Annual Reports 2024

Contents

Message from the Director: TMIMS 2024

Overview of 2024 and Prospects for 2025

Director
Hisao MASAI

2024 was a turbulent year that began with a devastating earthquake on the Noto Peninsula, which blew away the festive atmosphere of the New Year. Following the earthquake, Noto was hit by other disasters including heavy rains, and many people experienced great hardships. Even now, a year later, my heart aches when I think of the many people who are still living in evacuation shelters.

The war between Russia and Ukraine has been going on for almost three years, and there are signs of further escalation. The situation is bleak for the citizens who desire peace, with little hope in sight. The Israeli-Palestinian armed conflict in Gaza has entered its second year, with over 40,000 deaths and 100,000 injuries. 90% of the residents in the area have been forced to evacuate. The images of children suffering from serious injuries and severe food shortages tear at our hearts, making us feel helpless being so far away. We, as global citizens who yearn for world peace, need to seriously think about what we can do to end such tragedies as soon as possible. In this regard, the awarding of the 2024 Nobel Peace Prize to Nihon Hidankyo, an organization of survivors of the 1945 atomic bombings of Hiroshima and Nagasaki, gives us hope for the possibility of nuclear disarmament.

At the institute, we also faced personal tragedies. On July 23, our Chairperson, Keiji Tanaka, passed away. Tanaka sensei was a great researcher and a pillar of the institute, and his sudden departure from our midst was deeply shocking. Even now, after nearly six months, tears well up every time I see the door to his office. In March, Deputy Senior Researcher Ito Kawakami, in the Molecular Pathology and Histology Analysis Laboratory, also passed away making it a year of sad events for the institute.

Progress in the Life Science in 2024

In 2024, there were many news stories that delighted the Japanese people, such as Shohei Ohtani's 50-50 achievement and the outstanding performances of Japanese athletes at the Paris Olympics Games. What about the field of science? The 2024 Nobel Prize in Physiology or Medicine was awarded for the discovery of microRNAs, which play crucial roles in the regulation of gene expression. MicroRNAs are involved in cancer formation and aging of humans and will be important tools for the development of diagnostic and therapeutic measures for these diseases/phenomena. RNAs similar to microRNAs had previously been identified in Escherichia coli. The replication origin region of the drug-resistant plasmid R1, which I studied during my master's and doctoral programs, codes for a short, functionally unknown anti-sense RNA called CopA, and subsequent research revealed that CopA RNA controls the translation of proteins necessary for replication initiation. The replication of bacterial vectors (e.g. pUC18 and pET plasmids) widely used for cloning and expression is also controlled by a short anti-sense RNA called RNAI, and Dr. Junichi Tomizawa, the former director of the National Institute of Genetics and a member of the National Academy of Sciences, recognized the importance of RNAI and elucidated its mechanisms of action in the 1980s. The discovery of microRNAs in higher eukaryotes clearly demonstrates that the most important principles and mechanisms of life are always conserved throughout evolution.

The Nobel Prize in Chemistry was also awarded for work that deeply affects our research. The prize was awarded for the development of technologies for predicting protein structures and for designing proteins with new functions. Accurate prediction of protein structures by AlphaFold has become a routine research method. In particular, with the announcement of AlphaFold3, it has become possible to accurately predict the formation of protein complexes with various ligands such as nucleic acids and lipids, revolutionizing life science research.

There were many other discoveries in 2024. For example, research towards the development of drugs that enable rejuvenation has been advancing worldwide. Senolysis, which removes senescent cells, and reprogramming, which rejuvenates senescent cells, are two promising approaches for rejuvenation. The concept of "anti-aging," which delays aging and extends lifespan, has become a realistic possibility, leading to investments of hundreds of billions to trillions of yen by foundations and individual investors. However, it may be difficult to extend the maximum human lifespan beyond 120 years. What is currently most sought after is how to extend healthy lifespan.

In our institute, we conducted a two-year seminar series on "Aging and Health" and invited renowned researchers in aging research to give lectures. After more than 20 excellent lectures, healthy aging ultimately came down to the three fundamental principles that everyone has known for decades: having a proper diet, getting quality sleep, and engaging in moderate exercise. Whether anti-aging drugs contribute to extending healthy lifespan is still unknown, but we may have the answer in 10 years.

Outlook of TMIMS for 2025

At the Tokyo Metropolitan Institute of Medical Science, our mission is to "elucidate the causes of major diseases and develop preventive and therapeutic measures through innovative and original medical discovery. This will help improve health, medical care, and welfare, thus protecting the lives and health of the citizens in the Tokyo metropolitan area." We have been pursuing a combination of "basic medical research aimed at unraveling the mechanisms of life" and "practical medical research directly related to diseases", aiming for impactful results and early social contributions. We are currently at the end of our fourth project term (from fiscal year 2020 to 2024). In the upcoming fifth project term, which begins in April of 2025, we will continue to promote research with the same philosophy as the previous term. We have recently decided to add three new projects and have recruited three excellent new project leaders, who will start their research in 2025. Our institute aims to provide an environment where individual researchers' original ideas are respected and can flourish, supported by excellent research facilities and research support. Furthermore, we strive to advance "comprehensive" medical research from the cellular level to animals, people, and society. To achieve this, we promote free and open communication within the institute and support an environment conducive to productive collaborations in a harmonious atmosphere. Fortunately, the COVID-19 pandemic is finally over (although we must remain cautious as infections are still occurring—I was infected for the first time last year in July and experienced a month of pain, personally making me realize how COVID is different from the common cold). This has allowed various inter-departmental gatherings to take place. Last year, with the assistance of the Tokyo Metropolitan Government, we obtained an Orbitrap Exploris 480 mass spectrometer, enabling us to perform advanced mass analysis at the institute. Moving forward, we intend to further enhance the diverse research technology support system required for creative medical research.

In 2020, we established the "Research Center for Genome & Medical Sciences" and the "Research Center for Social Science & Medicine" to support the Tokyo Metropolitan Government's health, medical care, and welfare initiatives. However, as we learned from the toll caused by the COVID-19 pandemic, we also need to be prepared for unpredictable emergencies and will start the "Research Center for Infectious Diseases" in April of 2025. This new research center will conduct research on the mechanisms of various infectious diseases, focusing on those selected by the Health Science Council. Goals of this center include the development of antiviral drugs based on natural immune mechanisms and the generation of universal vaccines. In times of emergency, the institute, including the Research Center for Infectious Diseases, the Research Center for Social Science & Medicine, and the Center for Medical Research Cooperation, will work together as a whole to swiftly establish a system that can respond to infectious diseases. We will closely collaborate with the Tokyo Metropolitan Institute of Public Health, the Tokyo Center for Infectious Diseases Prevention and Control (iCDC), and metropolitan hospitals to understand emerging pathogens, elucidate infection mechanisms, understand immune responses, and conduct research on epidemiology.

Sciences in Japan

Recently, there has been heated discussion regarding the decline in Japan's research capabilities. Although the total number of papers is increasing, there is a decrease in the number of top 10% papers that are frequently cited and have high academic value. While there have been various arguments and multiple reasons proposed for this decline, one reason could be the decreasing attractiveness of pursuing research as a career, leading to talented students not choosing to become researchers. Many researchers still experience the joy of making discoveries and find excitement in research, but unfortunately, many students leave the research path before experiencing this joy. Moreover, witnessing senior researchers struggling to find jobs and being unable to fully focus on research due to time-limited positions may make students think, "I don't want to end up like that." Publishing papers in top journals is an aspiration for researchers, but the bar for achieving this is exceptionally high. Having a paper accepted in a top journal requires logically compelling content, multiple different experimental approaches to support the conclusions, and researchers who can persevere despite constant pressure and setbacks. The cultivation of successful researchers requires support for research systems that enable diverse experiments required for goal achievement and funding review systems that support long-term research necessary for groundbreaking findings. In Japan, these systems need significant improvement. Regarding funding reviews, it is necessary to establish a system that accurately assesses the proposed content, provides opportunities for feedback and resubmission based on comments, and supports research proposals with a high potential of scientific value.

Currently, Japan has high expectations for Nobel Prize laureates, and indeed, many laureates have emerged in the past 20 years or so. Many of these prizes were awarded for curiosity-driven research, which received support 30 to 40 years ago. Basic research is the root of "the tree of science," and as long as the roots exist, new buds will always sprout and flowers will bloom. However, it seems that the current science policy in Japan focuses too much on the flowers that are about to bloom, neglecting the invisible, but essential roots. If this continues, there is a possibility that in 10 or 20 years, the tree of science will fall and no flowers will bloom. The roots need to be nurtured for the coming decades, and as long as the roots grow stronger, the flowers and fruits will also grow. In order for Japan to continue leading the world in the development of science and technology in the coming years, it would be necessary to continue supporting basic research that nurtures the roots.

Wishes for 2025

The zodiac sign for 2025 is "Kinotomi" in the Japanese zodiac system. "Kinoe" represents the second Heavenly Stem and symbolizes the energy of the Yin Wood element. It signifies flexibility, cooperation, and the ability to progress towards personal goals while maintaining harmony with the surroundings. "Mi" represents the sixth Earthly Branch, which is the sign of the Snake. The snake is known for its strong life force and for its ability to heal surface wounds through the shedding of its skin, symbolizing resurrection and regeneration. In 2025, which marks the beginning of a new project, we anticipate the germination and growth of new seeds while reaping significant fruits from the trees nurtured during the previous project term.

During the transition to the new year, there have been many changes in leadership in both Japan and the United States. We find ourselves in an uncertain and challenging era, where predictions are difficult and a vague sense of anxiety lingers. Albert Einstein once said, "Peace cannot be kept by force. It can only be achieved by understanding." Unfortunately, the world peace that I prayed for in my previous year's message has not been realized. In 2025, we hope for people to come together, understand each other through dialogue, and restore peace.

For the zodiac information, I referred to the following website:
https://www.quocard.com/column/article/eto2025/
The quote from Albert Einstein was referenced from the following website:
https://news.yahoo.co.jp/expert/articles/65f921791897fc22d9594deddb3bb334c9dd6608

In Memory of Our Mentor, Keiji Tanaka

Our beloved Director, Dr. Keiji Tanaka (whom I will call Keiji with affection in this memorial message), passed away on the morning of July 23, 2024 (Tuesday). We were filled with deep sorrow and shock at the sudden parting. It was completely unexpected. I had just had a lengthy discussion with him during lunchtime the previous Friday. It was like he vanished like a mirage.

Keiji started his research career at the Enzyme Research Institute of Tokushima University and then studied at the Department of Physiology (now the Department of Cell Biology) at Harvard Medical School in the United States beginning in 1981. He became an Associate Professor at the Enzyme Science Research Center of Tokushima University in 1995, Department director of the Tokyo Metropolitan Institute of Medical Science (RINSHOKEN) in 1996, Deputy Director in 2002, and Acting Director in 2006. He served as the Director General of the Tokyo Metropolitan Institute of Medical Science (IGAKUKEN) between 2011 and 2018, and served as the Chairman starting in 2016. Altogether, he had been promoting research at our institute since 1996.

Keiji had a passion for reading from a young age. He was particularly fond of the works of Hideo Kobayashi and even considered becoming a novelist himself. Many of his written works are known for their high literary quality and elegant prose. Keiji began his research at the Enzyme Research Institute of Tokushima University under the guidance of Dr. Akira Ichihara. He then started his overseas studies in the laboratory of Professor Alfred Goldberg, where he initiated research that eventually led to the discovery of the proteasome. During the mid-1970s, the era of molecular biology and the central dogma, Keiji became interested in the fate of proteins. At the time, he had two particular questions about proteins. One involved the heterogeneity of protein lifespans. Protein lifespans vary greatly, ranging from a few minutes to several months, a difference of about ten thousand times, but the mechanism determining their lifespans was unknown. The second question arose from the fact that the body synthesizes approximately 200 grams of protein daily, while the amount of protein obtained from meals is only about 70 grams. Where do the remaining 130 grams come from? It was later discovered that proteins are degraded and recycled, but at that time, this process was completely unknown. Driven by these questions, Keiji decided to focus his research on mechanisms of protein degradation rather than synthesis, which many researchers were studying.

The discovery of the proteasome and the elucidation of its molecular structure and regulatory mechanisms fascinated researchers and led to the subsequent discovery of immunoproteasomes and thymoproteasomes by Keiji's research group, leaving a significant impact in the field of immunology. The immunoproteasome, which is formed by the replacement of the 1, 2, and 5 catalytic subunits of the constitutive 20S proteasome with the inducible subunits 1i, 2i, and 5i, possesses higher chymotrypsin-like activity, allowing the efficient generation of peptides that bind more effectively to MHC class I molecules during immune responses. The thymoproteasome, which contains the proteasomal subunit 5t exclusively expressed in the thymus, plays a central role in the fundamental process of self versus non-self discrimination through positive selection during T cell repertoire formation, challenging established concepts in immunology. Keiji's research findings have thus contributed to a comprehensive understanding of the proteasome and its biological functions.

Keiji took advantage of his extensive network of research connections and actively engaged in collaborative research, both within Japan and internationally. Through these efforts, he constantly incorporated cutting-edge techniques into his research to solve various problems. Keiji's abilities are rare among Japanese researchers, and his many collaborations were only possible because of his thirst for knowledge, his keen instinct for research, and his wide network of friendships resulting from his amazing research output and his outgoing and communicative personality.

Embarrassingly, I personally did not have a deep understanding of Keiji's accomplishments until I had an opportunity to attend a lecture of his at an international conference about 20 years ago. I still remember being deeply moved by the sheer beauty of his lecture. It was reminiscent of the overwhelming emotions one

experiences when encountering superb music or art. I realized that by revealing the truths and laws of nature, one could evoke profound emotions, and this was a once-in-a-lifetime experience for me.

Keiji has received numerous awards for his work, including the Encouragement Award from the Japanese Biochemical Society, the Naito Memorial Science Promotion Award, the Uehara Prize, the Asahi Prize, the Tokyo Spirit Award, the Toray Science and Technology Award, the Takeda Medical Award, the Japan Academy Prize, the Japan Endocrine Society Master Award, the Keio Medical Science Award, the Person of Cultural Merit award from the Minister of Education, Culture, Sports, Science and Technology, and AMED Research Award (Prime Minister's Award). Recently, his name had been mentioned as a candidate for the Nobel Prize every year during the Nobel season.

Keiji not only opened up the field of protein degradation through his outstanding research achievements, he also provided unwavering guidance and impartial support to many researchers. Keiji also nurtured numerous talented scientists in his laboratory. These researchers grew under his guidance and are now actively contributing to and leading research in their respective fields, carrying on Keiji's spirit and enthusiasm for knowledge.

When three previously separate research institutes were merged to form the Tokyo Metropolitan Institute of Medical Science, Keiji rose up to tackle many challenges and played a pivotal role in integrating the institutes to ensure that researchers from diverse backgrounds could develop their talents in a collaborative atmosphere. As a result of his efforts, our institute became better and more productive than the simple sum of three separate institutes. Even after the integration, he continued to lead the institute for eight years as the Director, demonstrating strong leadership and vision. He paid attention to even the smallest details within the institute, fostering a sense of unity within the institute and allowing it to flourish. I succeeded Keiji as the Director in 2018, which was a challenging job for me. However, he was always there to give me guidance and encouragement.

Keiji's friendly smile, warm personality, and sincere and rigorous attitude towards research are not only etched in our hearts but have also earned the respect and admiration of researchers worldwide. Keiji's words and actions have become a source of inspiration and guidance for many people. His sudden departure was extremely painful for us, and words cannot fully express the sadness we feel. However, we will never forget Keiji's great achievements and the invaluable teachings he left us. His spirit will continue to live on in our research and daily lives.

When we think of Keiji, many of us likely remember his love for drinking and having a good time with friends. His speech at the Asahi Prize ceremony, where he famously declared that he would use all the prize money for drinks, has become legendary. Recently, however, due to his declining health, he had to stop drinking. We had been looking forward to a day when he would recover, and we could again socialize, but unfortunately, that day will not come. I hope that in heaven, he is finally enjoying a long-awaited drinking session with his mentors, Professors Ichikawa, and Goldberg.

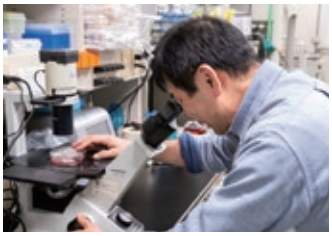
The first snow of the year is falling on the ground outside. I offered my prayers for Keiji's soul as I looked up at the falling snow and the snowy sky.

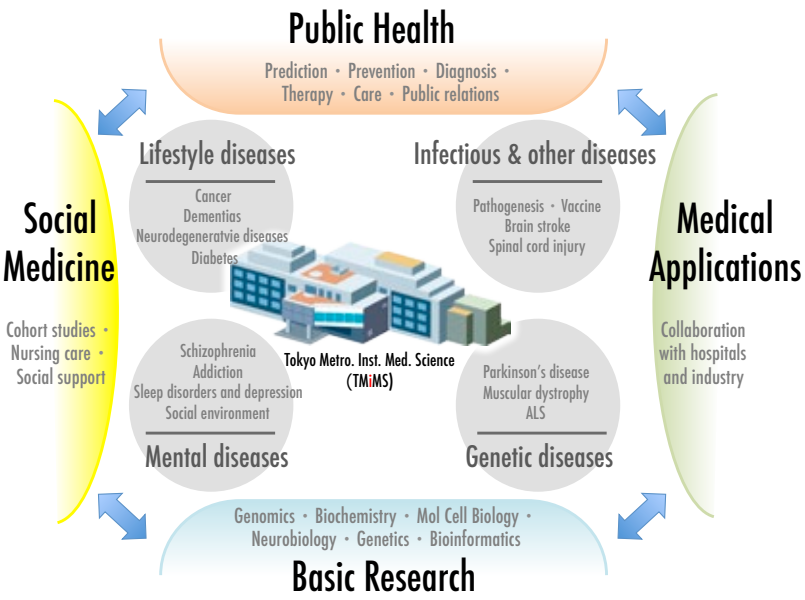
Keiji, thank you sincerely for everything you have done for us. Please rest in peace.

Hisao Masai March 4,2025

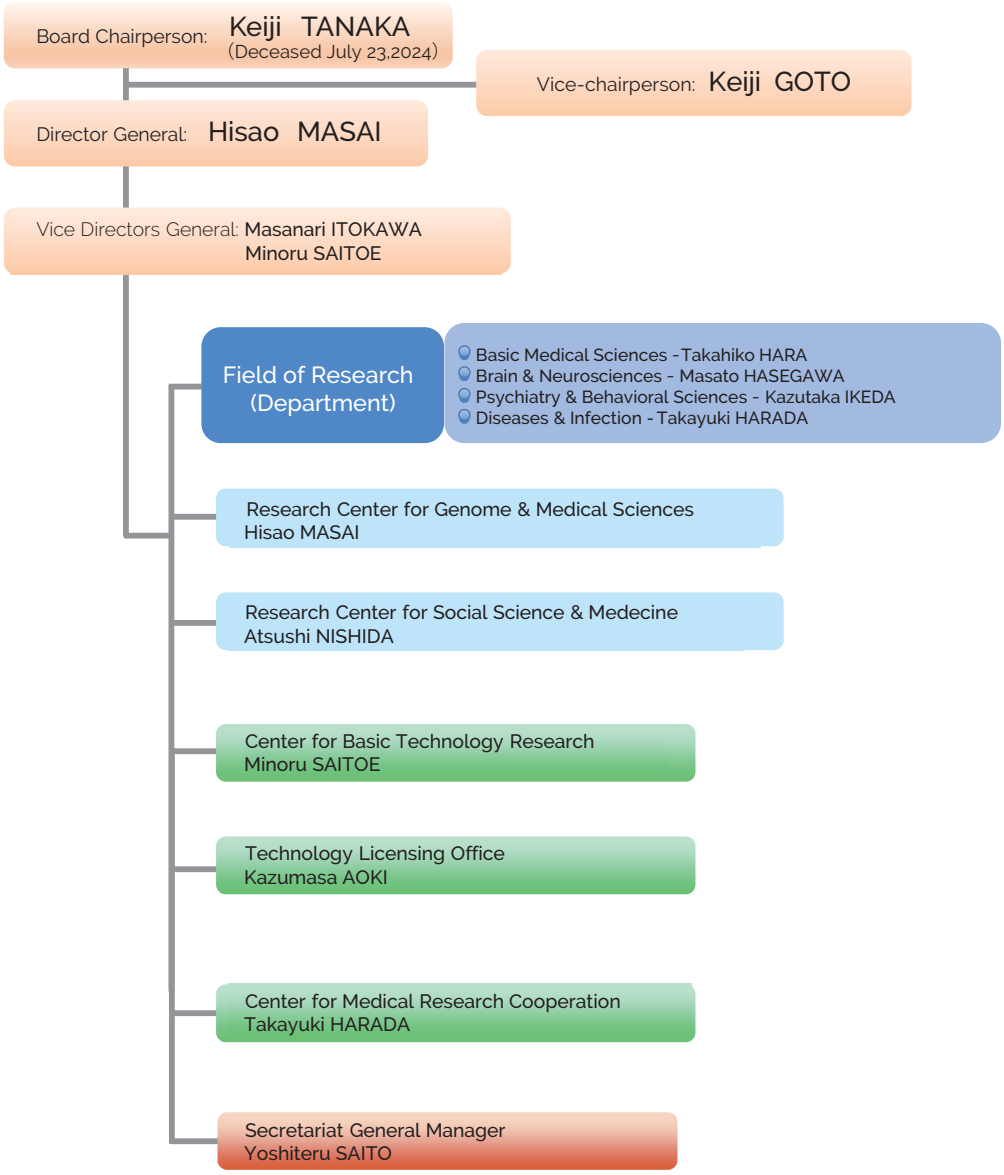
Our Mission

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.





