDO
Satoshi YAMAGUCHI

Research Summary

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

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

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

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

Selected Publications

Nishida A,et al (2022) " Comparison of lithium levels between suicide and non-suicide fatalities:cross-sectional study." ***Translational Psychiatry,***

Stanyon D, Nishida A , et al (2022) "Auditory hallucinations and self-injurious behavior in general population adolescents: modeling within-person effects in the Tokyo Teen Cohort." ***Schizophrenia Bulletin,***

Nishida A, et al (2022) "Ethnoracial variation in risk for psychotic experiences. ***Schizophrenia Bulletin, "***

Nakanishi M, Nishida A, et al (2022) "Neighborhood Social Cohesion and Dementia-Related Stigma Among Mothers of Adolescents in the Pre- and Current COVID-19 Period: An Observational Study Using Population-Based Cohort Data." ***Journal of Alzheimer's Disease,*** 88 (2) 493–502.

Unit Leader
Yuki NAKAYAMA

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

Intractable Disease Nursing Care

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

Staff

Researchers
Michiko HARAGUCHI
Chiharu MATSUDA
Akiko OGURA
Yumi ITAGAKI

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

Research Summary

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

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

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

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

Selected Publications

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

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

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

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

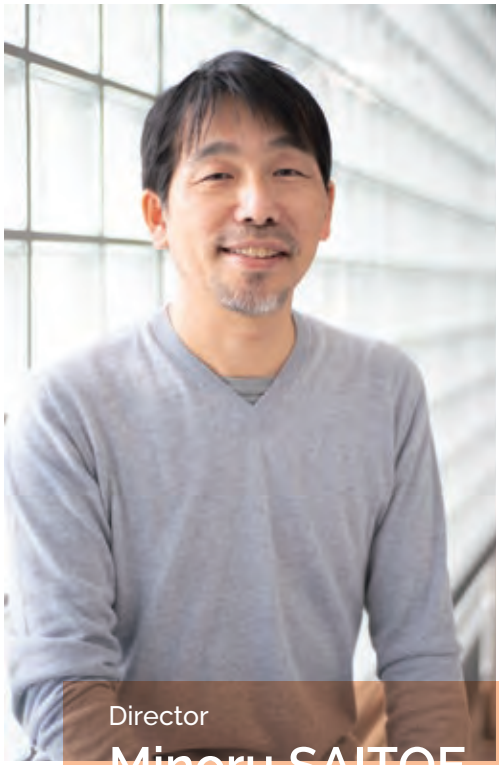
Matsuda C, Shimizu T, Nakayama Y, Haraguchi M. (2019) "Cough peak flow decline rate predicts survival in patients with amyotorophic lateral sclerosis" ***Muscle & Nerve***. 59(2) 168-173.

