TMiMS

Annual Reports 2025

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Message from the Chairperson

I am Tomoyo Narita, who has assumed the position of Chairperson of the Tokyo Metropolitan Institute of Medical Science effective March 28, 2025. I feel both humbled and deeply honored to have been entrusted with this significant role, and I am determined to contribute to the further advancement of this institute.

Since its founding, our institute has steadily accumulated achievements across a broad range of research fields—including basic medicine, clinical medicine, and social medicine—to contribute to the advancement of medical care and welfare for the citizens of Tokyo. We extend our deepest gratitude to all stakeholders for their tremendous cooperation and generous support over the years.

The health challenges faced by Tokyo residents are becoming increasingly diverse and complex. By 2025, the number of residents aged 65 and over in Tokyo will exceed 3 million, with the elderly population ratio reaching 23.4%. The population of those aged 75 and over, the late elderly, is projected to increase significantly going forward. Consequently, the number of patients with conditions such as dementia, cancer, and heart disease is also expected to rise further. Furthermore, in today's stressful society, there are concerns about an increase in mental health disorders, and preparedness against infectious diseases is also growing in importance.

The COVID-19 pandemic has reaffirmed the critical importance of infectious disease control measures. In our ongoing efforts against infectious diseases since 2020, we have pursued epidemiological research and vaccine development, with the results reflected in Tokyo Metropolitan Government policies. Furthermore, to prepare for future emerging and re-emerging infectious diseases, the Infectious Disease Medical Research Center will be established in April 2025. It will advance research activities through collaboration with Tokyo's infectious disease control departments, the Health and Safety Research Center, metropolitan hospitals, and national research institutions during peacetime, thereby preparing for emergencies.

This institute operates with support from the Tokyo Metropolitan Government. Its mission is to comprehensively conduct research on major unresolved diseases such as neurological disorders, psychiatric disorders, cancer, and infectious diseases, and to contribute to improving the medical care and welfare of Tokyo residents by widely disseminating the results. To fulfill this mission, we leverage the strengths of basic research, clinical research, and social medicine research, fostering collaboration and cooperation among researchers to advance our research activities. We are advancing research aimed at elucidating disease mechanisms and developing innovative prevention, diagnosis, and treatment methods, as well as initiatives to deliver these research outcomes to society. Through these efforts, we contribute to extending the healthy lifespan and improving the quality of life (QOL) of Tokyo residents.

In the fifth-phase project launched in fiscal year 2025, we are implementing this policy by advancing research through “Project Research”—which defines a five-year period to conduct research effectively and efficiently—and through the “Research Center,” which provides specialized support both within and outside the institute and contributes to Tokyo Metropolitan Government policies.

Chairperson
Tomoyo NARITA

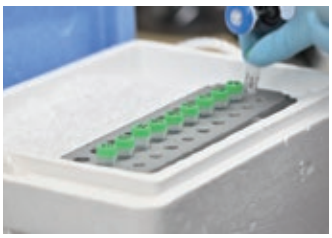
We will further strengthen the cooperative relationships we have built with metropolitan hospitals, universities, research institutions, and companies, actively promoting joint research, information sharing, and personnel exchanges. Through collaboration with the Tokyo Metropolitan Hospital Organization, we are advancing initiatives that leverage clinical expertise and research capabilities to enhance and improve medical care and medical research in Tokyo. By respecting each other's expertise and jointly creating reliable evidence to support clinical practice and policy decisions, we will present effective solutions to Tokyo's urban health challenges and widely disseminate these outcomes both domestically and internationally.

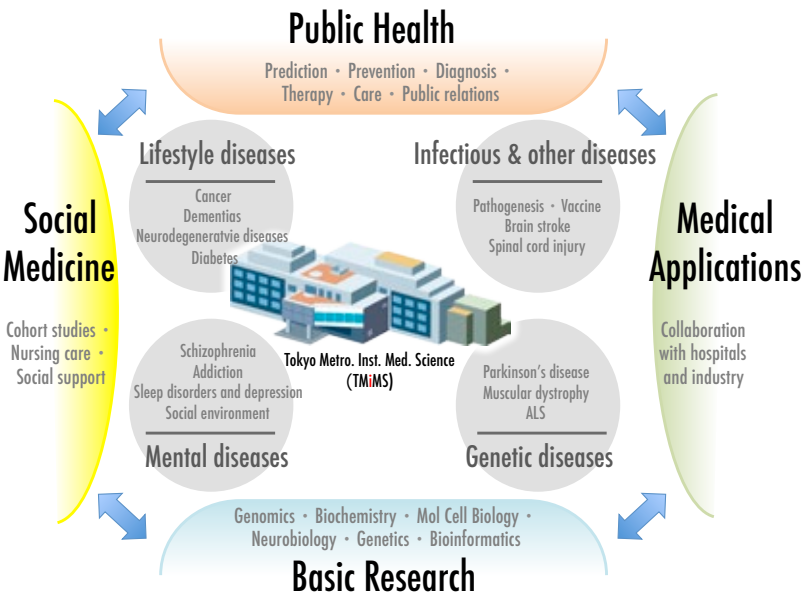
Our institute promotes internationalization through initiatives such as hosting international symposia and inviting foreign researchers. We hold international symposia two to three times a year, facilitating research exchanges with renowned researchers from various countries on diverse research themes, thereby advancing research and disseminating research findings. Regarding the invitation program for foreign researchers, we invite outstanding researchers from various countries. Through joint research, discussions, and exchanges of opinions with our institute's researchers, we advance our institute's research and widely disseminate our research findings to the international community. Through these initiatives, we collaborate with outstanding researchers worldwide to share cutting-edge knowledge and technology, contribute to solving global challenges, and disseminate our institute's research findings to the world.