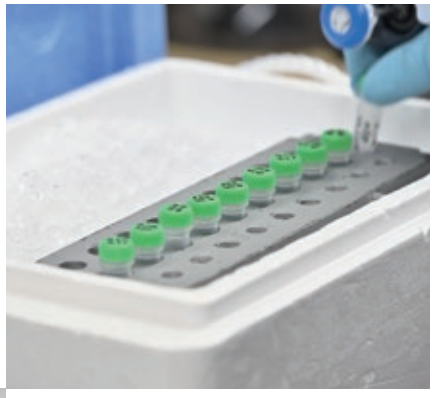
Organizational Chart

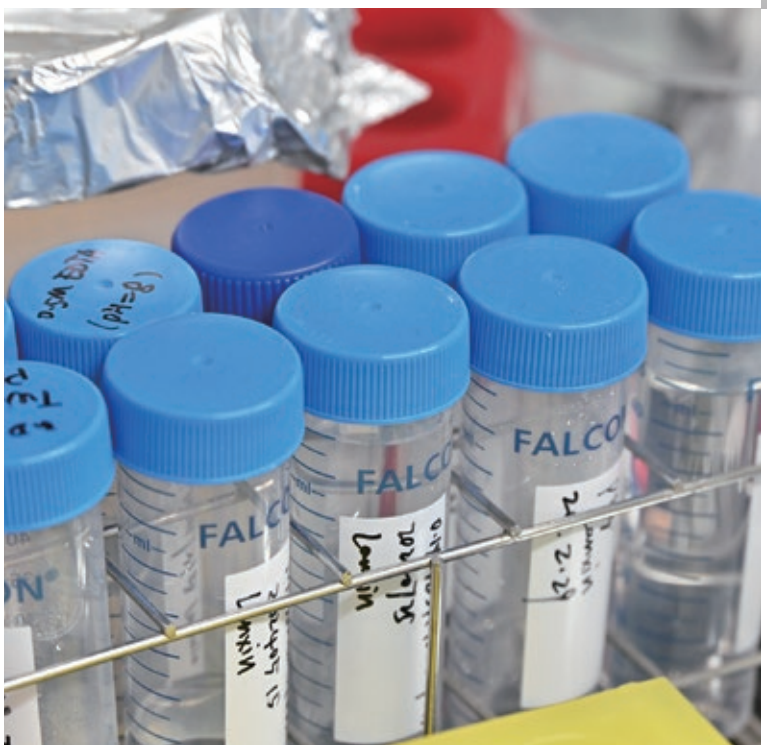


Our People at a Glance

Position	Number
Researchers	148
Postdoctoral Fellows	51
Students	120
Visiting Scientists	136
Guest Scientists	128
Administrative Staffs	34
Total	617

February 1, 2025

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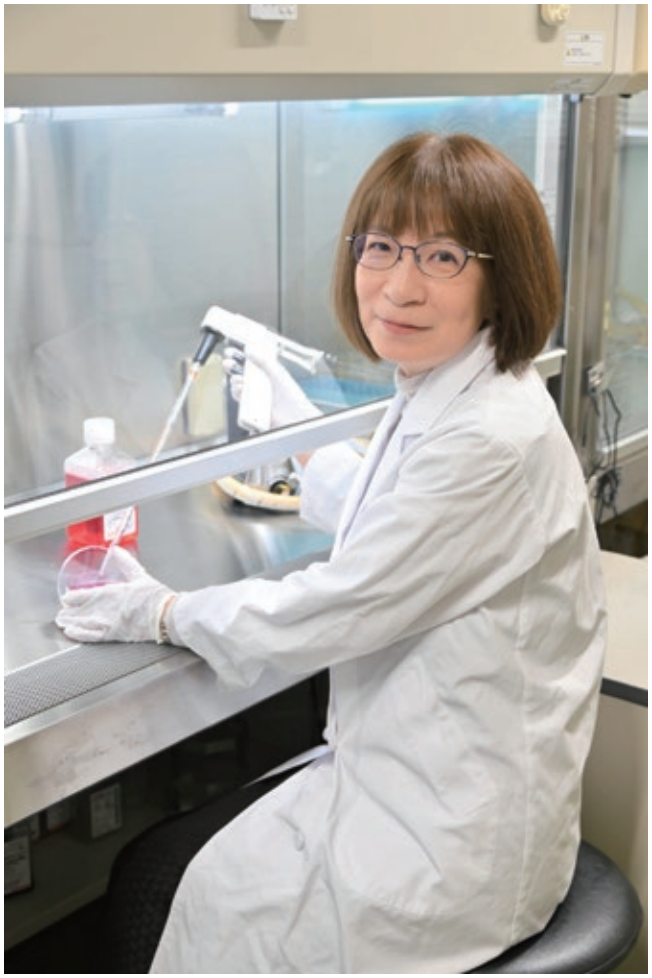
Meet Our Scientists!

Meet Our Scientists!

On July 23, 2024, we lost our Chairman Keiji Tanaka to ischemic heart disease. Dr. Tanaka was a well-loved figure in the institute. He was a pioneer and leader in the field of protein degradation, contributing extensively to the identification, cloning, and characterization of the mammalian proteasome and the ubiquitination system that targets proteins for degradation. In addition, Dr. Tanaka nurtured and mentored many further successful scientists and led TMIMS for many years, first as director, and later as chairman. Among his many protégés, Yukiko Yoshida, continues his research legacy at TMIMS by studying ubiquitination and proteasomal degradation. One of Dr. Tanaka's contributions to proteasome research was the identification of different types of proteasomes, including immunoproteasomes and thymoproteasomes, which are required for adaptive immunity. Likewise, there are many different ubiquitination pathways besides canonical ones, and Dr. Yoshida has been studying ubiquitination mechanisms that specifically recognize and target glycosylated proteins. While most ubiquitin-conjugating enzymes recognize protein substrates, Dr. Yoshida has identified a ubiquitin ligase complex, SCF^{FBS2}, that recognizes the sugar chains of glycosylated proteins. Further, while most proteins are modified by ubiquitination of free amino groups on proteins, Dr. Yoshida determined that SCF^{FBS2} can ubiquitinate a substrate glycoprotein, Nrf1, on free hydroxyl groups in a non-canonical manner. Nrf1 is important in the expression of proteasomal genes and Dr. Yoshida has shown that inactivation of Nrf1 by her identified ubiquitination pathway is responsible for symptoms of a rare genetic disorder, NGLY1 deficiency. She recently published this work (Molecular Cell 84, 3115-3127, August 22, 2024). We spoke to her about her work.



Yukiko Yoshida

Why did you decide to become a research scientist?
It was so long ago I've forgotten! After graduating from college, I started working at a chemical company, and the work there was fun, but it wasn't work where we'd discover anything new. I realized that I wanted to continue learning, so I entered graduate school and returned to academia. After graduate school and post-doc, I entered Rinshoken, which is a precursor of this institute. I studied proteins that bind to glycans, which are the sugar portion of glycoproteins. Many proteins are known to be modified by glycosylation (the attachment of sugars or sugar chains to proteins) and glycosylation is a very complicated process with more than 300 proteins functioning in forming glycans and oligosaccharides. While a lot is known about glycosylation, a lot of the functions of glycans are still unknown. At Rinshoken, I isolated glycan-binding proteins and found FBS1, 2, and 3, which work as ubiquitin ligases. Since Tanaka sensei was the foremost expert in ubiquitin, I later joined his lab and he was instrumental in helping with this work.

Tell me about Tanaka sensei.
He was subarashii (amazing, wonderful)! Now that he isn't here, my heart is broken and it's been difficult for

me. I miss him very much. He was a great researcher, of course, but he was also very friendly and knew many people. Because he was a great scientist and a leader in the field, because he made so many friends, and because of his thirst for good science, he was also naturally a great connector. For example, I didn't know how SCF^{FBS2}, a ubiquitin ligase that I am studying, recognizes sugars, so he put me in touch with a famous structural biologist to figure this out. He broadened research by bringing researchers together to collaborate on interesting projects. These collaborations and connections are so vital in our field. One of the molecules that I study, NGLY1, is associated with a rare disease, NGLY1 deficiency. Tanaka sensei introduced me to a pioneer in NGLY1 research, so I'm now part of the NGLY1 deficiency rare disease community, which is very active and enthusiastic. People from many fields, about sixty researchers, are part of this community, and they've helped me and given me advice to speed up my research. Before, my knowledge was narrow, but now it's so much broader.

Please tell us a little more about your work.

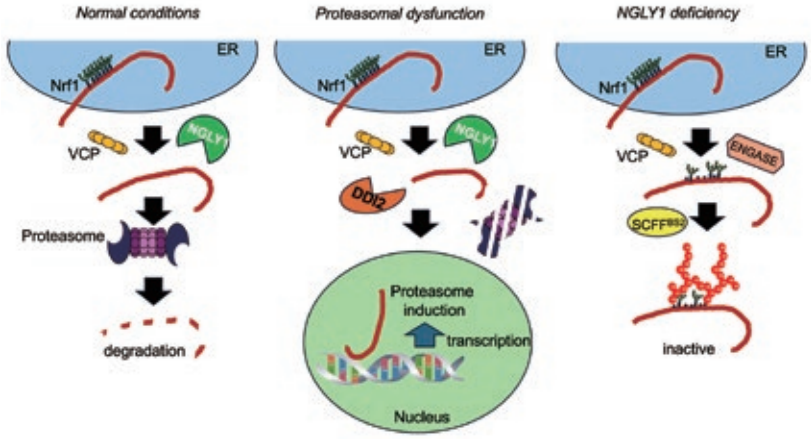
Protein degradation and recycling are critical for life, and the proteasome is required for this. So, when there aren't enough proteasomes or when proteasomes are damaged, they need to be replaced through increased expression of proteasomal genes. This occurs through activation of a transcription factor, Nrf1, which regulates proteasomal gene expression. Under normal conditions, when cells have enough proteasomes, Nrf1 is ubiquitinated and degraded, but when cells don't have enough proteasomes, Nrf1 doesn't get degraded. Instead, it is cleaved by an enzyme, DDI2, and de-glycosylated by another enzyme, NGLY1. This causes Nrf1 to translocate to the nucleus where it activates proteasomal gene expression. So Nrf1 has two fates, it can either be degraded or activated. However, we found a third fate for Nrf1. When cells don't have NGLY1, we found that the sugar molecules that are attached to Nrf1 are recognized by the sugar-dependent ubiquitin ligase, SCF^{FBS2}, that I study. This causes Nrf1 to be ubiquitinated in a distinct way that sends it to its third fate. In this third situation, Nrf1 is neither activated nor degraded, but enters an inactive, highly deleterious state. The importance of this pathway that we've discovered is that it seems to be the cause of the lethality of NGLY1 deficiency.

What are your plans for the future?

Now that we know that SCF^{FBS2} activity is responsible for the lethality and deleterious symptoms of NGLY1 deficiency, we need to find ways of inhibiting SCF^{FBS2} activity. Patient groups are also eager for us to find inhibitors of FBS2. So, in collaboration with Riken, we are screening for chemical inhibitors. We hope to find something promising.

Second, we are interested in understanding the normal biological function of SCF^{FBS2}. In our current paper, we uncovered a detailed and complex new mechanism by which glycoproteins, including Nrf1, are ubiquitinated. In "normal" or canonical ubiquitination, ubiquitin molecules are attached to the amino groups of lysine residues on proteins. However, we found that SCF^{FBS2} recruits an E3 ubiquitin ligase that ubiquitinates hydroxyl groups of serine and threonine residues of Nrf1 as well as a hydroxyl group on sugar molecules, GlcNAc residues, attached to Nrf1. This unconventional ubiquitination that we found is responsible for the lethality of NGLY1 deficiency, but this pathway didn't develop just to cause disease. It must have evolved for another purpose that is beneficial to cells. We're interested in identifying other substrates for SCF^{FBS2} in order to identify the normal cellular role of SCF^{FBS2}. I want to do this for myself, of course, but I also think I owe it to Dr. Tanaka to figure this out.

Interviewed and Written by Jun Horiuchi



Nrf1 is synthesized as an N-glycosylated, membrane protein in the endoplasmic reticulum (ER). Under normal conditions, Nrf1 is constitutively retrotranslocated to the cytosol by VCP, and degraded by the proteasome (left). Under conditions in which proteasomal activity is compromised, Nrf1 escapes degradation and is transported to the nucleus, where it activates proteasomal gene expression (middle). In the absence of NGLY1, Nrf1 is abnormally ubiquitinated by SCF^{FBS2} and enters an inactive, highly deleterious state (right).

Meet Our Scientists!

Anxiety and depression affect hundreds of millions of people worldwide, and these numbers increased significantly during the covid pandemic. Anxiety and depression are associated with stress, and decreased branching and complexity of neurons in various brain regions. However, the precise molecular pathways causing these disorders are not known. Takayuki Shimada and colleagues in the Child Brain Project at TMIMS recently elucidated a novel pathway through which stress induces these disorders and published this work in the October 9th, 2024 issue of the Journal of Neuroscience (44(41):e0129232024). They determined that stress reduces expression of an extracellular signaling molecule, neuritin. Neuritin, stabilizes the cell surface expression of the fibroblast growth factor (FGF) receptor, and FGF signaling controls axonal branching of serotonergic neurons in several brain regions. Thus, decreases in neuritin expression cause reductions in axonal branching of serotonergic neurons resulting in anxiety and depression. This work clarifies our understanding of the causes of anxiety and depressive disorders and paves the way for the development of new treatments. We spoke to Dr. Shimada about this work and his interest in science.

Tadayuki Shimada

How did you first become interested in science and research?

In high school, I remember learning about past scientists. I was very impressed when I learned about scientists such as Watson and Crick who discovered the structure of DNA, or Frederick Griffith, who used Pneumonia to suggest that bacteria are capable of transferring genetic information. These scientists discovered things that were not known before, and I decided that I, too, wanted to discover new things.

When did you become interested in studying depression and anxiety?

I wanted to know what causes cells to develop into different shapes. For example, neurons start out round, but then they extend processes that become dendrites and axons that are specialized in transmitting electrical signals. Neurons can extend axons that originate in the brain and extend all the way to the hips or intestines! I'm interested in understanding the mechanisms that control the extension, branching, and connections that these axons make. Since cell shape and branching are so important for cell function, I thought that there must be diseases that are caused by defects in cell shape. In this case, it turned out that the diseases resulting from defects in axonal branching are depression and anxiety.

So, your current findings are that changes in the shape of serotonergic neurons can cause anxiety and depression?

Yes, I think changes to the shape of serotonergic neurons contribute to these diseases. Most people think that anxiety and depression are caused simply by decreases in the amount of serotonin. If that's the case, increasing amounts of serotonin should quickly cure these diseases.

But that's not the case. SSRIs (selective serotonin reuptake inhibitors), drugs used to treat these diseases, increase amounts of serotonin quickly, but they take a long time to relieve disease symptoms. People have been focusing on understanding pathways downstream of serotonin, but I believe it's necessary to study the structure of serotonergic neurons and the release of serotonin itself. In our paper, we show that stress causes changes to the structure and branching of serotonergic neurons. Axons branch less and become less complex. So, I think less serotonin will be released, but it will be also released in fewer places. SSRIs may increase serotonin signaling in places where serotonin is still present, but they may not be optimal for restoring serotonin release to appropriate locations.

Please tell us the model you developed in your paper.

We found that a protein, neuritin, is important in depression and anxiety disorders. When we knocked out neuritin in mice, we found that these mice have less axonal branching in their serotonergic neurons and develop anxiety and depression symptoms. Conversely, we found that adding neuritin to cultured serotonergic neurons causes them to increase axonal branching. Chronic stress is known to cause depression and anxiety and we found that it decreases neuritin expression and decreases axonal branching of serotonergic neurons. From these results, we hypothesized that stress decreases neuritin expression, which in turn decreases serotonergic branching, causing depression and anxiety. If that is the case, we thought that overexpressing neuritin may protect mice from depression. And that turned out to be true. When we overexpressed neuritin in a brain region known as amygdala, we found that these mice became more resistant to depression caused by stress. They were also resistant to stress-induced decreases in serotonergic axonal branching.

How do you think neuritin controls axonal branching?

We found that neuritin affects the fibroblast growth factor (FGF) signaling pathway. The FGF signaling pathway is a well-known cellular pathway that affects many cellular processes including proliferation, regionnd survival. But, we've found that, besides its other well-characterized functions, FGF signaling is also important for axonal branching of serotonergic neurons. In particular, we've found that FGF-2 needs to bind to FGF receptor 1 on serotonergic neurons to promote axonal branching. We believe that neuritin binds to FGF receptor 1 and stabilizes its presence on the cell surface so that FGF-2 can bind to it to induce axonal branching. Consistent with this idea, we've found that inhibiting FGF signaling causes poor axonal branching of serotonergic neurons and leads to the development of depressive and anxiety behaviors.

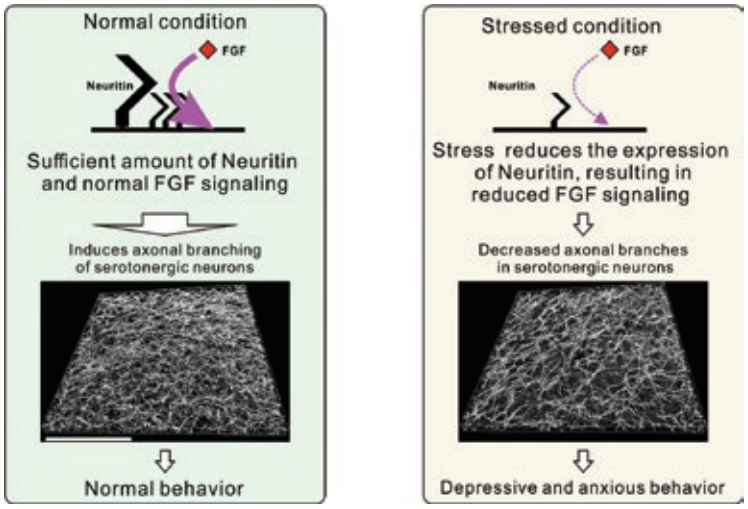
Do you think increasing FGF signaling may be a way to combat depression?

FGF signaling is involved in many pathways including cellular growth so I'd be concerned that indiscriminately increasing FGF signaling may induce cancers. Indeed, FGF inhibitors are used in anti-cancer therapies. However, a recent study showed that injection of FGF-2 into rat brains increased resistance to stress-induced depression. Therefore, I think that focusing on increasing neuritin or FGF in specific brain regions may be a better approach.

What are your future interests?

So far, we've found that alterations in axons are involved in diseases such as epilepsy, depression, and anxiety. I think there must be many other diseases that result from altered cell structures. So, I'd like to continue my work on studying the relationship between neuronal structures and diseases. In particular, I think that altered axonal structures must be present in developmental disorders including autism and intellectual disorders. I'd like to elucidate the mechanisms involved in those diseas

Interviewed and written by Jun Horiuchi



(Left panel) Under normal conditions, Neuritin is expressed in sufficient amounts to allow normal FGF signaling. FGF signaling promotes axonal branch formation in serotonergic neurons, resulting in normal behaviors.

(Right panel) Chronic stress decreases the expression of neuritin, resulting in impaired FGF signaling and decreased axonal branching of serotonergic neurons. This leads to the development of depressive and anxiety behaviors. Representative images of axons of serotonergic neurons in mouse amygdala are shown in both panels.

Meet Our Scientists!

We know intuitively that we have internal circadian clocks by our tendency to wake up in the mornings and go to sleep at night. This tendency continues even when we are in constant darkness where we shouldn't be able to tell whether it is day or night. But circadian clocks control many more behaviors than just sleep patterns. Clocks are found in plants, animals, and bacteria, and they govern almost all aspects of biology. The most important and intriguing characteristic of clocks is their oscillation. While we understand the physics behind oscillations of pendulums and springs, biological processes tend to approach a state of equilibrium where they become stable and don't oscillate. So, the study of biological clocks is important for biological and medical reasons, but also simply as a fascinating intellectual mechanism to understand. Currently, we've identified some aspects of circadian clocks. Two transcription factors, CLOCK and BMAL1, work together and bind to DNA sequences called E-boxes to activate transcription of genes, including PER and CRY. PER and CRY then inhibit CLOCK and BMAL1 activity, creating a rhythmic oscillation that is thought to be a core clock mechanism. However, this model is too simple and many questions still remain. Yuta Otobe and colleagues in the Circadian Clock Project at TMIMS are working on completely elucidating circadian clock mechanisms. Recently they found that phosphorylation affects DNA binding and PER-dependent inhibition of CLOCK and BMAL1 to regulate the function and frequency of the circadian clock (PNAS (2024), 121:23, e2316858121). We spoke to Dr. Otobe about his work.

Yuta Otobe

What first sparked your interest in biology?

When I was a child, there was a television show on reptiles hosted by Dr. Shouichi Sengoku. Dr. Sengoku loved reptiles and influenced many children, including me, to become fascinated by them. In my kindergarten, we raised a turtle, and I remember how worried I was when he escaped one day and how relieved I was when I found him six months later hibernating in the cold. Those early experiences made me love animals and made me want to become a researcher to understand them better.