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

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

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

Research Supports



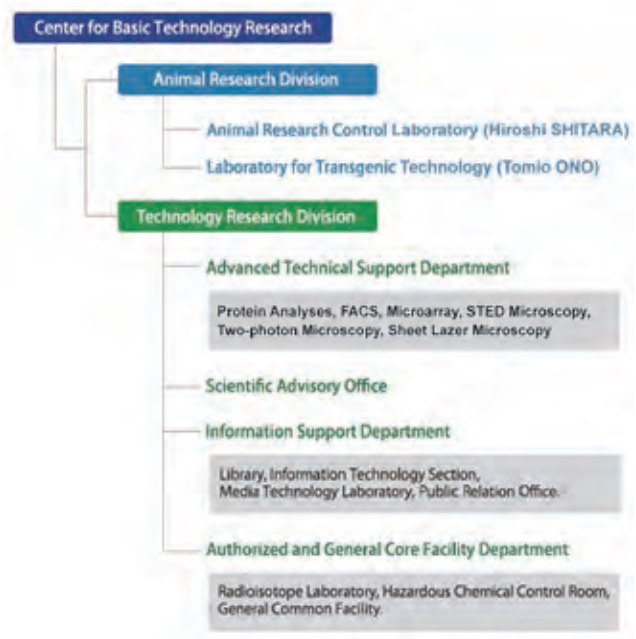
Director
Minoru SAITOE

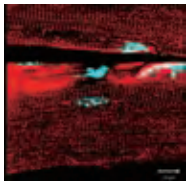
Basic Technology Research

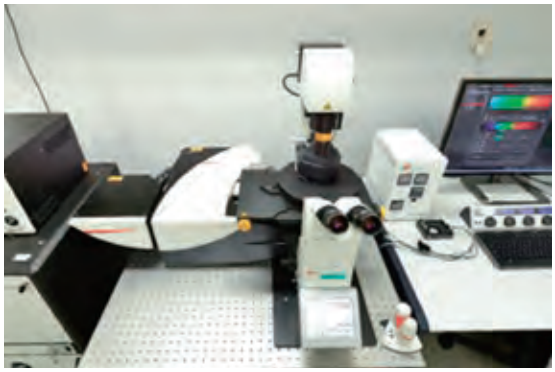
Laboratory HP: https://www.igakuken.or.jp/english/center/basic/basictech.html

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

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







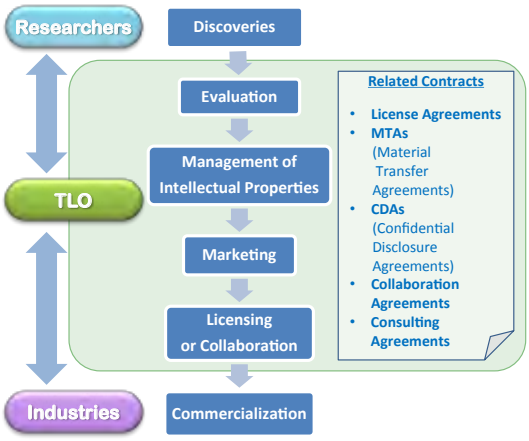
Technology Licensing Office

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

General Manager
Kazumasa AOKI

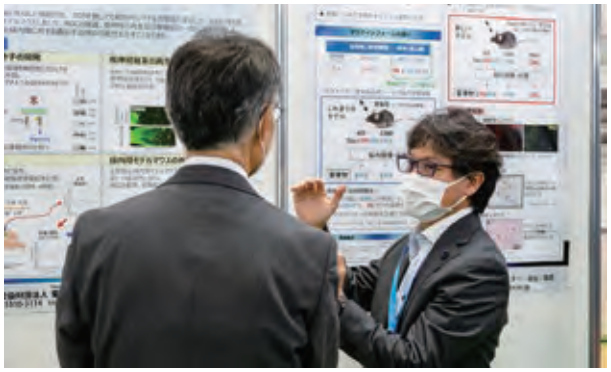
Who we are

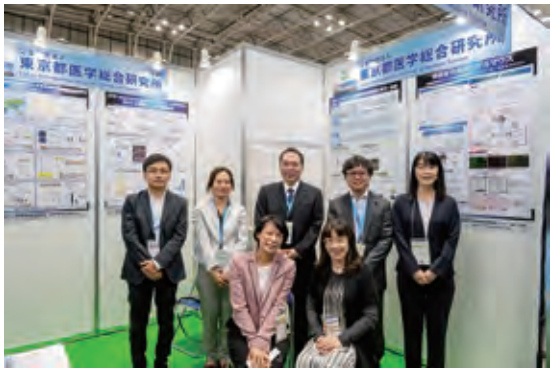
- The Technology Licensing Office (TLO) facilitates the conversion of scientific discoveries to innovative technologies with the ultimate goal of improving public health and welfare.
- We evaluate basic research findings (seeds) as intellectual property assets, and license promising candidates to industries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



What we do

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





Director
Takayuki HARADA

Medical Research Cooperation

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

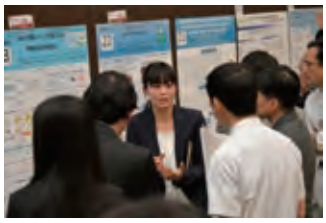
Staff

Kimi UEDA　Chikako ISHIDA　Hiroko KOUSAKA

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

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

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

Staff

Masato HASEGAWA　Rika KOJIMA　Tsunemi YAMANISHI
Kenichi OSHIMA　Nobuko UEKI　Keiko AKAMATSU
Erika SEKI　Tomoko YAGI

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.