My interest in circadian clocks came later when I was a student because I had a really hard time organizing my sleep/wake routines and other daily schedules. I wanted to know why my schedule kept getting later. I thought that if I could understand circadian rhythms, I could understand why it was so difficult for me to organize my daily rhythms.

How did you get involved in this current research?

I really have to acknowledge Mr. Shunsuke Ito, the third author of our paper. He was a former student who laid the foundations for this work. Cultured cells have circadian rhythms that we can measure through activity of reporter genes. Shunsuke knocked out CLOCK and BMAL1 in cultured cells and showed that these knockouts abolished circadian rhythms. He then added back CLOCK and BMAL1 and showed that rhythms were restored. The importance of this work was that it allowed us to now add back CLOCK and BMAL1 with different mutations to see how mutations affected rhythms.

We were interested in phosphorylation, which is a mechanism that modifies proteins to alter their function, so I inserted various mutations in phosphorylation sites in CLOCK and BMAL1. To summarize our results, I found that preventing phosphorylation of serine 38 and 42 in

CLOCK and serine 78 in BMAL1 by mutating these serines to alanine, shortened the circadian cycle. In the converse experiment, mimicking phosphorylation at these sites, by mutating them to glutamate, abolished rhythms. Previously, we'd found that phosphorylation of these sites inhibits CLOCK and BMAL1 from binding to DNA to activate transcription. In this current study, we showed that phosphorylation of these sites further regulates the period of the circadian clock.

How do your findings help us understand the circadian clock better?

We formed an international collaboration with Dr. Jae Kyoung Kim's group in Korea who helped us model the interactions between CLOCK, BMAL1, DNA, CRY, and PER. A previous model, called the Kim-Forger model, has been used to model oscillations of the circadian clock where CLOCK and BMAL1 activate transcription of PER and CRY which subsequently inhibit CLOCK and BMAL1 in a cyclic manner. In the Kim-Forger model, PER inhibits transcription by sequestering CLOCK and BMAL1 away from E-box DNA, while CRY inhibits transcription by directly binding to and inhibiting BMAL1. However, more recent studies have identified a different mechanism by which PER inhibits CLOCK-BMAL1-dependent transcription. In PER-dependent displacement, PER recruits the kinase, casein kinase I, which phosphorylates CLOCK to remove the CLOCK-BMAL1 complex from the E-box. We incorporated this new mechanism into the Kim-Forger model and conducted simulation studies to determine how our phosphorylation site mutations should affect the circadian period. While our serine-to-alanine mutations should decrease the dissociation constant of CRY-CLOCK-BMAL1 from DNA to lengthen the period, they were also able to decrease the dissociation constants of both PER-CLOCK-BMAL1 and PER-CRY-CLOCK-BMAL1 from DNA to shorten the circadian period in agreement with our experimental results. This indicates that our serine-to-alanine mutation may disrupt the PER-dependent displacement of the CLOCK-BMAL1 complex from DNA. Currently, I believe that serine 38 and 42 on CLOCK and serine 78 on BMAL1 are phosphorylated by a kinase, casein kinase I, which both decreases binding of CLOCK and BMAL1 to E-box DNA, and also affects the ability of PER to displace CLOCK and BMAL1 from E-box DNA. This mechanism is important, at least in fine-tuning the clock frequency.

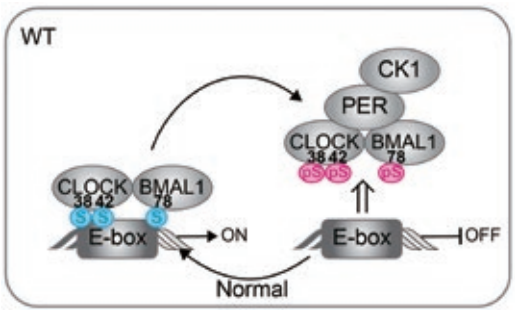
Wonderful work! What are your plans for the future?

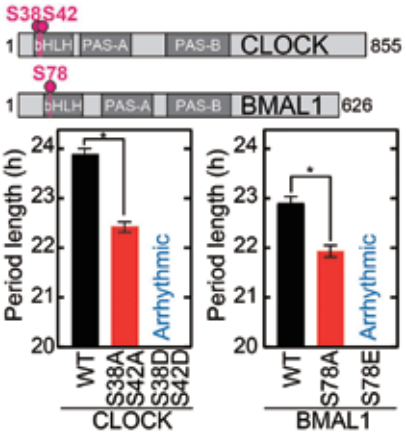
I've got many ideas I'd like to pursue for the future!

In the near future, I'd like to continue my current work of better understanding the circadian clock. This year, the institute obtained a next-generation mass spectrometer that can analyze 100,000 proteins at once. I'd like to comprehensively analyze protein changes and fluctuations at different time points in different mutants in order to develop more accurate models of clock function. Also, although our current work depends on feedback loops (PER and CRY) affecting transcription (CLOCK and BMAL1), this is likely only part of the circadian clock mechanism. We currently have solid evidence demonstrating the existence of a transcription- and translation-independent clock oscillator. I'd like to continue this work to identify the true core clock oscillator. Another idea I have is to try to reconstitute the circadian clock in vitro using cell extracts or purified CLOCK, CRY, BMAL1, PER, and CKI proteins.

Finally, in the far future, after I've obtained my own lab, I'd like to devote part of my time to studying reptiles or some other animal that might draw the interest of children. Similar to how Dr. Sengoku inspired me to pursue a career as a research scientist, I'd like to contribute in some way toward teaching children the joys of studying animals.

Interviewed and Written by Jun Horiuchi



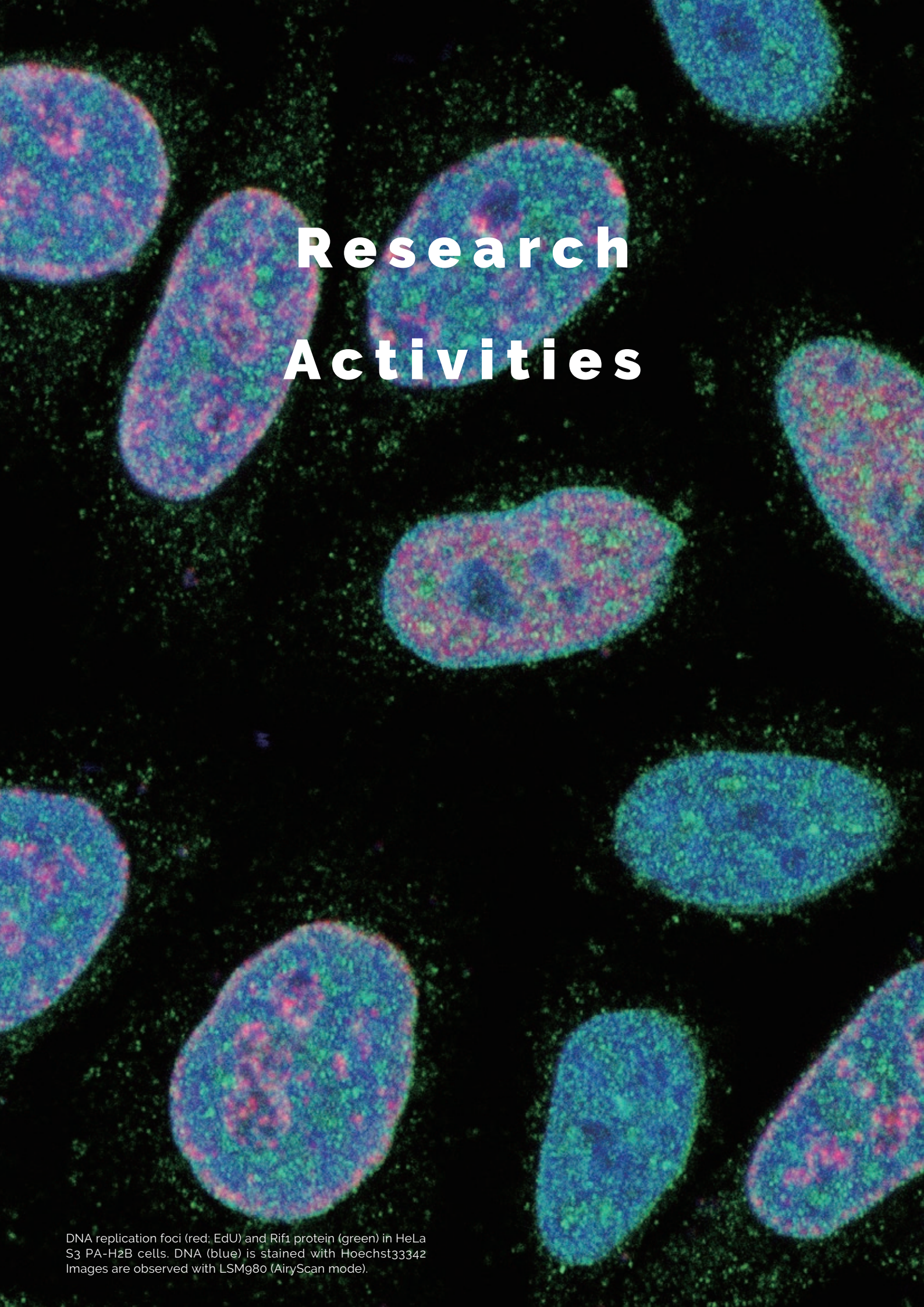


Ser38 and Ser42 in CLOCK and Ser78 in BMAL1 are important amino acid residues for period determination.

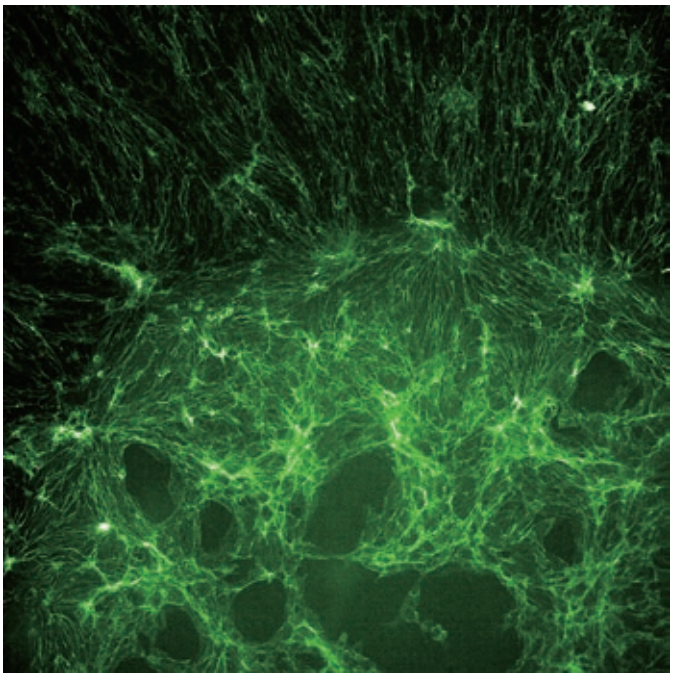
Our Goal

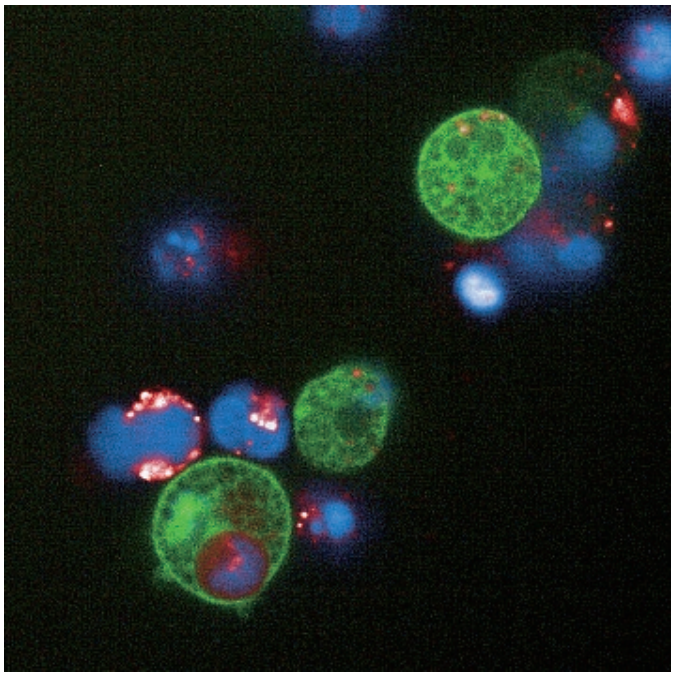
Our goal is to be a leading and role model institute for the life/medical science by conducting cutting-edge basic, clinical and social medical researches, that will help prediction, prevention, diagnosis, and treatment of various diseases and improve the care of patients, leading to longer healthy life.

Research Activities



DNA replication foci (red; EdU) and Rif1 protein (green) in HeLa S3 PA-H2B cells. DNA (blue) is stained with Hoechst33342 Images are observed with LSM980 (AiryScan mode).





CAR-M.pngPhagocytosis of leukemia cells (red) by human iPS cell-derived macrophages (green) expressing anti-CD19 chimeric antigen receptors. Nuclei were stained with DAPI (blue).
Organoid.pngHigh power fluorescent image of an endothelial/hematopoietic organoid derived from human iPS cells. Cells were stained with FITC-conjugated anti-CD31 antibody (green)

Basic Medical Sciences

Project Leader
Hiroyuki SASANUMA

Genome Dynamics

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

Sasanuma graduated from the Faculty of Science at Osaka University. He began his professional carrier in the drug discovery division of Ajinomoto Co., Inc.. Subsequently, he pursued doctoral studies at RIKEN and obtained his PhD from Saitama University. Dr. Sasanuma conducted research on meiotic recombination at both the University of Tokyo and Osaka University. His research interests later expanded to include chromosome instability and cancer development during his tenure at Kyoto University's Faculty of Medicine. In 2024, Dr. Sasanuma was appointed as the Project Leader of the Genome Dynamics Project.

Staff

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

Research Assistants
Naoko KAKUSHO
Rino FUKATSU
Akiko MINAGAWA

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

Research Progress in 2024

Background

The human genome, comprising approximately 3 billion base pairs, is frequently subjected to damage from both extrinsic and intrinsic factors. While the majority of this damage is effectively repaired, a subset remains unrepaired, leading to mutations. Although many of these mutations do not significantly impact cellular function, those that alter protein activity can influence cellular phenotypes, including growth rate and resistance to anti-cancer agents. In certain instances, cells may arise that are incapable of regulating their proliferation. These "cells that cannot cease proliferating" essentially represent cancer cells.

Achievements in 2024

Our laboratory is dedicated to elucidating the mechanisms underlying chromosomal instability, a hallmark of cancer, using model organisms such as E.coli, Yeast, human cell lines and mouse. Chromosomal instability is characterized by the inability to accurately transmit genetic information to daughter cells. For example, the incorporation of erroneous bases by DNA polymerase during DNA replication and repair processes can result in a deterioration of both the quality and quantity of genomic information. BRCA1 and BRCA2, which are tumor suppressor genes, play a crucial role in the process of homologous recombination HR and these losses also cause alteration of genomic information. Intriguingly, while HR is essential for cell proliferation in all organs, mutations in BRCA1/2 selectively lead to breast and ovarian cancers. This phenomenon presents a paradox in cancer biology, as the ubiquitous requirement for HR across all tissues contrasts with the specific cancer types associated with BRCA1/2 deficiencies. Elucidating the underlying mechanisms for this tissue specificity could provide crucial insights into cancer development and potentially leads to targeted therapeutic strategies. Our research focuses on dissecting the mechanisms of chromosomal instability induced particularly by defects in DNA replication and repair processes, as well as the consequent changes in genome dynamics. The goals of our research team are as follows:

1. Elucidation of how chromosome instability affects three-dimensional structure of the genome
2. Investigation of how genome integrity is maintained
3. Understanding organization and topology of the genome
4. Understanding molecular mechanism of tumorgenesis caused by genome instability

Publications

Papers in 2024

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"Sagi T, Sadato D, Takayasu K, Sasanuma H, Kanoh Y, "Masai H." RNA-DNA hybrids on protein coding genes are stabilized by loss of RNase H and are associated with DNA damages during S-phase in fission yeast, ***Genes Cells***. 2024 Nov;29(11):966-982. doi: 10.1111/gtc.13157.

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"Kim S, Yamada S (2/4), "Keeney S", Optimized methods for mapping DNA double-strand-break ends and resection tracts and application to meiotic recombination in mouse spermatocytes. ***bioRxiv***. 2024 doi: 10:2024.08.10.606181.

"Yamazaki K, Iguchi T, Kanoh Y, Takayasu K, Ngo TTT, Onuki A, Kawaji H, Oshima S, Kanda T, Masai H, "Sasanuma H", Homologous recombination contributes to the repair of acetaldehyde-induced DNA damage. ***Cell Cycle***. 2024 Feb;23(4):369-384. doi: 10.1080/15384101.2024.2335028.

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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
Liqin CAO
Ornjira PRAKHONGCHEEP

Research Assistants
Ai TAKAHASHI
Kayoko TAHARA

Students
Hiroko BEPPU

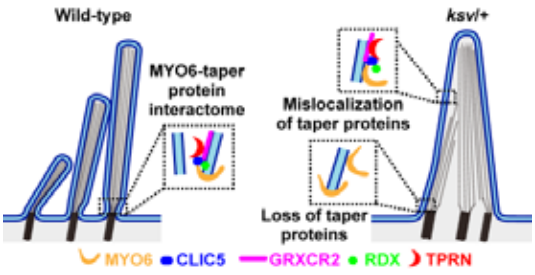
Research Progress in 2024

Background

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. While genes responsible for congenital hearing loss have been identified, genes associated with ARHL, which affects a far greater number of people, have not.

Achievements in 2024

An unconventional myosin, myosin VI gene (*MYO6*), contributes to recessive and dominant hearing loss in humans and mice. The Kumamoto shaker/waltzer (*ksv*) mouse is a model of deafness resulting from a splice-site mutation in *Myo6* (*PLoS One, 2017*). While *ksv/ksv* homozygous mice are deaf due to cochlear hair cell stereocilia fusion at the neonatal stage, the hearing phenotypes of *ksv/+* heterozygous mice have been less clear. Due to this splicing error, most MYO6 protein expression is lost in *ksv* mice; however, MYO6 with a single amino acid mutation (p.E461K) remains expressed. In this study, we investigated the hearing phenotypes and effect of a p.E461K mutation in *ksv/+* heterozygous mice. Hearing tests indicated that hearing loss in *ksv/+* mice arises concurrently at both low and high frequencies (*Exp Anim, in press*). In the low-frequency region, stereocilia fusions were detected in the inner hair cells of *ksv/+* mice. Expression analysis revealed abnormal MYO6 expression and localization, along with atypical expression of proteins in the basal region of the stereocilia, suggesting that these abnormalities may contribute to stereocilia fusion in *ksv/+* mice. Conversely, although the expression patterns of MYO6 and stereociliary basal-region proteins appeared normal in the cochlear area corresponding to high-frequency sounds, stereocilia loss was observed in *ksv/+* mice. These findings suggest that the *ksv/+* mice exhibit distinct mechanisms underlying hearing loss across areas responsible for low- and high-frequency hearing, differing from those previously reported in heterozygous *Myo6* mice with loss-of-function (*Neuroscience 2021*) and missense mutant alleles.



The heterozygous *ksv* mutation in the motor domain of MYO6 leads to disruption of the MYO6-taper specific protein interactome and stereociliary fusion in mice.

Publications

Papers in 2024

Seki Y, et al. "Dominant effect of a single amino acid mutation in the motor domain of myosin VI on hearing in mice." ***Exp. Anim***. in press

Mutai H, et al. "Genetic landscape in undiagnosed patients with syndromic hearing loss revealed by whole exome sequencing and phenotype similarity search." ***Hum. Genet***. in press

Fukuda M, et al. (2024) "Protein profile of mouse endolymph suggests a role in controlling cochlear homeostasis." ***iScience*** 27, 111214.

Key papers

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

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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 functions of calpain-mediated proteolysis, evolutionary aspect of calpain family, and mechanisms of calpain regulation.

Staff

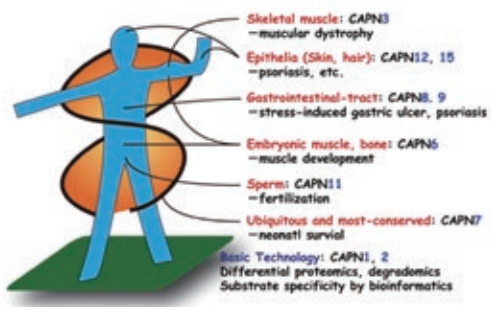
Researchers
Shoji HATA
Atsushi IRIE
Chihiro HISATSUNE
Fumiko SHINKAI-OUCHI
Aya NOGUCHI

Research Assistants
Naoko DOI

Research Progress in 2024

Background
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 their functions cause various health problems. These conditions include muscular dystrophy, stomach ulcers, dysfunctional cellular development and/or motility etc.
Calpains cut their substrate proteins, but in a very moderate way (like an established gardener taking care of garden trees).

So, we question;
- why calpains work that way,
- what happens if calpains do not work properly, and
- how can we mend and counteract cellular situations suffering from calpains' malfunction.



Achievements in 2024
Calpains are intracellular proteases, but they do function in coordination with extracellular circumstances and/or signal intracellular situations. This year, we focused on calpains expressed in several different tissues.
One of calpain species, CAPN3, which is predominantly expressed in skeletal muscle is a critical protease for the tissues and its genetic defects cause a muscular dystrophy called LGMDR1.
We are developing a methodology to witness when and where CAPN3 undergoes activation, which will enable us to identify CAPN3 substrates. In skeletal muscle, several different calpain species, e.g., CAPN1, 2, and 7, coexist and functional differences among them are becoming evident using gene-targeted myoblast culture systems.
Another exciting achievement of this year is a finding that there is an ancestral link between calpains and the ubiquitin-conjugating system. CAPN15, a widely conserved species across the invertebrate to human, has a ubiquitin-binding domain in its N-terminus which is likely to direct the interaction of CAPN15 with its substrate proteins. Importantly, the *CAPN15* mutations are associated with oculogastrointestinal neurodevelopmental syndrome, leading our focus on functional significance of CAPN15 in early development.

Publications

Key papers

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

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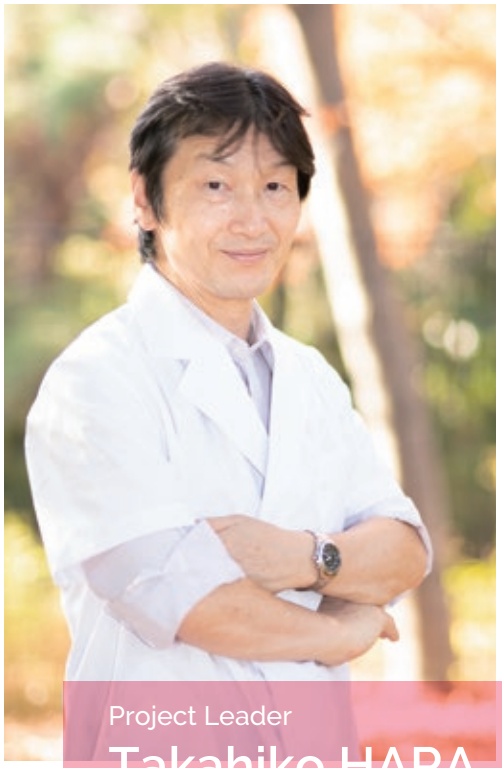


Project Leader
Takahiko HARA

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 (AGM) region of mouse embryo. Since then, molecular mechanism of HSC development has been his major research interest. In the mean while, he started toinvestigate regulators of spermatogonial stem cells and muscle regeneration factors. Subsequently, he focused on a RNA helicase DDX1 and a CXC-type chemokine CXCL14, as they are involved in tumorigenesis and anti-tumor immunity, respectively.

Stem Cell

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

Staff

Researchers
Kenji KITAJIMA
Kosuke TANEGASHIMA
Teruhiko SUZUKI
Masatoshi MURAOKA

Research Assistants
Tsuruyo TANIGUCHI
Mana YAMAKAWA

Students
Satoko TAKAGI
Yuka EGAWA
Manaka HASEBE
Junta FUNADA

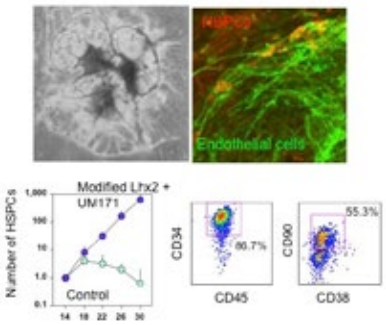
Research Progress in 2024

Background

In 2011, we discovered that overexpression of Lhx2 transcription factor in hemogenic endothelial cells (HECs) resulted in *ex vivo* expansion of transplantable HSCs from mouse embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). Since then, we have been making efforts for applying this method to human iPSCs. Meanwhile, we found that CXCL14 carries CpG DNA into dendritic cells. This resulted in activation of TLR9 signaling pathway for anti-tumor immune reactions. Importantly, CXCL14 also played a critical role in protecting skin from over-proliferation of *Staphylococcus* aureus. We are vigorously investigating physiological roles of CXCL14.

Achievements in 2024

Hematopoietic stem and progenitor cells (HSPCs) emerge in the AGM region during mid-embryonic development. Developmental process of HSPCs in the mouse AGM region can be reproduced in a 3D culture of ESCs/iPSCs. We developed a unique human iPSC organoid culture system that mimics the embryonic HSPC development. In addition, by overexpression of FLT3, we were able to generate more human HSPCs and macrophages *in vitro*.
In contrast to mouse ESCs/iPSCs, Lhx2 showed no effects on the HSPC production from human iPSCs. This year, we elucidated a reason for this phenomenon and finally succeeded in expanding human iPSC-derived HSPCs *in vitro* by employing an genetically modified Lhx2 in combination with an epigenetic regulator UM171. This *in vitro* culture system of human iPSCs was also effective for producing a large number of macrophages that can directly kill tumor cells. Furthermore, we expressed a chimeric antigen receptor that recognizes CD19, which has been used in the CAR-T therapy, in human iPSC-derived macrophages. They efficiently phagocytosed CD19-high leukemia cells. These results proved the applicability of our experimental system for cancer immunotherapy.



Newly developed organoid differentiation culture of human iPSCs. In this system, HSPCs were efficiently generated from HECs. Furthermore, an enforced expression of modified Lhx2 and addition of UM171 resulted in robust production of CD34+CD90+ human HSPCs.

Publications

Papers in 2024

Kitajima, K., et al. (2024) "Modification of Lhx2 activity for ex vivo amplification of human induced pluripotent stem cells." ***Front. Cell Dev. Biol.***, 12: 1482989.

Miyajima, R., et al. (2024) "Identification of low-density lipoprotein receptor-related protein 1 as a CXCL14 receptor using chemically synthesized tetrafunctional probes." ***ACS Chem. Biol.***, 19: 551-562.

Kitajima, K., et al. (2024) "FLT3 signaling augments macrophage production from human pluripotent stem cells." ***Int. Immunol.***, 36: 99-110.

Key papers

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.

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.

Project Leader
Hikari YOSHITANE

Hikari Yoshitane has been the leader of the Circadian Clock Project 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
Tomoko TANAKA
Yuki KATO
Yuta OTOBE

Research Assistants
Arisa KURABAYASHI
Yuri KATO

Visiting Scientist
Yoshitaka FUKADA
Miho YOSHIMURA
Satoshi KAWAKAMI

Students
Etsuko MITSUYOSHI
Taiki MORIMURA
Anna UCHIDA
Ryutaro SHIMAZAKI
Haruka YASUMOTO

Research Progress in 2024

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.

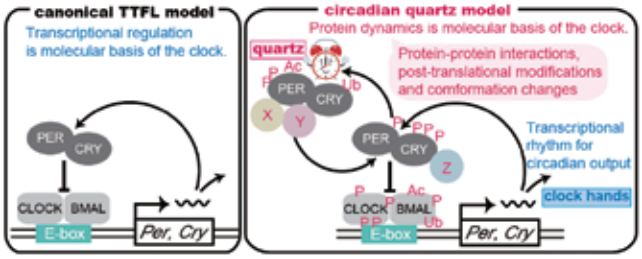
Achievements in 2024

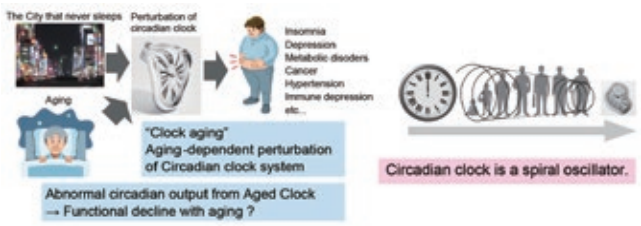
<objective 1. circadian quartz>

How does the circadian clock autonomously oscillate with a period of 24 hours? While the canonical TTFL is an important component of the clock that regulates circadian expression of downstream genes, we believe that the time-counting mechanism of the clock is regulated by protein dynamics, which includes protein-protein interactions, post-translational modifications and conformational changes of clock proteins. 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 timer 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.





Publications

Papers in 2024

Otobe et al., (2024) “Phosphorylation of DNA-binding domains of CLOCK-BMAL1 complex for PER-dependent inhibition in circadian clock of mammalian cells.” ***Proc. Natl. Acad. Sci. USA***, 121(23): e2316858121

Hiroki and Yoshitane (2024) “Ror homolog nhr-23 is essential for both developmental clock and circadian clock in C. elegans.” ***Communications Biology***, 7(1):243

Masuda et al., (2024) “TRAF7 determines circadian period through ubiquitination and degradation of DBP.” ***Communications Biology***, 7(1):1280.

Key papers

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

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.

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

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

Laboratory Head
Yukiko YOSHIDA

Protein Metabolism

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

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

Staff

Researchers
Akinori ENDO
Hiromichi YONEKAWA

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

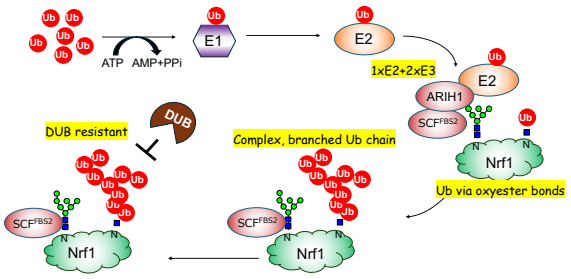
Research Progress in 2024

Background

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

Achievements in 2024

We have studied glycoprotein-specific ubiquitin ligases in the cytosol, and found that a disease, so-called NGLY1 deficiency, associated with reduced deglycosylation activity in the cytosol causes accumulation of ubiquitylated glycoproteins and proteasomal dysfunction (PNAS, 2021). Ubiquitination normally binds to lysine in proteins, but in this reaction, it bound to serine, threonine, and GlcNAc near sugar chains in Nrf1, a transcription factor of the proteasome. This non-canonical ubiquitination by two ubiquitin-ligase complex (SCF^{FBS2}-ARIH1) inactivates Nrf1 and prevents restoration of proteasome dysfunction (see figure) (Mol Cell, 2024). We have also elucidated the structure of the enzyme Fbs2 and how it binds to glycans (FEBS lett, 2024). These finding paves the way for therapeutic target for NGLY1 deficiency. Further, we have found that a deubiquitylating enzyme protects cells from organelle stress (JCB, 2024: BioEssays, 2024). Thus, our goal of understanding cellular proteostasis and the ubiquitin-proteasome system is important for understanding the pathogenesis of many diseases affecting our health.



Ubiquitin is a small protein consisting of 76 amino acids that binds to lysine residues of substrates, usually by a combination of three enzymes: a ubiquitin-activating enzyme (E1), a ubiquitin-conjugating enzyme (E2), and a ubiquitin ligase (E3). This reaction is repeated to form ubiquitin chains. This study found that the ubiquitination that inactivates Nrf1 was performed by two E3s (SCF^{FBS2}-ARIH1) and one E2 (UBE2L3), which bind to the hydroxy groups of Ser and Thr near N-glycans and GlcNAc generated by the removal of N-glycans by ENGASE. The ubiquitin chains formed were complex and branched. These atypical ubiquitin chains were resistant to deubiquitinating enzymes. Thus, in the absence of NGLY1, Nrf1 is detected as a stable ubiquitinated protein in the cytosol, and this ubiquitination prevents Nrf1 from nuclear transport.

Publications

Papers in 2024

Endo A, et al. (2024) "USP8 prevents aberrant NF-kB and Nrf2 activation by counteracting ubiquitin signals from endosomes." ***J. Cell Biol***. 223:e202306913.

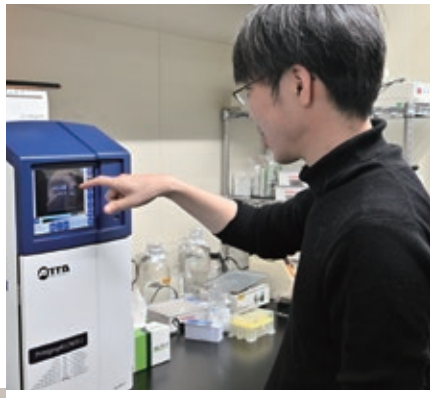
.Yoshida Y, et al. (2024) "Sugar-mediated non-canonical ubiquitination impairs Nrf1/NFE2L1 activation." ***Mol Cell*** 84: 3115-3127.

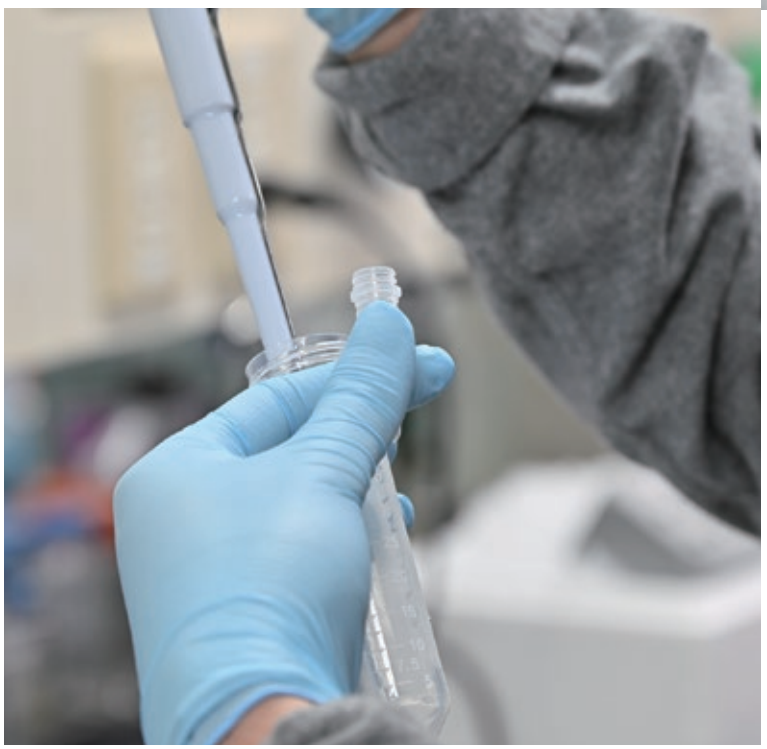
Satoh T, et al. (2024) "Structural basis of sugar recognition by SCFFBS2 ubiquitin ligase involved in NGLY1 deficiency." ***FEBS Lett***. 598:2259-2268.

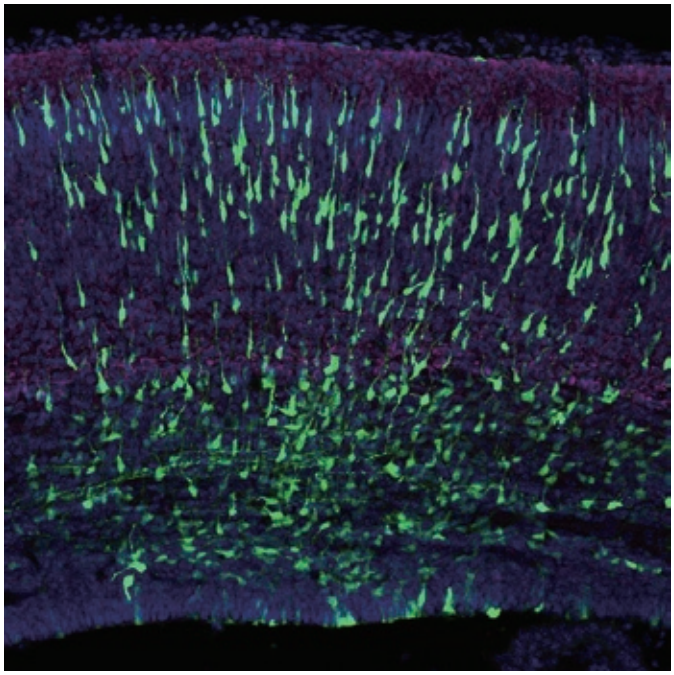
Endo A, et al. (2024) "Ubiquitin-mediated endosomal stress: A novel organelle stress of early encosomes that initiates cellular signaling pathways." ***BioEssays***. 46: 2400127.

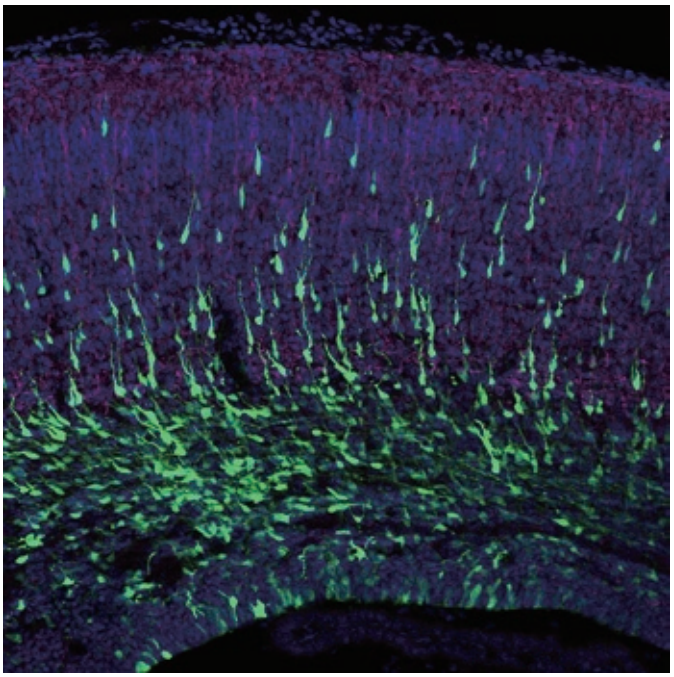
Key papers

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



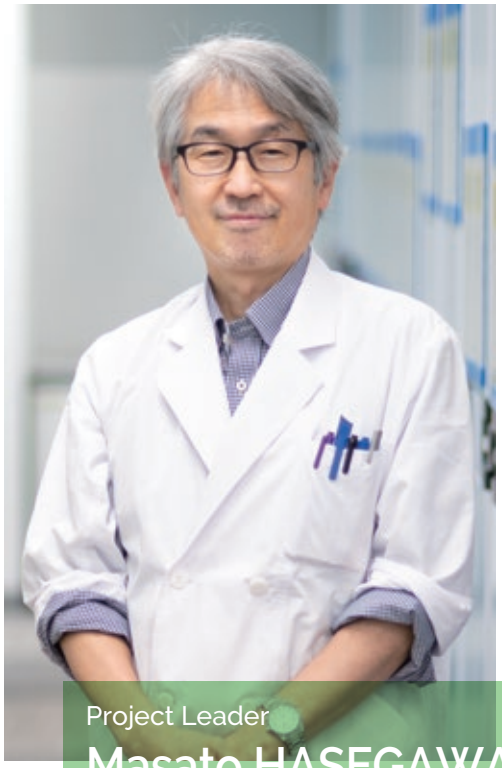






In utero electroporation of neuroD1-Adamts2 plasmids with GFP plasmids was performed at mouse E14 stage, and the brains were dissected at E17. Neuron-specific overexpression of Adamts2 resulted in impaired migration(right) compared to the control(left).

Brain & Neurosciences



Project Leader
Masato HASEGAWA

Masato Hasegawa, Head of the Department of Brain and Neurosciences, studies the molecular pathogenesis 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
Naomi NIHONMATSU
Fuyuki KAMETANI
Airi TARUTANI
Shotaro SHIMONAKA

Research Assistants
Reiko OHTANI
Marina TAHIRA

Students
Shohei TAKAKI
Yuta SATO
Shunsuke KANNO
Araki KIMURA

Research Progress in 2024

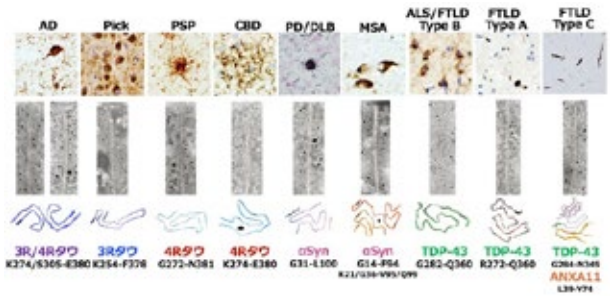
Background

Many neurodegenerative diseases are associated with intracellular accumulation of abnormal amyloid-like proteins, including tau in Alzheimer's disease (AD), alpha-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 correlates with clinical presentation and disease progression.

We have been studying these disease-associated proteins using immuno-histochemical, ultrastructural, and biochemical methods. In collaboration with the groups of Michel Goedert, Sjors Scheres, and Benjamin Ryskeldi-Falcon in MRC LMB, we have determined the structures of pathological tau, alpha-synuclein, and TDP-43 filaments extracted from patient brains. We have found that these proteins have characteristic folding structures that form unique amyloid-like filaments in different diseases. This indicates that different folding variants of the same protein can cause different diseases and that structural analysis of pathological proteins is useful for disease classification.

Achievements in 2024

In 2024, we found that tau from a patient with a VCP D395G mutation contained CTE (chronic traumatic encephalopathy)-type folds instead of AD-type folds. We also analyzed TDP-43 filaments from a patient with FTLD-TDP type C and found that TDP-43 forms heteromeric filaments with a second protein, ANXA11. Previously pathological proteins were only known to form homomeric filaments. These studies show that the pathogenesis of neurodegenerative diseases is much more varied and complex than previously thought.



Publications

Papers in 2024

Arseni D, Nonaka T, et al. (2024) "Heteromeric amyloid filaments of ANXA11 and TDP-43 in FTLD-TDP Type C". ***Nature***. 634(8034):662-668.

Qi C, et al. (2024) "Tau filaments with the chronic traumatic encephalopathy fold in a case of vacuolar tauopathy with VCP mutation D395G". ***Acta Neuropathol***. 147(1):86.

Kametani F, et al. (2024) "Analysis and comparison of post-translational modifications of -synuclein filaments in multiple system atrophy and dementia with Lewy bodies". ***Sci Rep***. 14(1): 22892 .