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 2022, we conducted 2 on-line lectures and 6 hybrid lectures. Lecture topics included hay fever, dementia, cancer treatment, sleep disorders and circadian clock.

Latest trends in the therapies and reserch for Japanese ceder pollinosis
Development of curative therapy for pollinosis by SLIT
..... Minoru GOTOH (Nippon Medical School)
SLIT: How does it work?
..... Mayumi SAEKI (TMIMS, The Laboratory of Allergy and Immunology)

Heart-reaching Care for people with dementia: psychosocial approach and family support
..... Miharu NAKANISHI (Tohoku University)

Molecular biology of cancer and current trends for novel therapies
Molecular biology of cancer and current trends for novel therapies
..... Takuro NAKAMURA (Tokyo Medical University)
Stem cell-mediated novel cancer immunotherapy and drug development
..... Takahiko HARA (TMIMS, Stem Cell Project)

Revolution in treatment of spinal muscular atrophy led by mass screening
Novel therapies for spinal muscular atrophy facilitated by mass screening.
..... Kayoko SAITO (Tokyo Women's Medical University)
Mass screening of newborns for treatment of spinal muscular atrophy
..... Tomoko MIZUNO (Tokyo Medical and Dental University)

Vaccine development: past, present and future
Science of vaccine: from molecules to ethics
..... Ken ISHII (The University of Tokyo)
Vaccine development with vaccinia virus vectors: classic approach with a new touch
..... Fumihiko YASUI (TMIMS, Viral Infection Control Project)

Sleepy?
Sleep apnea and Sleepiness
..... Hideaki NAKAYAMA (Tokyo Medical University)
Evaluating excessuve daytime sleepiness and "inemuri-byo"(narcolepsy)
..... Makoto HONDA (TMIMS, Sleep Disorders Project)

Circadian rhythm: body clock for healthy life
Circadian rhythm: body clock for healthy life
..... Yoshitaka FUKADA (The University of Tokyo)
How do living species count 24 hours?
..... Hikaru YOSHITANE (TMIMS, Circadian Clock Project)

What is BPSD (Behavioral and Psychological Symptoms of Dementia)?
..... Shunichiro SHINAGAWA (The Jikei University School of Medicine)

TMIMS Seminar Series on "Aging and Health"

In 2022, we have initiated a special TMiMS seminar series, "Aging and Health", where we have invited prominent scientists in the field, to have lectures of the forefront research on aging as well as on how to promote healthy life. We had 3 lectures in 2022, and 8 more lectures are being planned in 2023.

TMIMS Seminar Series on "Aging and Health"
Can we overcome aging?
..... Makoto NAKANISHI
(The University of Tokyo)
Mental health and aging
..... Masanari ITOKAWA (TMIMS)
Exercise that activates brain-how to move your body for healthy aging
..... Kando KOBAYASHI
(The University of Tokyo)




Science café

In the past eleven years we have had 41 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 2022, we had three on-line science cafes on human body operation and genomes. The participants enjoyed our on-line quizzes in these events.

Battle between cancer and immune system in our body
..... Hidetaka TANNO
(TMIMS, Cancer Immunology project)

Let us zoom in cells: Proteins in action
..... Yasushi SAEKI
(TMIMS, Protein Metabolism project)

Let us zoom in cells: Injured genomes
..... Hiroyuki SASANUMA
(TMIMS, Genome Dynamics project)



Institutional seminars (Igakuken Seminars)

We have institutional seminars on a regular basis. In 2022, despite the continued coronavirus pandemic, we had 25 seminars (9 on zoom and 16 on hybrid format) by both domestic and foreign scientists (seven scientists based outside the country) including those from Saint John's College Oxford 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.