Key papers

Qi C, et al. (2023) "Tau filaments from amyotrophic lateral sclerosis/parkinsonism-dementia complex adopt the CTE fold". ***Proc Natl Acad Sci U S A***. 120(51): e2306767120.

Tarutani A, et al. (2023) "Distinct tau folds initiate templated seeding and alter the post-translational modification profile". ***Brain*** 146(12):4988-4999.

Arseni D, et al. (2023) "TDP-43 forms amyloid filaments with a distinct fold in type A FTLD-TDP." ***Nature***. 620(7975):898-903.

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

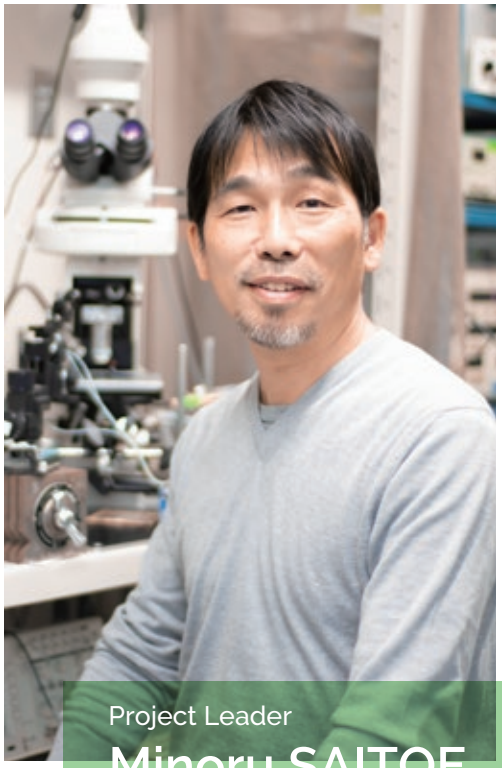
Schweighauser M, et al. (2022) "Age-dependent formation of TMEM106B amyloid filaments in human brains". ***Nature***. 605(7909):310-3148.

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.

Hosokawa M, et al. (2022) "Development of a novel tau propagation mouse model endogenously expressing 3 and 4 repeat tau isoforms." ***Brain***. 145(1):349-361.

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

Shi Y, et al. (2021) "Structure-based classification of tauopathies." ***Nature***. 598(7880):359-363.



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 learnin g and memory and synaptic plasticity. He is especially interested in glial-neuron networks, functional diversity of the monoamine system, and age-related memory impairments. Other interests include the molecular and neural bases of psychological phenomenon such as empathy and causality.

Learning and Memory

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

Staff

Researchers
Kohei UENO
Tomoyuki MIYASHITA
Motomi MATSUNO
Shintaro NAGANOS
Takahiro ISHIKAWA
Akinobu SUZUKI
Hiroaki ISHIDA

Postdoctoral fellows
Hiroshi KUROMI
Takashi ABE

Research Assistants
Maiko NAGAMINE
Yayoi ONODERA
Akane OOGIYA
Tomoko TAKAMISAWA

Students
Maximiliano Martinez-Cordera

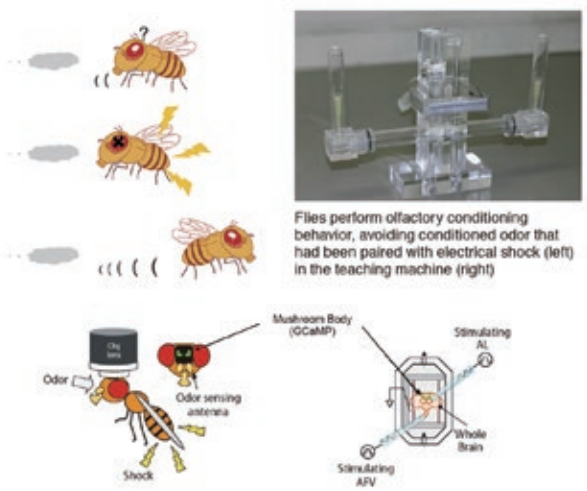
Research Progress in 2024

Background

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.

Achievements in 2024

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.

Publications

Key papers

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

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

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

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

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

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

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

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

Project Leader
Yukio NISHIMURA

Neural Prosthetics

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

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

Staff

Researchers
Toshiki TAZOE
Sho K. SUGAWARA
Kyuengbo MIN
Osamu YOKOYAMA
Michiaki SUZUKI
Masafumi NEJIME
Noboru USUDA
Kei OBARA
Hironori TSUJI

Research Assistants
Naoko YOSHIDA
Shoko HANGUI
Yukie AIZAWA
Tsuta UCHIDA
Ayumi ITO
Yuka KANNO
Akiko KAGEKAWA

Students
Norihiro IWAMOTO
SIBO LIN
Ayane OZAKI

Visiting Researcher
Kazutake KAWAI
Yoshihisa NAKAYAMA

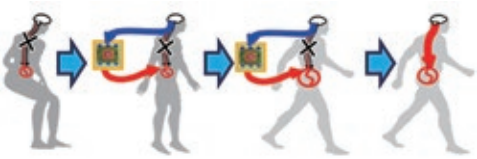
Research Progress in 2024

Background

We are committed to developing innovative strategies for neuro-rehabilitation to restore lost function following nervous system damage and translating these breakthroughs into clinical applications that significantly improve the quality of life for individuals with neural impairments.

At the forefront of our work is the Artificial Neuronal Connection (ANC), a cutting-edge neural interface designed to bridge spinal lesions by connecting supraspinal systems to spinal networks distal to the lesion. This approach effectively restores lost motor function. Through ongoing clinical trials, we are rigorously assessing the efficacy of ANCs in enhancing motor recovery in paralyzed patients while investigating the neural adaptations underpinning the recovery process.

Depression often hinders, while motivation enhances, functional recovery after neuronal damage. Although increased motivation is known to boost motor performance, the neural substrates driving this psychological effect remain elusive. Our research seeks to identify these substrates by uncovering the functional role of the mesocortical pathway in motor control.

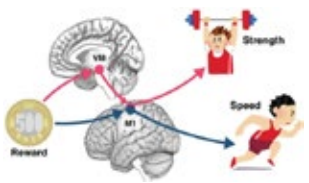


Achievements in 2024

We identified a novel pathway where the primary motor cortex (M1) predicts and integrates spinal reflexes into motor control. By simultaneously recording cortical, afferent, and muscle activities in monkeys during reaching tasks, we demonstrated that M1 drives spinal reflex-mediated muscle activity via a "transafferent pathway." This finding advance the development of ANC, enabling optimal motor output by incorporating spinal reflex pathways (Sci Adv 2024).

We revealed the functional role of the mesocortical pathway in mind-motor interactions during incentive motivation. Using functional magnetic resonance imaging, we showed that dopaminergic midbrain activity enhances grip force by modulating premovement activity in M1. This result highlight how motivation optimizes motor performance, providing critical insights into the neural mechanisms linking motivation and motor control (Neurosci Insights 2024).

Together, these studies deepen our understanding of motor control mechanisms and motivation, contributing to the development of neuro-rehabilitation strategies.



Publications

Papers in 2024

Umeda T, Yokoyama O, Suzuki M, Kaneshige M, Isa T, Nishimura Y. (2024) "Future spinal reflex is embedded in primary motor cortex output." ***Science Advances*** in press.

Yokoyama O, Nishimura Y. (2024) "Preselection of potential target spaces based on partial information by the supplementary eye field." ***Communications Biology*** 7: 1215.

Sugawara SK, Nishimura Y. (2024) "The Mesocortical System Encodes the Strength of Subsequent Force Generation." ***Neuroscience Insights***. doi:10.1177/26331055241256948.

Key papers

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Sawada M et al. (2015) "Function of nucleus accumbens in motor control during recovery after spinal cord injury." ***Science***, 350 no. 6256, 98-101

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
Mariko KASAI
Kuniko KOHYAMA

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

Research Assistants
Fumie MASUDA
Nobuko OGAWA

Students
Asako HORINO
Hiroya NISHIDA
Kengo MORIYAMA
Motoshi FUJITA
Rie NAKAI
Takayuki MORI
Yumie TAMURA
Shinpei MATSUDA
Eri OHASHI

Research Progress in 2024

Background

Our research focuses on central nervous system diseases in childhood. They are significant social burden because of poor prognosis and high mortality.

Neurological diseases are eventually caused by neuronal dysfunction regardless of their causes. We focus on developmental and intellectual disabilities caused by neuronal dysfunction, and aim to elucidate the pathogenesis of these diseases using various mouse models of disease with special focus on neuronal morphology.

We have established a sustainable platform (a multicenter registry of patients and sample repository) for a prospective cohort studies based on nationwide and international collaboration. We use multi-omics approaches to identify human disease-specific biomarkers. This multifaceted approach using high-throughput methods enables us to explore novel molecular targets for the treatment of pediatric brain diseases.

Achievements in 2024

Chronic stressful environments are known to induce depressive and anxiety-like behaviors in mice. We demonstrated that chronic stress conditions induce depressive and anxiety-like behaviors by decreasing the expression of Neuritin, which in turn suppresses the activation of FGF signaling and reduces axonal branching of serotonergic neurons.

In clinical research, as a result of our multi-institutional clinical studies, we developed a diagnostic prediction score for NMDAR encephalitis in children and clarified the clinical characteristics of SARS-CoV-2 associated encephalopathy. We also led an international collaborative study on virus-related acute encephalopathy that proposed the new concept of infection-triggered encephalopathy syndrome (ITES) and published consensus guidelines for it.

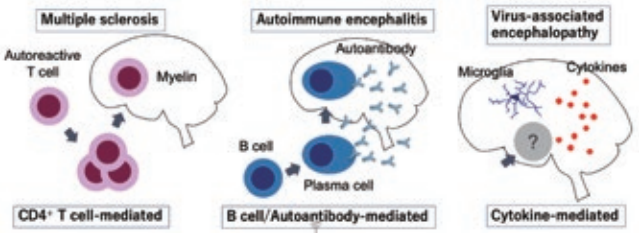


Figure Pathomechanisms of inflammatory and autoimmune neurological diseases
Multiple sclerosis has been regarded as CD4 T-cell mediated disease, in which autoreactive T cells are activated, proliferate, migrate into brain, and cause myelin damage. Autoimmune encephalitis is caused by autoantibodies against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

Publications

Papers in 2024

Shimada T, et al. (2024) " Neuritin controls axonal branching in serotonin neurons: A possible mediator involved in the regulation of depressive and anxiety behaviors via FGF signaling. " *J Neurosci*. 44: 1-17.

Kasai M, et al. (2024) " Clinical characteristics of SARS-CoV-2-associated encephalopathy in children: Nationwide epidemiological study. " *J Neurol Sci*. 457:122867.

Sakuma H, et al. (2024) " International consensus definitions for infection-triggered encepha- lopathy syndromes. " *Dev Med Child Neurol*. doi: 10.1111/dmcn.16067.

Key papers

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.

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

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

Project Leader
Chiaki OHTAKA-MARUYAMA

Chiaki Ohtaka-Maruyama obtained her Ph.D. from the Department of Biology at the University of Tokyo. She then worked as a post-doctoral fellow at NEI, NIH (Bethesda, MD, USA), and Riken (Wako) and became a Research Scientist at the Tokyo Metropolitan Institute for Neuroscience (the predecessor of the Tokyo Metropolitan Institute of Medical Science) in 2006. She studies neural development and has been a project leader since April 2019. Her research focuses on understanding the molecular and cellular mechanisms of cortical development. In particular, she is interested in how the mammalian six-layered structure developed during evolution. Using time-lapse imaging and functional analyses, she discovered a novel function of subplate neurons in regulating radial neuronal migration.

Developmental Neuroscience

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

Staff

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

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

Students
Hitomi ACHIWA
Kyosuke WADA
Ayako YOKOKAWA
Haruka NOMURA
Yusuke SUGITA
Ryoka KATAYAMA
Xianghe SONG
Shoma ISHIZUKA
Sota YAMAZAKI
Yurika NOGUCHI
Kokono SATO
Akihito SHINOHARA
Senri DOI

Research Progress in 2024

Background

How does the mammalian neocortex acquire the unique six-layered structure that is thought to be the structural basis of complex neural circuits? To answer this question, we focus on subplate neurons (SpNs) that develop and mature first during cortical development. During fetal brain development, the migration, arrangement, and neuronal circuitry of a large number of neurons are precisely controlled, and SpNs play a crucial role in this process. Although altered SpN dynamics are associated with developmental disorders, the detailed mechanisms for SpN function remains unclear. Our research team studies the relationship between SpNs and neural network development in mice and humans to understand how transient early neural networks affect permanent neural networks that last throughout life(Fig.1).

Achievements in 2024

We previously found that SpNs convert the migration mode of developing neurons from multipolar to bipolar (Science, 2018). In 2024 we showed that migrating neurons secrete the metalloprotease, Adamts2, which cleaves extracellular matrix proteins to activate TGF-β, which facilitates multipolar to bipolar transitions (EMBO Rep, 2024, Fig2). In a separate study, we also found that thalamic activity is critical for the differentiation of sensory input cells in the avian cerebellum (JCN, 2024).

Fig.1 Comparison of subplate markers by spatial transcriptome across species

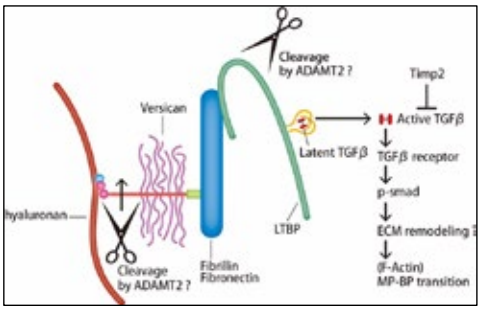


Fig.2 Adamts2 activates TGFβ signaling through ECM remodeling in the SP layer

Publications

Papers in 2024

Kaneko N et al.(2024) "ADAMTS2 promotes radial migration by activating TGF- signaling in the developing neocortex. " ***EMBO reports*** 7, 3090-3115

Katayama R et al.(2024) "Thalamic activity-dependent specification of sensory input neurons in the developing chick entopallium." ***J Comp Neurol***. 6, e25627.

Key papers

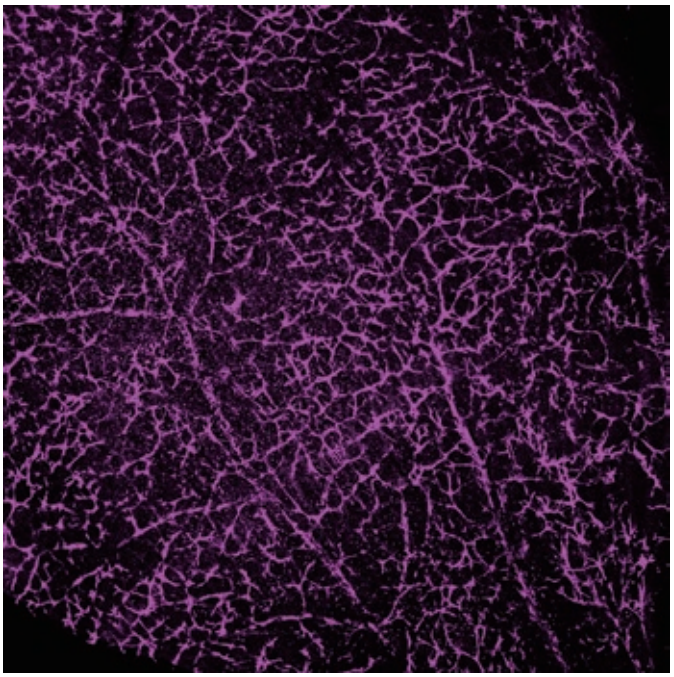
Kumamoto T and Ohtaka-Maruyama C (2022) "Visualizing Cortical Development and Evolution: A Toolkit Update" ***Front Neurosci***., 16,876406

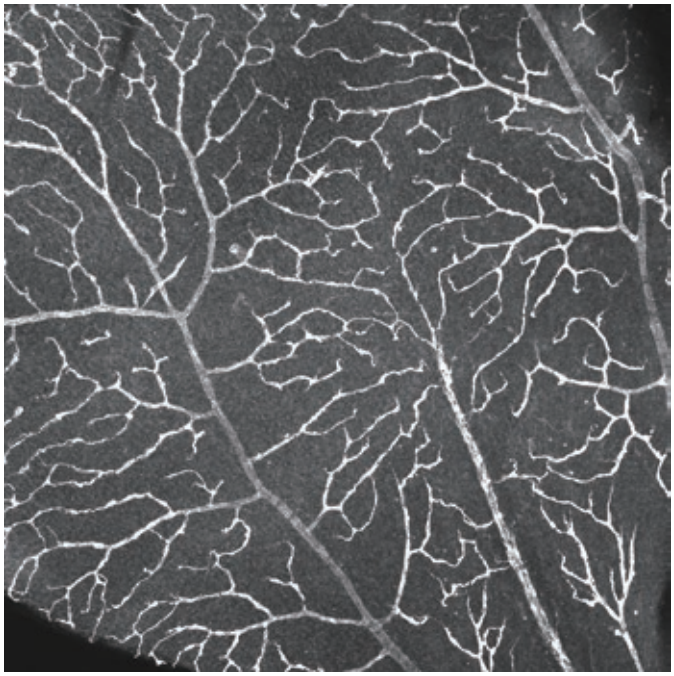
Ohtaka-Maruyama C (2020) "Subplate neurons as an organizer of mammalian neocortical development. "***Front. Neuroanat***. 14, 8.

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





The staining patterns of superficial retinal vessels and astrocytes in a wild-type mouse retina. After retinal flat-mount preparation, vascular endothelial cells were stained with an anti-CD31 antibody (left panel), and astrocytes were stained with an anti-GFAP antibody (right panel). Images were captured using a confocal microscope.

Psychiatry & Behavioral Sciences

Project Leader
Makoto ARAI

Schizophrenia Research

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

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

Staff

Researchers
Masanari ITOKAWA
Kazuya TORIUMI
Isabella Supardi PARIDA

Research Assistants
Eriko MAKIYAMA
Koichi TABATA
Hidetoshi TAKAGI

Students
Mai ASAKURA
Tianran WANG
Kyoka IINO
Mayuko MASADA
Azuna OZAWA
Yasufumi TOMITA

Research Progress in 2024

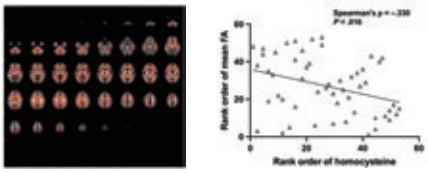
Background

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 prevention and treatment of schizophrenia. We focus on developing individualized medicine for the treatment of schizophrenia, investigating factors involved in disease onset, and understanding molecular pathology using biomarkers to overcome the barrier of heterogeneity. Our research results will be applied to drug development by establishing a new biomarker-based research field in molecular psychiatry. Data from metabolomics, genomics, cellular models, animal models, post-mortem brain analysis and neuropsychological research will be consolidated to elucidate the genetic and environmental factors relevant to psychiatric disorders such as schizophrenia.

Achievements in 2024

Recently, it has been reported that increased plasma homocysteine (Hcy) levels are associated with the risk of developing schizophrenia (SZ) and its severity. *In vivo* and *in vitro* studies have shown that Hcy promotes oxidative stress and inflammation, and damages of white matter (WM).

Additionally, large-scale studies using diffusion tensor imaging (DTI) have reported lower fractional anisotropy (FA), an indicator of WM dysconnectivity, in people with SZ. However, the underlying mechanism of WM dysconnectivity in SZ remains unclear. We investigated the relationship between plasma Hcy levels and WM microstructure in 53 individuals with SZ and 83 healthy controls (HC) using DTI. A significant negative correlation between plasma Hcy levels and WM microstructural disruption was found in the SZ group but not in the HC group. Our results suggest that increased Hcy may be associated with WM dysconnectivity in SZ, and the interaction between Hcy and WM dysconnectivity may be a potential mechanism of the pathophysiology of SZ (***Schizophrenia***. 2024).



Areas of significant FA reduction in individuals with SZ and correlation between plasma Hcy levels and mean FA. Individuals with SZ showed widespread FA reduction on skeletonized FA images compared to those in the HC group. These reductions extended into the bilateral deep WM areas in the frontal, temporal, parietal, and occipital lobes, a large part of the corpus callosum, and the corona radiata. In the SZ group, there was a significant negative correlation between the plasma Hcy levels and mean FA of the clusters with a significant group difference.

Publications

Papers in 2024

Tabata K, et al. (2024) "Association of homocysteine with white matter dysconnectivity in schizophrenia." ***Schizophrenia (Heidelb)***. 10(1):39.

Asakura M, et al. (2024) "Anthocyanins as potent inhibitors of pentosidine synthesis: Antioxidant-mediated effects." ***Biochem Biophys Res Commun***. 740:151007.

Wang T, et al. (2024) "Amyloban, extracted from Hericium erinaceus, ameliorates social deficits and suppresses the enhanced dopaminergic system in social defeat stress mice." ***Neuropsychopharmacol Rep***. 44(4):728-736.

Watanabe A, et al. (2024) "The origin of esterase activity of Parkinson's disease causative factor DJ-1 implied by evolutionary trace analysis of its prokaryotic homolog HchA." ***J Biol Chem***. 300(7):107476.

Lo T, et al. (2024) "Association between copy number variations in parkin (PRKN) and schizophrenia and autism spectrum disorder: A case-control study." ***Neuropsychopharmacol Rep***. 44(1):42-50.