Creation of multicellular network by designing cell-to-cell communication
.....Satoshi TODA (Kanazawa University)

Challenge for sustainable medicare
.....Taro UENO (SUSMED, Inc)

The genome of the Mus musculus, the wild house mouse
.....Hitoshi SUZUKI (Hokkaido University)

Business strategy of Brain Therapeutics, Inc.: development of drug delivery system to brain
.....Fumikazu WANIBUCHI (Braizon Therapeutics, Inc.)
.....Masahiro Ohtsu (Braizon Therapeutics, Inc.)

The Scent of food; physiological roles
.....Motoko OHATA (Nihon University)

Evolution of human brain function: Probing primate brain by non-invasive brain Electroencephalogram
.....Kosuke ITOH (Niigata University)

Detection and analysis of the sound-evoked nanoscale vibrations in cochlear sensory epithelium by an advanced interferometer
.....Takeru OTA (Osaka University)

Understanding the mechanism of chromosome segregation: lessons from diversity
.....Bungo AKIYOSHI (University of Oxford)

Neurons of development in the adult brain
.....Zoltán Molnár (Saint John's College Oxford)

Transient neurons and transient networks in the developing cerebral cortex
.....Heiko LUHMANN (University Medical Center Mainz)

Behavioral addiction to internet games
.....Ichiro SORA (Kobe University)

Regenerative medicine of retina by using ES/iPS-derived retinal tissue / cells
.....Michiko MANDAI (Kobe City Eye Hospital)

X-chromosome Inactivation, Color Vision, and the Female Advantage
.....Jeremy NATHANS (Johns Hopkins Medical School)

Plasticity of neuronal excitability and synaptic transmission in Drosophila: functional implications from milliseconds to lifetime
.....Atsushi UEDA (University of Iowa)

Brain dysplasia: insight from studies on the human brain evolution
.....Takashi NANBA (University of Helsinki)

Life and GTP, a new frontier
.....Atsuro SASAKI (University of Cincinnati)

"Red Queen Hypothesis" in human-specific immune receptors
.....Kohyuki HIRAYASU (Kanazawa University)

Novel functions of glutamic acid in brain
.....Miho TERUNUMA (Niigata University)

Perception, memory and evolution of life, a view from multi time scale theory
.....Yasushi HIRAI (Fukuoka University)

Social inequalities in adolescent mental health in London: the Resilience, Ethnicity, and AdolesCent Mental Health (REACH) cohorts.
.....Gemma Knowles(King's College London)

Strategic plans of PhoenixBio
.....Takashi SHIMADA (PhoenixBio Co., Ltd.)

Successfully completing the final stretch – termination of DNA replication in the bacterial chromosome
.....Christian RUNDOLPH (Brunel University London)

Circadian RNA Biology – How do RNAs regulate circadian rhythms?
.....Shihoko KOJIMA (Virginia Tech)

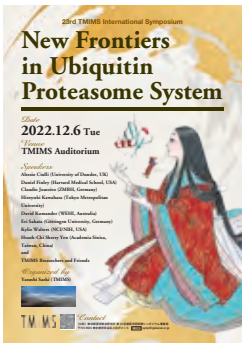
TMIMS International Symposium

After more than three years of interval, we were able to have 23rd TMIMS International Symposium "New Frontiers in Ubiquitin Proteasome System" in 2022 (December 6) at the auditorium. We had 7 invited foreign speakers, 4 domestic invited speakers, and 7 speakers from our institute. It was a very active meeting with a lot of discussion and scientific interactions.

We give lectures to high-school and university students who visit our institute and we also send staffs to visit schools and deliver lectures. This year, we gave face-to-face lectures at Toyama high school delivered by Makoto HONDA and Taku MIYAGAWA and at Gakugeidai-Fuzoku high school by Sho SUGAWARA. We also gave on-line seminars for the undergraduate students of Department of Biosciences, College of Humanities and Sciences, Nihon University.

Joint programs with universities

Many scientists at TMIMS have joint appointments as visiting professors or lecturers at various
universities. In 2022, we held our annual "open institute" events for prospective graduate students
on-line with close to 100 attendants. We currently have 108 students from affiliated universities and
other schools, who conduct their research here.