Nakatochi M, et al. "Copy number variations in RNF216 and postsynaptic membrane-associated genes are associated with bipolar disorder: a case-control study in the Japanese population." ***Psychiatry Clin Neurosci***. in press

Key papers

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

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). 2022;8(1):44.

Project Leader
Makoto HONDA

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

Sleep Disorders

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

Staff

Researchers
Taku MIYAGAWA
Akiyo NATSUBORI
Yoshiki MATSUDA
Tohru KODAMA

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

Visiting Scientist
Mihoko SHIMADA

Research Progress in 2024

Background

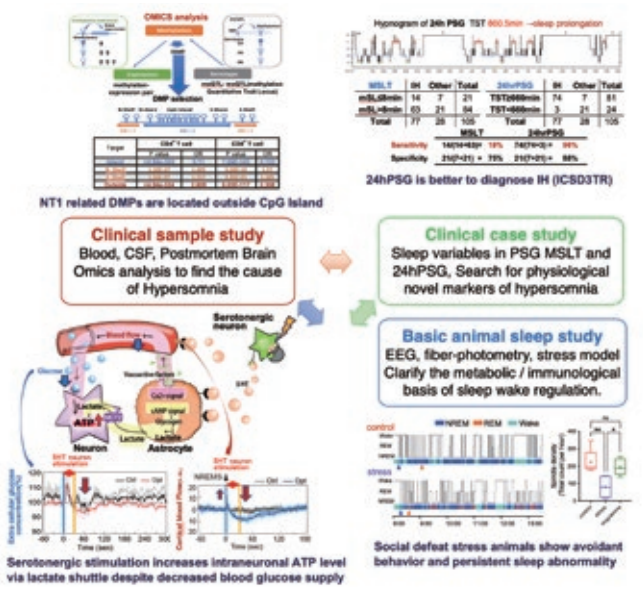
Narcolepsy(NT1) and idiopathic hypersomnia(IH)are caused by abnormal regulation of intrinsic sleep-wake brain centers but the pathogenesis remain to be clarified. Hypersomnia patients shows cognitive dysfunction leading to severe impairment in daily/ social life, but we only have inadequate symptomatic therapy. So underlying physiological/pathological sleep wake regulation in hypersomnia is necessary.

Achievements in 2024

We continue to recruit clinical cases suspected of hypersomnia (total >1000) with PSG-MSLT data and DNA sample. By omics analysis we identified fatty acid/metabolic abnormalities in NT1 and IH and global hypomethylation in NT1

We organized diagnostic 3-day sleep study system comprising of 24hPSG-PSG-MSLT and found 24hPSG is better test to detect IH patients.

Animal sleep study demonstrated that serotonergic stimulation increases intraneuronal ATP level during Wake by two pathways. We also identified persistent sleep dysregulation in animal with social defeat stress.



Publications

Papers in 2024

Natsubori A et al Serotonergic regulation of cortical neurovascular coupling and hemodynamics upon awakening from sleep in mice. *J Cereb Blood Flow Metab* 271678X24128843.

Matsuda Y et al Physiological paradigm for assessing reward prediction and extinction using cortical direct current potential responses in rats. *Sci Rep*14:10422.

Shimada M et al Identification of region-specific gene isoforms in the human brain using long-read ttranscriptome sequencing. *Sci Adv* 10 eadj529

Key papers

Natsubori A et al. (2023) Serotonergic neurons control cortical neuronal intracellular energy dynamics by modulating astrocyte-neuron lactate shuttle *iScience* 26, 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

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

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
Masayo FUJITA
Seii OHKA
Hiroki FURUIE
Hiroko KOTAJIMA
Yuiko IKEKUBO

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

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

Research Progress in 2024

Background

Addiction to various substances (e.g., drugs, alcohol, and tobacco) and behaviors (e.g., internet and gambling) is a serious public health problem. 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 by studying action mechanisms of opioids, dopamine, and hallucinogens. (2) Improving personalized pain treatment based on the genome information. (3) Developing novel treatments for developmental disorders including attention deficit hyperactivity disorder and autism spectrum disorder.

Achievements in 2024

Dopamine plays an important role in motor control as well. Impairment of the striatal dopaminergic projection causes Parkinson's disease, which shows mainly motor symptoms. In addition to motor symptoms, patients of Parkinson's disease show apathy, a state of low motivation that manifests as a decrease in goal-directed behaviors. We prepared model mice of Parkinson's disease by 6-hydroxydopamine injection into bilateral dorsal striatum. The model mice showed impairment of novelty seeking as a symptom related to the cognitive apathy component (Int J Mol Sci 2024). This study indicated that depletion of the dorsal striatal dopaminergic injection may be involved in the onset of cognitive apathy.

Apathy-related behavior analysis in Sham and 6-hydroxydopamine (6-OHDA) treated mice. (Left) Hole board test. The number of the mice introduced their head in the holes was measured and significantly decreased in the 6-OHDA group compared with the sham group. (Right) The interaction time for the novel object significantly decreased but did not change for the social object (Mouse) in the 6-OHDA group compared with the sham group. These results indicated 6-OHDA group showed decreased object/inanimate novelty seeking while maintained social novelty.

Publications

Papers in 2024

Okitsu M, et al. (2024) "Mouse model of Parkinson's disease with bilateral dorsal striatum lesion with 6-hydroxydopamine exhibits cognitive apathy-like behavior." ***Int J Mol Sci*** 25:7993.

Ide S, et al. (2024) "Caenorhabditis elegans for opioid addiction research." ***Curr Opin Neurobiol*** 88:102914.

Kosaki Y, et al. (2024) "Gamma-aminobutyric acid type A receptor beta1 subunit gene polymorphisms are associated with the sedative and amnesic effects of midazolam." ***Mol Brain*** 17:70.

Kang Y, et al. (2024) "TMEM132C rs7296262 single-nucleotide polymorphism is significantly associated with nausea induced by opioids administered for cancer pain and postoperative pain.." ***Int J Mol Sci*** 25:8845.

Araida J, et al. (2024) "rs12411980 single-nucleotide polymorphism related to PRTFDC1 expression is significantly associated with phantom tooth pain." ***Mol Pain*** 2:17448069241272215.

Key papers

Ide S, et al. (2017) "Distinct roles of opioid and dopamine systems in lateral hypothalamic intracranial self-stimulation." ***Int J Neuropsychopharmacol*** 20:403.

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

Head researcher,
independent research group

Shinobu HIRAI

Frontier Research Laboratory

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

Dr. Shinobu Hirai has been deeply committed to research on brain development and maturation. She received her Ph.D. in Medicine in 2011 from the Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University. Following her Ph.D., she joined our institute as a researcher in 2012. In 2022, Dr. Hirai was selected for the JST FOREST Research Support Program, establishing her as an independent researcher. Currently, she leads the Brain Metabolism Control Group at the Frontier Research Laboratory, focusing on preventing, predicting, and developing treatment strategies for refractory brain disorders, including metabolic encephalopathy and mental disorders, using diverse approaches.

Staff

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

Research Progress in 2024

Background

We are dedicated to tackling the prediction, prevention, and treatment of severe brain disorders, including metabolic encephalopathy and mental illnesses. Particularly, for genetic metabolic encephalopathies that manifest early in life and are challenging to prevent, we focus on developing novel treatment strategies. For instance, we are advancing gene therapy using adeno-associated virus (AAV) vectors for conditions like GLUT1 deficiency syndrome, with the goal of clinical application.

Regarding mental disorders such as schizophrenia, bipolar disorder, and depression, our emphasis is on developing predictive measures and preventive interventions. Specifically, we are quantitatively evaluating structural and functional abnormalities in brain and retinal vasculature to establish biomarkers for early disease detection and prevention.

In both metabolic encephalopathies and mental disorders, a detailed understanding of pathophysiology is crucial. To achieve this, we employ cutting-edge technologies such as tissue clearing, spatial transcriptomics, fiber photometry, and biosensors. Through a multiscale approach spanning gene, molecular, cellular, tissue, and organism levels, we aim to comprehensively elucidate brain metabolism–including blood flow dynamics–and the impact of metabolic dysfunction on the onset and progression of brain disorders.

Achievements in 2024

A combination of genetic predisposition and environmental factors contributes to the development of psychiatric disorders such as schizophrenia, bipolar disorder and major depressive disorder. Previous studies using mouse models suggested that prolonged high sucrose intake during puberty can serve as an environmental risk factor for the onset of psychiatric disorders. However, the impact of both the duration and timing of high sucrose consumption during different developmental stages on pathogenesis remains poorly defined. We therefore investigated the effects of a long-term high sucrose diet on cognitive deficit, a core symptom of psychiatric disorders, using Disrupted-in-Schizophrenia 1 locus-impairment heterozygous mutant ($Disc1^{het}$) mice as a model for genetic predisposition. Compared to those on a standard chow diet, high sucrose intake caused deficits in spatial memory in both WT and $Disc1^{het}$ mice, with more pronounced effects in $Disc1^{het}$ mice. In particular, $Disc1^{het}$ mice on a sucrose diet during adolescence showed more pronounced cognitive deficit than those fed after adolescence. Our results suggest that adolescence is particularly vulnerable to nutritional environmental risk factors, and that high sucrose consumption may cause hippocampus-dependent memory deficits via decreased the high parvalbumin-expressing interneurons function when combined with Disc1-related genetic predisposition. (Park J., et al., 2024)

Publications

Papers in 2024

Tanaka T., et al. (2024) "Minocycline prevents early age-related cognitive decline in a mouse model of intellectual disability caused by ZBTB18/RP58 haploinsufficiency" ***J Neuroinflammation*** 21(1):260.

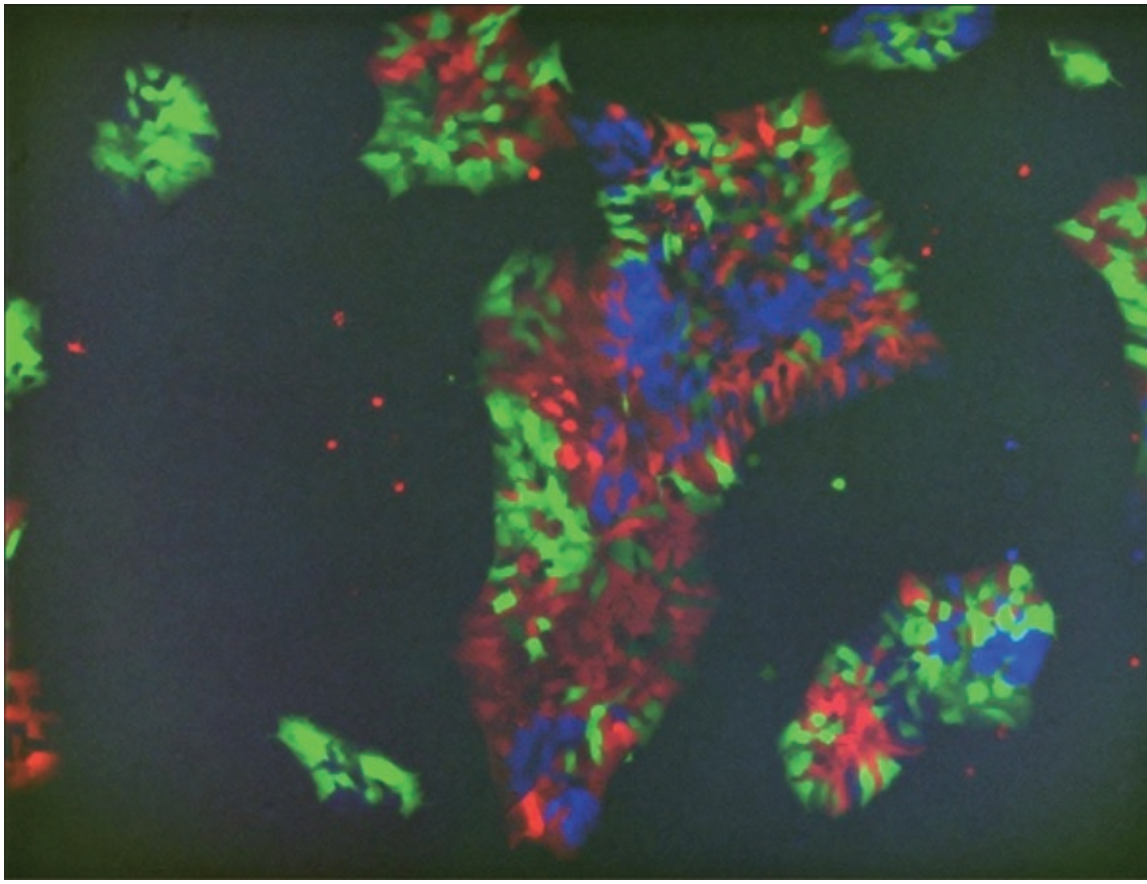
Park J., et al. (2024) "Impact of feeding age on cognitive impairment in mice with Disrupted-In-Schizophrenia 1 (Disc1) mutation under a high sucrose diet." ***Behav Brain Res*** 476:115291.

Key papers

Hirai S. et al., (2023). "Disease specific brain capillary angiopathy in schizophrenia, bipolar disorder, and Alzheimer's disease." ***J Psychiatr Res***, 163 74-79.

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.


NEPTUNE



Colonies of human iPS cells labeled by green, red, and blue fluorescent proteins. These colors allowed us to trace these cells individually.

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
Takahiro SANADA
Kenzaburo YAMAJI
Naoki YAMAMOTO
Tomoko HONDA
Sakiko TOYAMA
Ahmad faisal AMIRY

Research Assistants
Asako TAKAGI
Risa KONO
Ryusei FURUSAWA
Midori NAGAI

Research Progress in 2024

Background

Emerging infectious diseases caused by previously unknown new pathogens and re-emerging infectious diseases that have begun to spread again have occurred around the world, posing major public health problems. In order to combat the spread of unpredictable viruses, we need to deepen our understanding by conducting a wide range of research activities, including epidemiological surveys, basic research, and applied research, focusing on "priority infectious diseases" that are feared to cause enormous damage, and "intractable infectious diseases" for which control methods have not been fully established. Currently, we are focusing on liver disease, acute viral pneumonia, dengue fever, and Mpox, and are conducting epidemiological surveys such as large-scale antibody measurements, analyzing mechanisms using cultured cells, and analyzing the pathology of diseases in animal models and developing control methods.

Achievements in 2024

1. We established a system to recapitulate COVID-19-like pneumonia in mice infected with SARS-CoV-2 after inducing hACE2 with rAd5 pEF1-hACE2-L (*Front Immunol*. 2024).
2. We demonstrated that intranasal inoculation using the recombinant S protein of SARS-CoV-2 combined with carboxy-vinyl polymer (CVP) strongly induces antibody production in the serum and mucosa of mice and enhances cellular immunity. Furthermore, this strategy effectively induced a long-lasting immunity against a wide range of SARS-CoV-2 variants (*Vaccines (Basel)*, 2024) .
3. We successfully constructed models for describing the kinetics of antibody decay against SARS-CoV-2 following vaccination using a power law model. The ability to predict the kinetics of antibody levels after mRNA vaccination offers valuable insights for understanding the immune status at both individual and population levels, contributing to more informed public health decision-making (*Vaccine*, 2024).
4. In a joint research project with Innovation Center of NanoMadicine and Tokyo Medical and Dental University, we have successfully demonstrated the effectiveness of a vaccine against SARS CoV-2 by intradermal administration of naked mRNA. This is a pioneering report demonstrating the protective effect of naked mRNA vaccines in an infectious disease model (*Mol Ther*, 2024).

Selected Publications

Papers in 2024

Matsumoto Y, et al. (2024) "Generation of a SARS-CoV-2-susceptible mouse model using adenovirus vector expressing human angiotensin-converting enzyme 2 deriven by an elongation facot 1a promoter with leftward orientation." ***Front Immunol***. 15: 1440314.

Honda T, et al. (2024) "Intranasally inoculated SARS-CoV-2 Spike Protein Combined with Mucoadhesive Polymer Induces Broad and Long-Lasting Immunity." ***Vaccines (Basel)***. 12(7):794.

Snada T, et al. (2024) "Modeling of anti-spike IgG and neutralizing antibody waning after anti-SARS-CoV-2 mRNA vaccination." ***Vaccine***. 42(21): 126146.

Abbasi S, et al. (2024) "Carrier-free mRNA vaccine induces robust immunity against SARS-CoV-2 in mice and non-human primates without systemic reactogenicity." ***Mol Ther***. 32(5):1266-1283.

Key papers

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

Ishigaki H, et al. (2022) "An attenuated vaccinia vaccine encoding the SARS-C oV-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.

Project Leader
Takayuki HARADA

Visual Research

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

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.

Staff

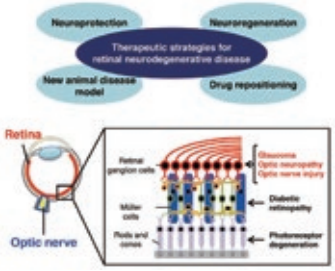
Researchers
Kazuhiko NAMEKATA
Youichi SHINOZAKI
Xiaoli GUO
Chikako HARADA
Takahiko NORO
Euido NISHIJIMA
Yuta KITAMURA
Akiko SOTOZONO

Research Assistants
Mayumi KUNITOMO
Tomoko HARA
Ryoko YAMAGISHI

Research Progress in 2024

Background

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



Achievements in 2024

Neurotrophic factor signaling holds significant promise as therapeutic target for neuroprotection and optic nerve regeneration. However, the temporal efficacy of ligand-mediated activation remains limited. To address this challenge, we developed a novel gene therapy approach that utilizes forced membrane translocation of the intracellular domain of tropomyosin receptor kinase B (iTrkB), a receptor for brain-derived neurotrophic factor (BDNF). The system enabled us to achieve notable neuroprotection in an experimental glaucoma model. Furthermore, we observed robust axon regeneration following optic nerve injury in response to iTrkB expression (Nishijima et al., 2023).

Insulin, a key endocrine hormone regulating glucose homeostasis, also plays a crucial role in brain function. Accumulating evidence indicates that impaired insulin signaling is associated with cognitive decline and neurodegenerative diseases. While recent studies have suggested that insulin can stimulate dendrite regeneration in retinal ganglion cells (RGCs), a neuronal population vulnerable in glaucoma, ligand-mediated activation has limitations in terms of sustained efficacy. Inspired by the iTrkB system, we developed constitutively active forms of the insulin receptor and insulin-like growth factor receptor. We achieved in activating downstream signaling pathways implicated in dendrite regeneration in vitro (Sotozono et al., 2024). These novel tools hold promise for neuroprotection and promoting dendrite regeneration in various neuronal populations.

Publications

Papers in 2024

Sotozono A, Namekata K, Guo X, Shinozaki Y, Harada C, Noro T, Nakano T, Harada T (2024) "Membrane-anchored intracellular insulin receptor or insulin-like growth factor-1 receptor elicits ligand-independent downstream signaling." ***Biochemistry and Biophysics Reports*** 39, 101799.

Namekata K, Noro T, Nishijima E, Sotozono A, Guo X, Harada C, Shinozaki Y, Mitamura Y, Nakano T, Harada T (2024) "Drug combination of topical ripasudil and brimonidine enhances neuroprotection in a mouse model of optic nerve injury." ***Journal of Pharmacological Sciences*** 154, 326-333.

Wang Y, Brahma MM, Takahashi K, Hernandez ANB, Ichikawa K, Minami S, Goshima Y, Harada T, Ohshima T (2024) "Drug treatment attenuates retinal ganglion cell death by inhibiting collapsin response mediator protein 2 phosphorylation in mouse models of normal tension glaucoma." ***Neuromolecular Medicine*** 26, 13.

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

Key papers

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.

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.

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 neurodegene rative 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
Hideji YAKO
Naoko NIIMI
Shizuka TAKAKU

Research Assistants
Kumi SUMIDA

Visiting Scientists
Koichi KATO
Tatsufumi MURAKAMI
Junji YAMAUCHI
Hitoshi KAWANO
Ken MURAMATSU
Keiichiro MATOBA
Mizuho OKAMOTO

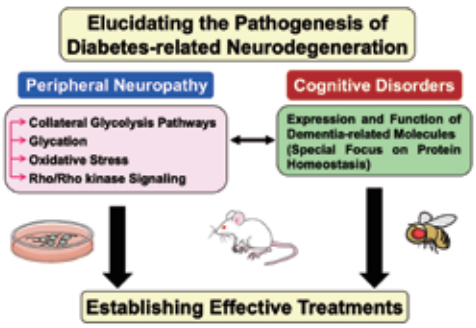
Research Progress in 2024

Background

Diabetic neuropathy is 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:



Establishing effective pathogenesis-based treatments for diabetic peripheral neuropathy.

Elucidating mechanistic links between metabolic dysfunction and neurodegenerative diseases.

Achievements in 2024

1) Exogenous pyruvate plays a crucial role in maintaining ATP production under hyperglycemic conditions through poly-(ADP-ribose) polymerase (PARP)-dependent glycolysis and PARP-independent TCA cycle in Schwann cells (Yako et al., ***Int J Mol Sci*** 2024).

2) Glucoselysine (GL), a novel advanced glycation product, is produced from glucose and fructose via the polyol pathway and released from Schwann cells under diabetic conditions. Serum GL levels in patients with type 2 Diabetes Mellitus are correlated with the presence of chronic complications (Yamaguchi et al., ***J Biol Chem*** 2024).

3) Mice deficient in chondroitin sulfate (CS) N-acetyl-galactosamine transferase 1 do not suffer from peripheral neuropathy following induced hyperglycemia. Extracellular CS may be involved in mediating diabetic neuropathy through blood-nerve-barrier dysfunction and transforming growth factor β-related signaling activation (Ishiguro et al., ***iScience*** 2024).

Publications

Papers in 2024

Miyata W, et al. (2024) Bcl2l12, a novel protein interacting with Arf6,triggers Schwann cell differentiation program. ***J Biochem*** 2024 Nov7:mvae078.

Yako H, et al. (2024) Role of exogenous pyruvate in maintaining adenosine triphosphate production under high-glucose conditions through PARP-dependent glycolysis and PARP-independent tricarboxylic acid cycle. ***Int J Mol Sci*** 25:11089.

Yamaguchi H, et al. (2024) Glucoselysine, a unique advanced glycation end-product of the polyol pathway and its association with vascular complications in type 2 diabetes. ***J Biol Chem*** 300:107479.

Ishiguro H, et al. (2024) Reduced chondroitin sulfate content prevents diabetic neuropathy through transforming growth factor- signaling suppression. ***iScience*** 27:109528.

Niimi N, et al. (2024) Gut microbiota dysbiosis as a novel pathogenic factor of diabetic peripheral neuropathy. ***J Diabetes Investig*** 15:817-819.

Nihei W, et al. (2024) Hyperglycaemia aggravates oxidised low-density lipoprotein-induced Schwann cell death via hyperactivation of Toll-like receptor 4. ***Neurol Int*** 16:370-379.

Key papers

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

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

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
Daisuke MATSUMOTO

Students
Ittetsu NAKAJIMA
Lanyu HUANG
Kayoko SHINOZAKI
Kanata IMAMURA
Yuga YASUDA
Kai ZHANG

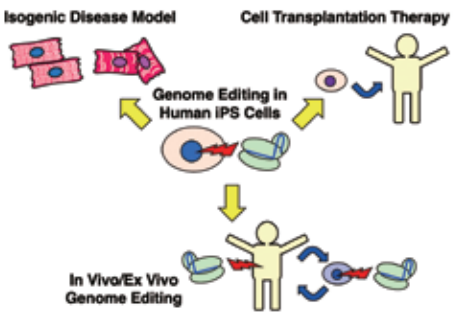
Research Progress in 2024

Background
Genome editing technology allows us to rewrite the genetic information in any species and cell type, including human cells. We focus on human iPS cells, a type of pluripotent stem cell that can be generated from patients' cells by the introduction of specific transcription factors and differentiated into other cell types. Our goal is to use genome editing in iPS cells to model human diseases and develop new therapies (see figure).

Achievements in 2024
Genome editing induces a double-strand break (DSB) at the target site to activate two endogenous DNA repair pathways in the cell: homology-directed repair (HDR) and non-homologous end joining (NHEJ). HDR is based on DNA recombination between the genomic DNA and homologous template DNA, which facilitates precise genome editing when the exogenous donor DNA is provided to the cells. In contrast, NHEJ is a template-free, error-prone repair mechanism in which the broken ends of DNA are joined together, often with random insertions or deletions (indels).

We are interested in how the balance between HDR and NHEJ is determined, and how we can enhance HDR. We previously reported that CRISPR-Cas9 systems with improved proof-reading enhance HDR (Nucleic Acids Res, 2018). To enhance HDR more, we focused on proteins involved in DNA repair and found that the fusion of Cas9 and Histones suppresses NHEJ (PLoS One, 2024).

Furthermore, we have analyzed the frequencies and combinations of HDR and NHEJ induced in single cells. We previously investigated genome editing outcomes in single human cultured cell lines such as HEK293T cells (iScience, 2022). We expanded this study to explore genome editing outcomes in single human iPS cells. We found that identical genetic modifications, including insertions and deletions with different lengths, tend to be induced in both alleles of single iPS cells (bioRxiv, 2024.09.18.613641).



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.

Publications

Papers in 2024
Kato-Inui T, et al. (2024) "Fusion of histone variants to Cas9 suppresses non-homologous end joining." ***PLoS One***. 19:e0288578.

Key papers
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.

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

Project Leader
Hidetaka TANNO

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

Cancer Immunology

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

Staff

Researchers
Mayumi SAEKI
Rikio YABE
Kazuhisa AOKI

Research Assistants
Sayaka ONO
Yuri TANNO

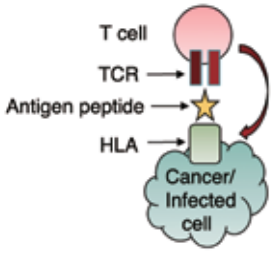
Research Progress in 2024

Background

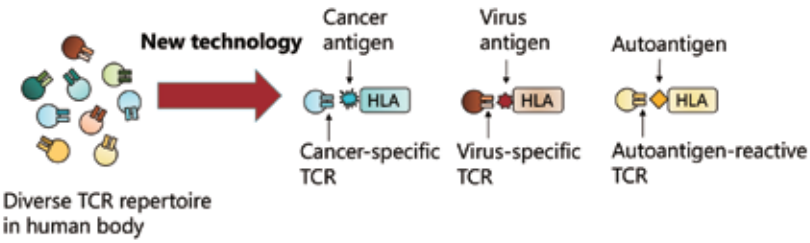
T cells play a critical role in adaptive immunity. They express an enormous repertoire of TCRs on their surfaces. Using these TCRs, T cells recognize antigen-HLA complexes presented by pathogenic cells and eliminate them. Therefore, elucidating the interactions between TCRs and antigen-HLA complexes 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.

Achievements in 2024

In previous work, we developed a high-throughput technology capable of determining TCR and antibody sequences at the single-cell level, which was published in PNAS (2020) and Science Advances (2020). However, this technology was unable to determine the antigen specificity of TCRs and antibodies. In 2024, we independently developed a proprietary platform that can identify antigen-specific TCRs as well as TCR-like antibodies. Using this technology, we are generating various cancer-specific TCRs and TCR-like antibodies. In parallel, we established cell lines derived from cancer patients to provide a clinically relevant model system. We are currently evaluating the cancer-killing efficacy of these TCRs and antibodies using both *in vitro* and *in vivo* models.



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.

Publications

Key papers

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

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

Laboratory Head
Daisuke YAMANE

Neurovirology

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

Daisuke YAMANE is the Laboratory Head of Neurovirology, where he leads a research lab focused on host-virus interactions to understand mechanisms underlying diseases associated with virus infections. He received his PhD in Veterinary Medicine from the University of Tokyo. After completing a post-doctoral fellowship at the University of North Carolina at Chapel Hill under the direction of Dr. Stanley Lemon, he moved to the Tokyo Metropolitan Institute of Medical Science as a Senior Scientist in 2016, at which time he started his work on host factors affecting replication of a wide variety of important human viruses, including neurotropic flaviviruses and enteroviruses, and hepatotropic viruses.

Staff

Researchers
Kyousuke KOBAYASHI
Satoshi KOIKE

Research Assistants
Masako UKAJI
Marie URANO

Students
Kotomi SHINOZAKI

Research Progress in 2024

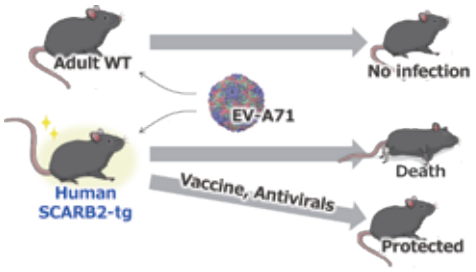
Background

Pathogenic viruses have evolved mechanisms to evade the host immune response and establish infection after the battle between the host innate immunity. The host defense system is comprised of multiple layers, yet how such mechanism is maintained, or activated in response to infection, remains largely uncharacterized. Our aim is to (i) identify host signal transduction/metabolic pathways that play functional role in restricting virus replication, (ii) identify druggable target that shuts-off viral mechanism to evade innate immunity, (iii) and develop antiviral compounds that recapitulate the mode of action of host antiviral effectors.

Our lab also focuses on pathogenesis and replication mechanism of picornaviruses, including enterovirus A71 (EV-A71), one of the causative agents of hand-foot-and-mouth disease (HFMD) that can occasionally be complicated by neurological manifestations. Using a mouse model expressing the human receptor for EV-A71 identified in our lab (Yamayoshi et al., *Nat Med*, 2009), we aim to develop prophylactic vaccines and antiviral drugs based on the understanding of how the virus hijacks the host factors.

Achievements in 2024

- We have identified host factors that modulate the constitutive defense against virus infection in hepatocytes.
- We have narrowed down the virulence determinant region within the EV-A71 genome that affects the onset of lethal neuropathogenesis using a mouse model.
- We have mapped lipid metabolic pathways essential for secretion of lipo-viro particles of an hepatotropic virus that may be targeted for pharmacological intervention.



Transgenic mice expressing human SCARB2 developed in our laboratory (Fujii et al., *PNAS*, 2013) are permissive to EV-A71 infection and can be used as a tool for studies of neuropathogenesis associated with the virus infection and vaccine development.

Publications

Papers in 2024

Matsuda M, et al. (2024) "Loxapine inhibits replication of hepatitis A virus in vitro and in vivo by targeting viral protein 2C." ***PLoS Pathog***. 20(3):e1012091.

Key papers

Matsumoto M, Shinozaki K, et al. (2023) "CSNK2B modulates IRF1 binding to functional DNA elements and promotes basal and agonist-induced antiviral signaling." ***Nucleic Acids Res***. 51(9)4451-4466.

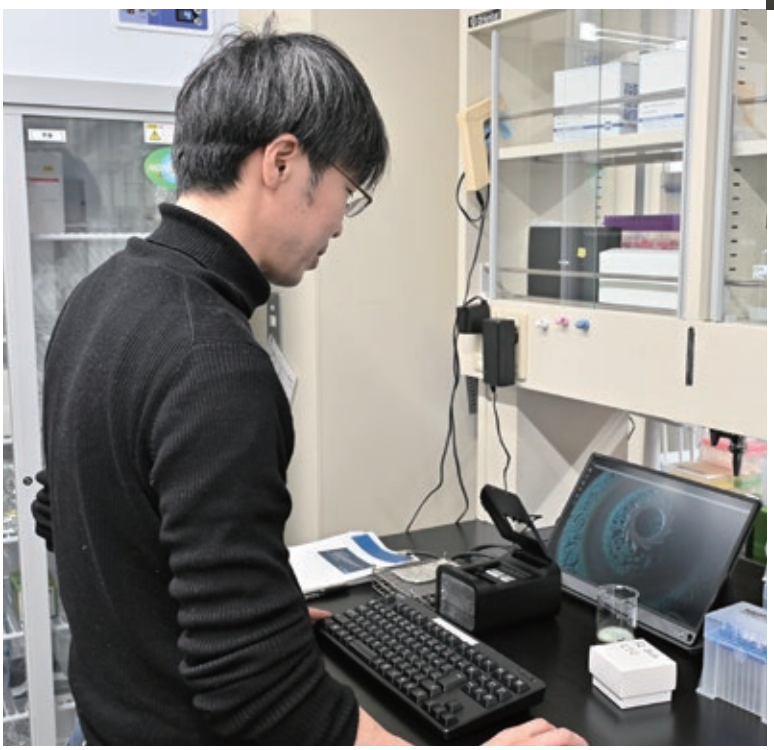
Yamane D, et al. (2022) "FADS2-dependent fatty acid desaturation dictates cellular sensitivity to ferroptosis and permissiveness for hepatitis C virus replication." ***Cell Chem. Biol***. 29(5):799-810.e4.

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***. 16(3)e1008428.

Yamane D, et al. (2019) "Basal expression of interferon regulatory factor 1 drives intrinsic hepatocyte resistance to multiple RNA viruses." ***Nat. Microbiol***. 4(7):1096-1104.

Yamane D, et al. (2014) "Regulation of the hepatitis C virus RNA replicase by endogenous lipid peroxidation." ***Nat. Med***. 20(8):927-35.

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, unitleader, 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
Satoru IDE
Saki SAITO
Research Assistant
Ryoko WADA
Naomi IDA

Research Progress in 2024

Background

The human body is composed of approximately 37 trillion cells, each containing nearly identical genetic information. However, despite this shared genomic blueprint, individual cells transcribe distinct subsets of the genome into RNA molecules, forming the molecular foundation that dictates their unique functions and behaviors. Understanding the complexity of RNA transcription and the logic of transcriptional regulation is critical for elucidating the molecular mechanisms underpinning health and disease and for assessment of genetic risk based on individual genome variations.

A key focus of our research is on the diversity of RNA isoforms generated through cell-dependent splicing events and the elucidation of cis-regulatory elements, such as promoters and enhancers, that regulate transcription in proximity to and at a distance from their target genes respectively. We devise high-throughput and/or high-resolution experiments, with advanced computational approaches to address these challenges. In addition to the study of transcription, we also contribute to other research projects and hospitals by applying the genomics technologies as the research center of the genome science.

Achievements in 2024

・Recent advancements in long-read sequencing technologies have enhanced our ability to explore transcriptomic complexities. The Long-read RNA-Seq Genome Annotation Assessment Project (LRGASP), an international effort, benchmarked distinct protocols proposed to study RNA isoforms alongside computational tools. We contributed by applying our computational pipeline to the shared dataset, and the study revealed clear differences across the strategies. The result provided a baseline for improving transcriptomic analyses (Pardo-Palacios et al. 2024).
・We participated in a study creating an atlas of transcribed enhancers in helper T cells, pioneering a single-cell RNA-seq based strategy to identify enhancers. We contributed to the development of the analytical framework. The result uncovered novel enhancers and diversity of helper T cell subpopulations, and shed light on the genetic underpinnings of immune-mediated diseases (Oguchi et al. 2024).
・To evaluate lymph node metastasis in endometrial cancer, we developed a statistical model incorporating 18 preoperative clinical variables in collaboration with clinicians. This noninvasive system has the potential to enhance the clinical management and treatment strategies (Ueno et al., 2024).

Publications

Papers in 2024

Oguchi A, et al. "An atlas of transcribed enhancers across helper T cell diversity for decoding human diseases" ***Science***. 385: eadd8394.

Pardo-Palacios FJ, et al. "Systematic assessment of long-read RNA-seq methods for transcript identification and quantification" ***Nat Methods***. 21: 1349–1363.

Ueno Y, et al. (2024) "Use of clinical variables for preoperative prediction of lymph node metastasis in endometrial cancer" ***Jpn J Clin Oncol***. 54: 38–46.

Yamazaki K, et al. (2024) "Homologous recombination contributes to the repair of acetaldehyde-induced DNA damage" ***Cell Cycle***. 23: 369–384.

Key papers

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.

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

Director Unit Leader
Atsushi NISHIDA

Mental Health Promotion

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

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.

Staff

Researchers

Syudo YAMASAKI
Mitsuhiro MIYASHITA
Kaori BABA
Junko NIIMURA
Satoshi YAMAGUCHI

Research Progress in 2024

Background

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 livelihoodsof 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.

Achievements in 2024

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.

Publications

Papers in 2024

Yamaguchi S, Foo JC, Sasaki T, (2024)The effects of a teacher-led online mental health literacy program for high school students: a pilot cluster randomized controlled trial. ***Journal of Mental Health***,2024 Aug.

DeVylder J, Yamaguchi S, Hosozawa M, Yamasaki S, Ando S, Miyashita M, Endo K, Stanyon D, Usami S, Kanata S, Tanaka R, Minami R, Hiraiwa-Hasegawa M, Kasai K, Nishida A (2024) Adolescent Psychotic Experiences before and during the COVID-19 Pandemic: a Prospective Cohort Study. ***Journal of Child Psychology and Psychiatry***, 2024 Jun;65(6):776-784.

Narita Z, Ando S, Yamasaki S, Miyashita M, Devylder J, Yamaguchi S, Hosozawa M, Nakanishi M, Hiraiwa-Hasegawa M, Furukawa TA, Kasai K, Nishida A (2024) Association of Problematic Internet Use with Psychotic Experiences and Depression in Adolescents: A Cohort Study. ***Schizophrenia Bulletin***, 2024 Jun 2:sbae089.

Stanyon D, Nakanishi M, Yamasaki S, Miyashita M, Yamaguchi S, Baba K, Nakajima N, Niimura J, Devylder J, Hiraiwa-Hasegawa M, Ando S, Kasai K, Nishida A (2024) Investigating the Differential Impact of Short- and Long-Term Informal Caregiving on Mental Health Across Adolescence: Data From the Tokyo Teen Cohort. ***Journal of Adolescent Health***,2024 Jul 10:S1054-139X(24)00288-X.

Nakanishi M, Yamasaki S, Nakashima T, Miyamoto Y, Cooper C, Richards M, Stanyon D, Sakai M, Yoshii H, Nishida A (2024)Association Between Dementia, Change in Home-Care Use, and Depressive Symptoms During the COVID-19 Pandemic: A Longitudinal Study Using Data from Three Cohort Studies. ***Journal of Alzheimer's Disease***, 2024;99(1):403-415.

Hosozawa M, Ando S, Yamaguchi S, Yamasaki S, DeVylder J, Miyashita M, Endo K, Stanyon D, Knowles G, Nakanishi M, Usami S, Iso H, Furukawa TA, Hiraiwa-Hasegawa M, Kasai K, Nishida A (2024) Sex difference in adolescent depression trajectory before and into the second year of COVID-19 pandemic. ***Journal of the American Academy of Child & Adolescent Psychiatry***, 2024 May;63(5):539-548.

Unit Leader
Yuki NAKAYAMA

Intractable Disease Nursing Care

Yuki Nakayama worked as a nurse before receiving her Ph.D. from the Tokyo University of Health and Science in 2006. In 2007, she joined the Tokyo Metropolitan Institute of Medical Science, and she has been the leader of the Intractable Disease Nursing Care Unit since 2015. Her specialty is research on nursing for patients with intractable diseases, and she focuses on methods to improve respiratory management, quality of life (QOL), and social participation of patients on ventilators.

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 Progress in 2024

Background

Since the establishment of our laboratory, we have focused on improving the QOL of Amyotrophic Lateral Sclerosis (ALS) patients through three key approaches:

1. Development of safe nursing care techniques based on basic and clinical research findings
2. Improvement of environments and support systems
3. Creation of community-based care systems

By analyzing the effects of different care methods, environments, support systems, and community efforts, we aim to optimize the quality of care for patients suffering from ALS. Central to our approach is the active participation of patients who point out their needs and evaluate the effectiveness (Patient-Reported Outcomes) of different nursing, care, and support systems to ensure patient-centered care.

Achievements in 2024

We are establishing a "Rare Disease Care Registry" to enroll consenting patients visiting the ALS/MND Center at the Neurological Hospital. This registry will enable long-range, periodic follow-up studies on patients' living conditions and care environments. By longitudinally analyzing changes in care needs due to disease progression, we aim to:

1. Identify factors that promote or inhibit disease progression, contributing to a better understanding of ALS pathology.
2. Investigate when non-motor symptoms of ALS begin to manifest.

These efforts should improve care strategies and support systems for rare disease patients.

Publications

Papers in 2024

Funai A , Hayashi K , Kawata A, Nakayama Y, Matsuda C, Haraguchi M, Takahashi K, Komori T. An autopsy report of a long-survival case of familial amyotrophic lateral sclerosis with SOD1 G93S gene mutation: Lack of SOD1-positive inclusion in the remaining neurons ***Neuropathology***. 2024 Sep 23. doi: 10.1111/neup.13004

Kamei T, Kawada A, Kakai H, Yamamoto Y, Nakayama Y, Mitsunaga H, Nishimura N. Japanese nurses' confidence in their understanding of telenursing via e-learning A mixed-methods study ***DIGITAL HEALTH*** Volume 10: 1–16

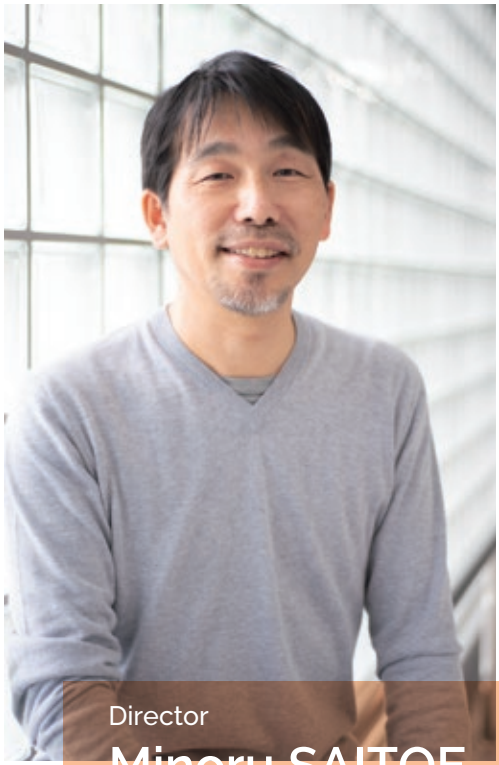
Key papers

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

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

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.