Support for students and young scientists

Research Associate Fellowships

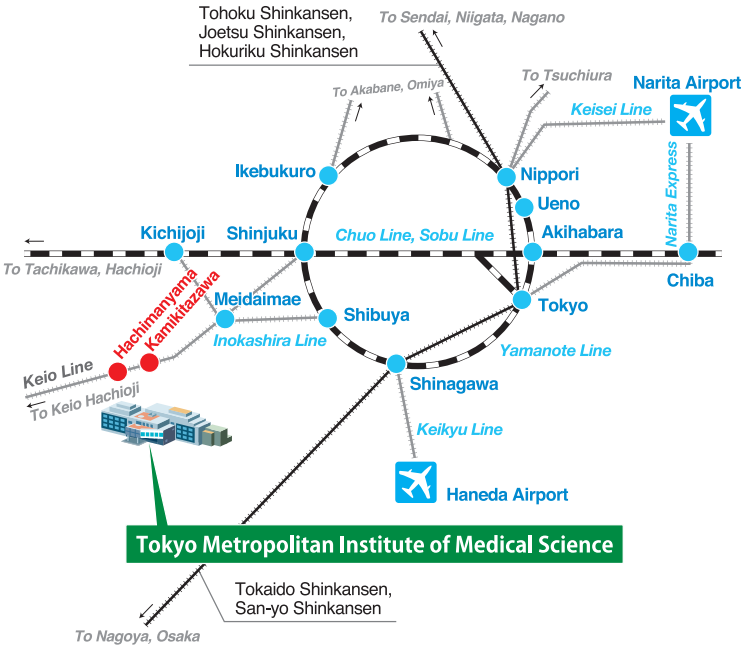
We provide graduate students who conduct their masters/Ph.D. research at TMIMS with research associate fellowships that allow them to concentrate on their studies and research.

Travel support for young scientists attending international meetings

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

Access Map

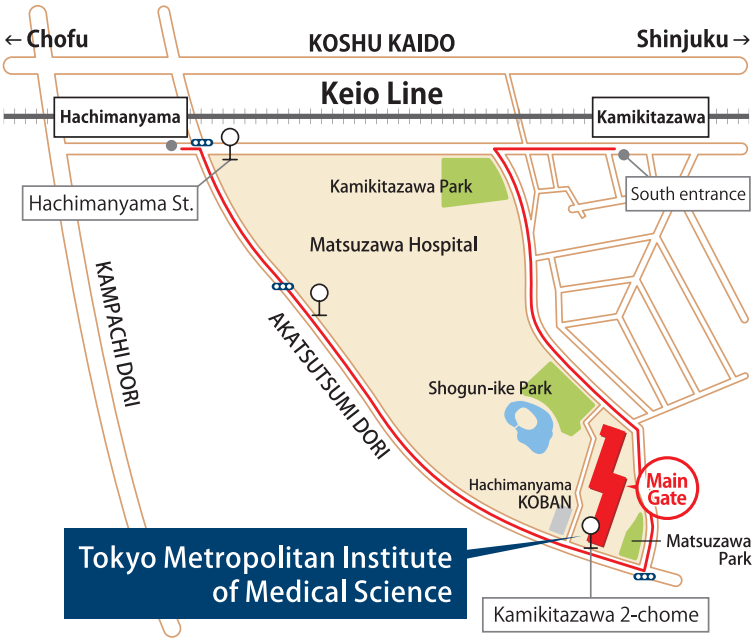
Tokyo Metropolitan Institute of Medical Science	
Address	2-1-6 Kamikitazawa, Setagaya-ku, Tokyo, 156-8506, Japan
Tel	+81-3-5316-3100
Fax	+81-3-5316-3150



AIRPORT to INSTITUTE

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

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



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

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

TOKYO METROPOLITAN INSTITUTE OF MEDICAL SCIENCE

2-1-6 Kamikitazawa, Setagaya-ku,

Tokyo, 156-8506, Japan

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

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

As of March 1, 2023