Research Supports



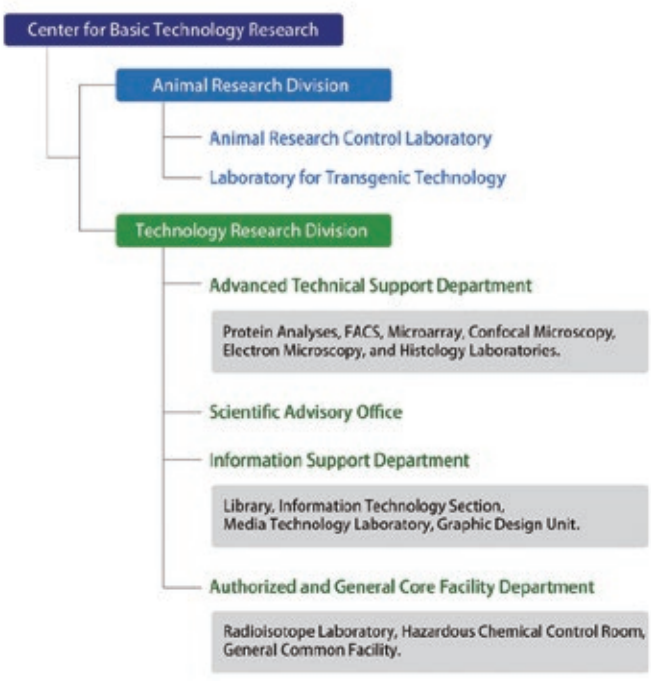
Basic Technology Research

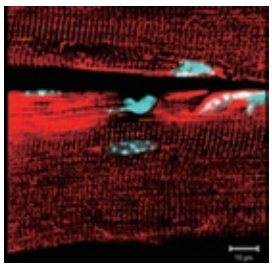
Laboratory HP: https://www.igakuken.or.jp/english/center/basic/basictech.html

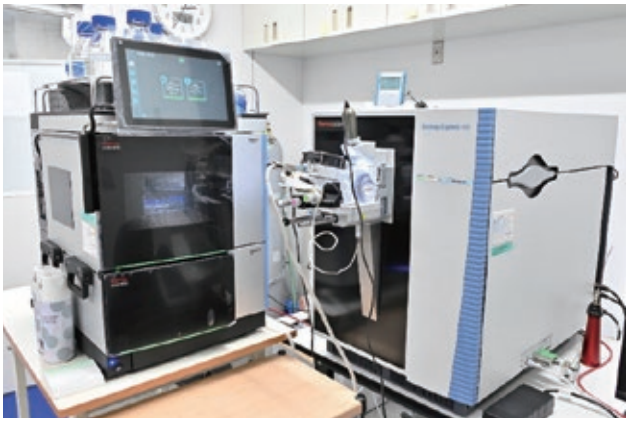
Director
Minoru SAITOE

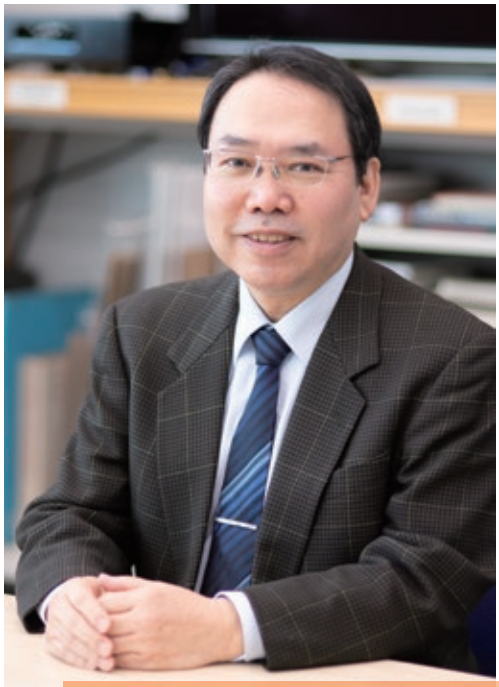
The Basic Technology Research Center provides resources to assist scientists to conduct their research efficiently. We provide state-of-the-art technologies required for biomedical and life science research and maintain various facilities used by researchers.

1. The Animal Research Division maintains our animal facilities and provides care and welfare for the animals used in research. This division assists researchers in generating transgenic and knockout/knockin animals and maintains sperm and embryos 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.
5. The Tokyo Metropolitan Institute of Medical Science has an annual budget of approximately 100 million yen for research equipment. In 2024, this budget was used to obtain a new liquid chromatography-mass spectrometry system, Orbitrap Exploris 480 (Thermo Fisher Scientific).





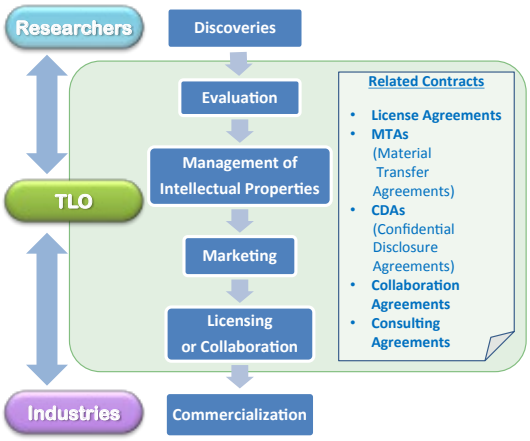




Technology Licensing Office

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

General Manager
Kazumasa AOKI



Who we are

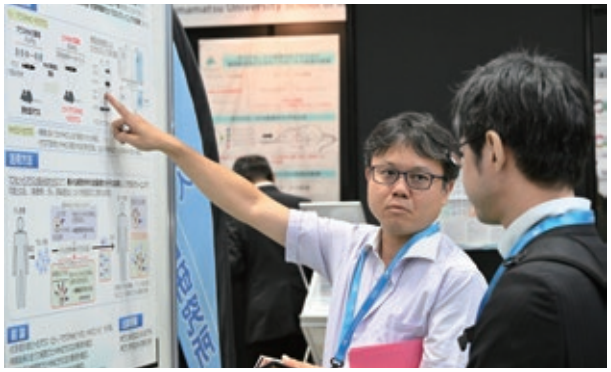
- The Technology Licensing Office (TLO) facilitates the conversion of scientific discoveries to innovative technologies with the ultimate goal of improving public health and welfare.
- We evaluate basic research findings (seeds) as intellectual property assets, and license promising candidates to industries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

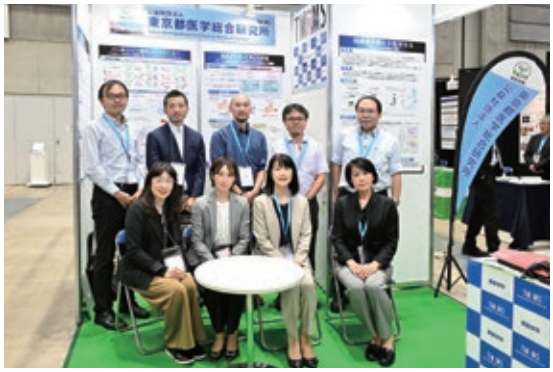
What we do

- 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.

Activities in 2024

- License agreements: 55
- Joint research agreements: 71





Medical Research Cooperation

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

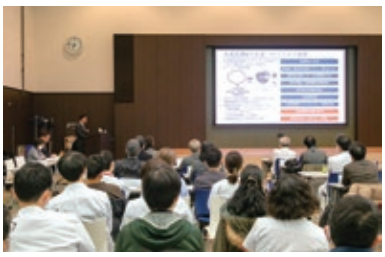
Director

Takayuki HARADA

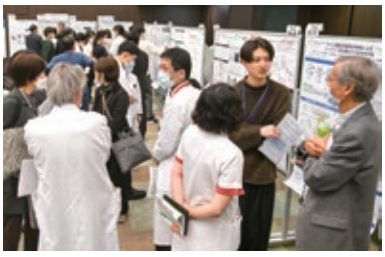
Staff

Kimi UEDA
Chikako ISHIDA
Junya MAEDA
Hiroko KOUSAKA

Strengthening Medical Research by Bridging 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.

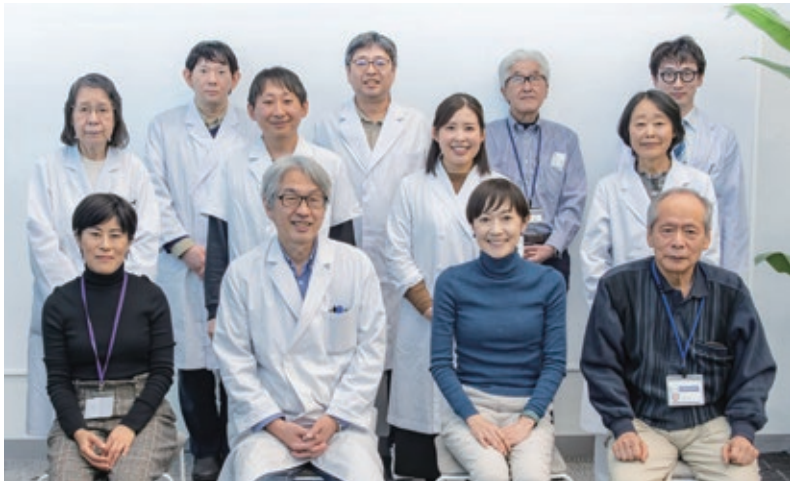


Conference with researchers and medical doctors



A young scientist discussing with researchers and medical doctors in conference

Molecular Pathology and Histology



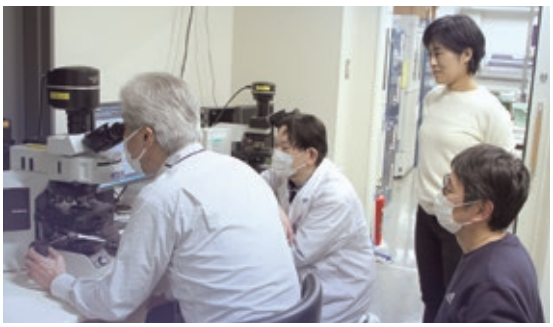
Laboratory HP: https://www.igakuken.or.jp/hist_kaiseki/

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

Staff

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

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



Public Relations and Other Activities

TMIMS Programs

Public Lectures

Each year we present 8 pubic lectures to inform the public of our research progress and enlighten people on various medical issues pertinent to the health and welfare. In 2024, we conducted both hybrid and face-to-face lectures. Lecture topics included, alcohol and related diseases, Alzheimer's disease, autism and brain development, neurodevelopmental disorders, gene counseling and diabetes related diseases..

The Latest Trends in Cancer Gene Panel Testing
..... Masachika IKEGAMI (Komagome Hospital)
Advancements in Gene-Based Cancer Therapies
..... Hidetaka TANNO (TMIMS)

Dental Care in the Future: Take Steps Now to Prevent Oral Flail
Eat Better, Live Better
..... Haruka TOHARA (Tokyo Medical and Dental University)

Alcohol: A Journey Through History and Science
An Introduction to Alcohol Production
..... Tomomasa KANDA (Asahi Quality & Innovations Asahi Quality & Innovations)

The Future of Alzheimer's Disease: Hope and Progress
..... Kensaku KASUGA (Niigata University)

Understanding Brain Development and Autism Spectrum Disorder: Insights from Brain Development and Robotics Research
Cognitive Development and Developmental Disorders Based on Predictive Processing of the Brain
..... Yukie NAGAI (The University of Tokyo)
Elucidating the Developmental Trajectories of Neural Circuits Associated with Autism Spectrum Disorder
..... Goichi MIYOSHI (Gunma University)

Neurodevelopmental Disorders: What Mouse Models Can Teach Us
Understanding Neurodevelopmental Disorders Through Mice
..... Atsushi SATO (Tums Wanpaku Clinic)

What Your Genes Can Tell You: Clinical Genomics and Genetic Counseling
..... Yasue HORIUCHI (Shizuoka Graduate University of Public Health)

Essentials for Healthy Vision To Enjoy Lifetime Beautiful Views
Advancements in Diagnosis and Treatment of Diabetic Macular Edema
..... Yoshinori MITAMURA (Tokushima University)
Basic Research on Glaucoma Being Conducted at TMIMS
..... Takayuki HARADA (TMIMS)

TMIMS Seminar Series on "Aging and Health"

In 2022, we 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 11 lectures in 2024.

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

II-IV. Blood and Healthy Long Life
..... Takahiko HARA (TMIMS)
II-V. Gut and Rejuvenation
..... Yuji NAITO (Kyoto Prefectural University of Medicine)
II-VI. AI and Medicare for Healthy Long Life
..... Kazuhiro SAKURADA (Keio University)
II-VII. What is Known About Frailty and How to Prevent it.
..... Kazuhiro SHIGEMOTO (Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology)
II-VIII. Understanding the Circadian Rhythm to Achieve Healthy Long Life
Circadian Clock and Aging: Mechanisms of Clock Aging.
..... Hikari YOSHITANE (TMIMS)
II-IX. Insomnia in the Elderly
Quality Sleep Improves Healthy Lifespan and Quality of Life
..... Naohisa UCHIMURA (KURUME University)
II-X. Precision Time Nutrition
When to Eat for Healthy Well-being
..... Yu TAHARA (Hiroshima University)
II-XI. Aging and Genomes: Summary
..... Hisao MASAI (TMIMS)



Science café

In the past 13 years we have had 47 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 2024, we had three science cafes on electricity-driven body movement, DNA extraction and science of fragrance. The participants enjoyed experiments with us in these events.

Explore the Electric-Powered Human Body!
..... Yukio NISHIMURA (TMIMS)

Let's Experience Being a Researcher! DNA Extraction and Centrifugation
..... Yuga YASUDA / Tomoe NISHIMURA / Kohji KASAHARA(TMIMS)

The Science of Fragrance
..... Tomoe NISHIMURA / Kohji KASAHARA(TMIMS)



Institutional seminars (Igakuken Seminars)

We have institutional seminars on a regular basis. In 2024, finally completely out of the pandemics, we had 29 seminars, (17 in face to face, and 12 on a hybrid format) by both domestic and foreign scientists (seven scientists based outside the country) including those from Harvard University and Queen's University in UK. We were particularly delighted to have many seminars in a face-to-face manner this year.

Local synthesis of CaMKII: Where, how and why?
.....Leslie C. GRIFFITH
Nancy Lurie MARKS (Brandeis University)

(1) Targeting macrophage for host directed therapy against tuberculosis
.....Xinchun CHEN (Shenzhen University)

(2) Regulation of the ATR-CHK1 checkpoint signaling
.....Xingzhi XU (Shenzhen University)

Establishment of Ultra-High Precision Gene Editing Methods for the Treatment of Inherited Incurable Diseases
.....Shinichiro NAKATA
(Graduate School of Medicine, Osaka University)

Spatial Context Analysis of Tissues and Organs Enabled by Cell Omics
.....Etsuo SUZAKI (Jsuntendo University)

Exploration of Therapeutic Strategies Using a Mouse Model of Circadian Rhythm Sleep-Wake Disorder
.....Kazuhiko KUME (Nagoya City Unversity)

AAV Vectors: Opening New Avenues for Incurable Diseases
.....Shinichi MATSUMURA (Jichi Medical University)

Small G Proteins and Kidney Disease
.....Keiichiro MATOBA (The Jikei University School of Medicine)

Reflecting on My Research Life at the Rinshoken, Shinkeiken and Igakuken
.....Satoshi KOIKE (TMIMS)

Overseas Research Report: Advance Care Planning and Behavioral and Psychological Symptom Management Programs in Dementia
.....Miharu NAKANISHI (Tohoku University)

Building our brains: From RNA to evolution
.....Debra Lynn SILVER (Duke University School of Medicine)

Old stories: gene therapy vectors and xenotransplantation
.....Yasu TAKEUCHI (University College London)

Periodontal Disease and Systemic Diseases - The True Dangers of Periodontal Disease and Its Countermeasures
.....Keiko NARUSE (Aichi Gakuin University)

Assessing the contribution of transcriptional and posttranslational mechanisms in the clockworks: understanding circadian period and phase via CK1 dissections, and transcriptional rewiring.
.....Luis F. LARRONDO (P. Universidad Catolica de Chile)

Casein Kinase 1 and its history in circadian rhythms
.....David VIRSHUP (Duke-NUS Medical School)

Psychoneurological Functions of SHATI/NAT8L
.....Atsumi NITTA (University of Toyama)

Spatio-temporal replication program of the human genome and its impact on genome instability
.....Chunlong CHEN (Institut Curie)

The Role of Plasminogen Activator Inhibitor in Brain and Neuronal Function
.....Eri KAWASHITA (Kyoto Pharmaceutical University)

Curing the Incurable Diseases: Genome Medicine and the Rare and Undiagnosed Diseases Initiative (IRUD)
.....Hidehiro MIZUSAWA
(National center of Neurology and Psychiatry)

The Schedule for the evaluating of the individual Quality of Life-direct weighting: SEIQoL-DW
.....Takashi NAKAJIMA (Niigata Hospital)
.....Akira YAMAMOTO (R102 Co., Ltd.)

The leading strand DNA polymerase - what's so special about it?
.....Huilin LI (Van Andel Institute)

Functions of Reproductive Cells and Organs in the Mechanical Environment
.....Tomoko KAWAI (Okayama University)

Activity Dynamics and Role of Orexin Neurons During Sleep: Involvement in REM Sleep-Related Symptoms of Narcolepsy
.....Hiroto ITO (Nagoya University/National Institute for Physiological Sciences)

TMIMS International Symposium

In 2024, we have hosted four TMIMS International Symposia, as shown below. We invited foreign scientists, and had very exciting face-to-face presentations and heated discussion. In 26th TMIMS International Symposium "Social Determinants of Mental Health" organized by Dr. Atsushi Nishida and Dr. Kiyoto Kasai, 27th TMIMS International Symposium "Neurodegenerative Disorders: Understanding Mechanisms and Toward Therapies" organized by Dr. Masato Hasegawa and Dr. Takashi Nonaka, 28th TMIMS International Symposium "The Tokyo Glia Symposium: Glial Cells in Health and Disease" organized by Dr. Yoichi Shinozaki and 29th TMIMS International Symposium "A New Era for Diagnosis and Treatment of Diabetic Neuropathy" organized by Dr. Kazunori Sango. In these symposia, top-flight scientists in the field gathered at TMIMS, and high-quality science was discussed.

Joint programs with universities

Many scientists at TMIMS have joint appointments as visiting professors or lecturers at various universities. In 2024, for the first time in the last four years, we held our annual "open institute" events for prospective graduate students face to face. More than 50 students came to the event, and joined the lectures and visited laboratories. We currently have 149 students from affiliated universities and other schools, who conduct their research at our institute.

Support for students and young scientists

Research Associate Fellowships

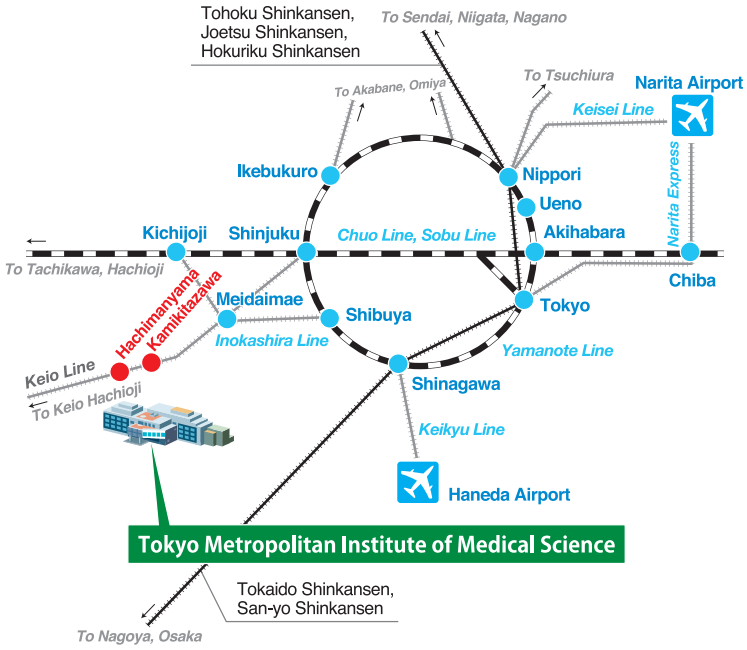
We provide graduate students who conduct their masters/Ph.D. research at TMIMS with research associate fellowships that allow them to concentrate on their studies and research.

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

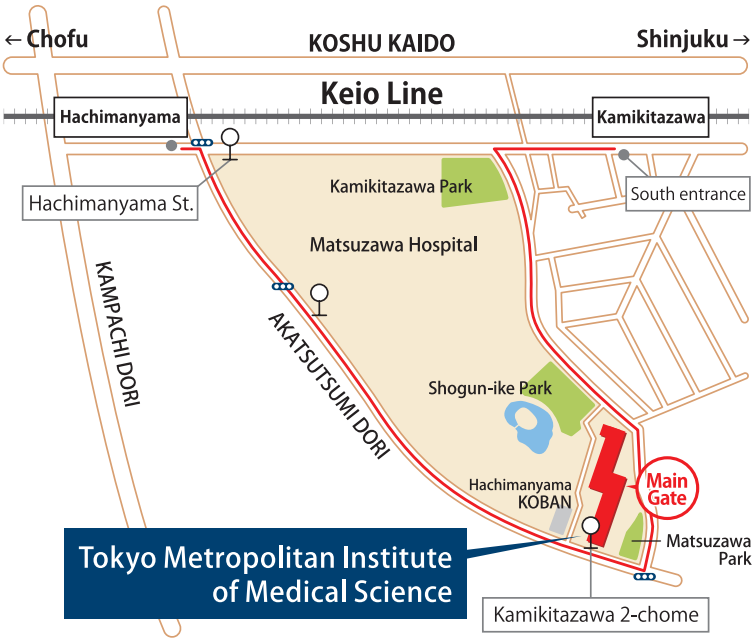
Tokyo Metropolitan Institute of Medical Science	
Address	2-1-6 Kamikitazawa, Setagaya-ku, Tokyo, 156-8506, Japan
Tel	+81-3-5316-3100
Fax	+81-3-5316-3150



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, 2025