In closing, we recognize that our own spirit of inquiry is deeply intertwined with society's expectations. We are committed to dedicating our utmost efforts to ensure that each research achievement supports tomorrow's healthcare, enriches someone's life, and delivers hope to Tokyo residents and society. We sincerely ask for your continued support and guidance moving forward.

Our Mission

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





Message from the Director: TMIMS 2025

Director
Hisao MASAI

As I write this essay in late January of 2026, the scorching heat of the summer of 2025 already feels like a distant memory. After a brief autumn, the year seems to have passed with astonishing speed — am I alone in feeling this way?
In this booklet, we report our achievements in 2025. I would like to take this opportunity to reflect on our key discoveries in 2025 and share our outlook for the future. I will also share some of my views on science and my own field.

TMiMS in 2025

In 2025, the Institute launched its Fifth-Term Project Research Program. In the project call held in the previous year, we received 81 applications, from which three new projects were selected: the Intracellular Quality Control Project (led by Dr. Koji Yamano), the Stress-imprinted Immunity Project (led by Dr. Yukiteru Nakayama), and the Stem Cell Regulation Project (led by Dr. Goro Sashida).
Under this renewed research framework, many important scientific achievements were reported during the year. The Center for Genome & Medical Sciences (led by Dr. Hideya Kawaji) comprehensively analyzed drug-induced enhancers in human hepatocytes, identifying novel genomic regulatory regions potentially involved in drug side effects. This work was published in *Nature Communications* and provides important insights into individual differences in drug efficacy and adverse effects, contributing to the advancement of precision medicine.
The Visual Research Project (led by Dr. Takayuki Harada) identified HAUS7, a component of the Augmin complex involved in cytokinesis, as a molecule that promotes optic nerve regeneration, and published this work in *Science Advances*. This finding will contribute to the development of effective strategies for recovery of visual function in glaucoma and after optic nerve injury.
The Unit for Mental Health Promotion, the Research Center for Social Science and Medicine (led by Dr. Atsushi Nishida) performed large-scale, longitudinal cohort studies of teens in Tokyo and compared their results with similar studies from London to determine that increased depression in girls is caused by social factors and thus should be preventable through social and structural changes. This work was published in *Lancet Child and Adolescent Health* and should contribute to earlier and more effective treatment of adolescent depression. Please look at the "Meet Our Scientists" articles (page 8-13) for more details of these three works.
The Circadian Clock Project (led by Dr. Hikari Yoshitane) constructed a database of circadian variations in approximately 19,000 mouse proteins using state-of-the-art mass spectrometric techniques and reported these findings in *Molecular Cell*. This resource will provide important information for understanding the mechanisms of circadian rhythms and how their disruption affects human health. Please look at the "Featured paper" (page 14-15) for more details.
Many other research achievements are highlighted in the Topics section of the Institute's website. In our outreach activities, large numbers of people participated in our public lectures, science cafés, and symposia. In addition, we published nearly 60 articles in 2025 and introduced recent research findings related to human health on our website, in order to disseminate our research activities widely to the public.

Science in Japan 2025

The year 2025 brought encouraging news to Japanese researchers. In the medical research field, Professor Shimon Sakaguchi of Osaka University was awarded the Nobel Prize for his discovery of regulatory T cells, which act as a brake to prevent excessive immune responses.
As a graduate student, Professor Sakaguchi became convinced that there must exist T cells that suppress immune attacks against the self. Thus, in the midst of his graduate studies, he moved to the Aichi Cancer Center Research Institute where the paper that inspired his idea had been published, devoting himself entirely to pursuing this idea. Although his hypothesis

was not accepted at first, he persisted in continuing his research, ultimately leading to a groundbreaking achievement.
Today, his discovery has led to the development of treatments for diseases that affect many people, including autoimmune disorders such as rheumatoid arthritis, and allergies and cancer. Research driven by the curiosity to unravel the mysteries of life can ultimately make profound contributions to human welfare. Dr. Sakaguchi's career path and achievements are very encouraging to researchers in the medical field, and teach us the importance of persistent endeavor.
Nobel laureates consistently emphasize the importance of basic research grounded in free and creative thinking. For our Institute to make an impact in the world, it is essential that individual researchers pursue the fundamental principles underlying life phenomena and disease mechanisms based on their own ideas, supported by the state-of-the-art research infrastructure provided by the Tokyo Metropolitan Government and the diverse research perspectives that characterize our Institute. This will lead to groundbreaking discoveries and impactful publications, enhance the Institute's international standing, and ultimately, allow us to improve the health and welfare of Tokyo's citizens in a meaningful way.

Looking back on my scientific journey that began in the USA

During the first year of my master's program, I had an opportunity to study abroad at a research institute in California, the DNAX Research Institute. I went on to complete my graduate and postdoctoral studies at this institute (1981-1990). I was a young student arriving from a distant foreign country on the first airplane flight in my life, and was uncertain about what would be in store for me. However, I was warmly welcomed by the people I met in the United States. Although I was a complete foreigner, I felt accepted and included at the institute just like everyone else, which made my first experience abroad deeply comfortable and rewarding.
The strength of scientific research in the United States depends on the diversity created by its policy of accepting researchers from around the world. At our institute as well, the number of international trainees and researchers has been increasing. I firmly believe that respecting such diversity and encouraging inclusiveness contribute significantly to the development of the institute, and more broadly, to the advancement of society.
The experiences I gained during my first nine years of research life in the United States profoundly shaped my worldview as a scientist. Just as those experiences instilled in me deep gratitude and affection for the United States, I hope that international students and researchers who come to Japan to study and work at our Institute will return to their home countries with similarly positive sentiments. If that can be achieved, it would represent a small way of reciprocating the tremendous benefits I received during my time abroad.

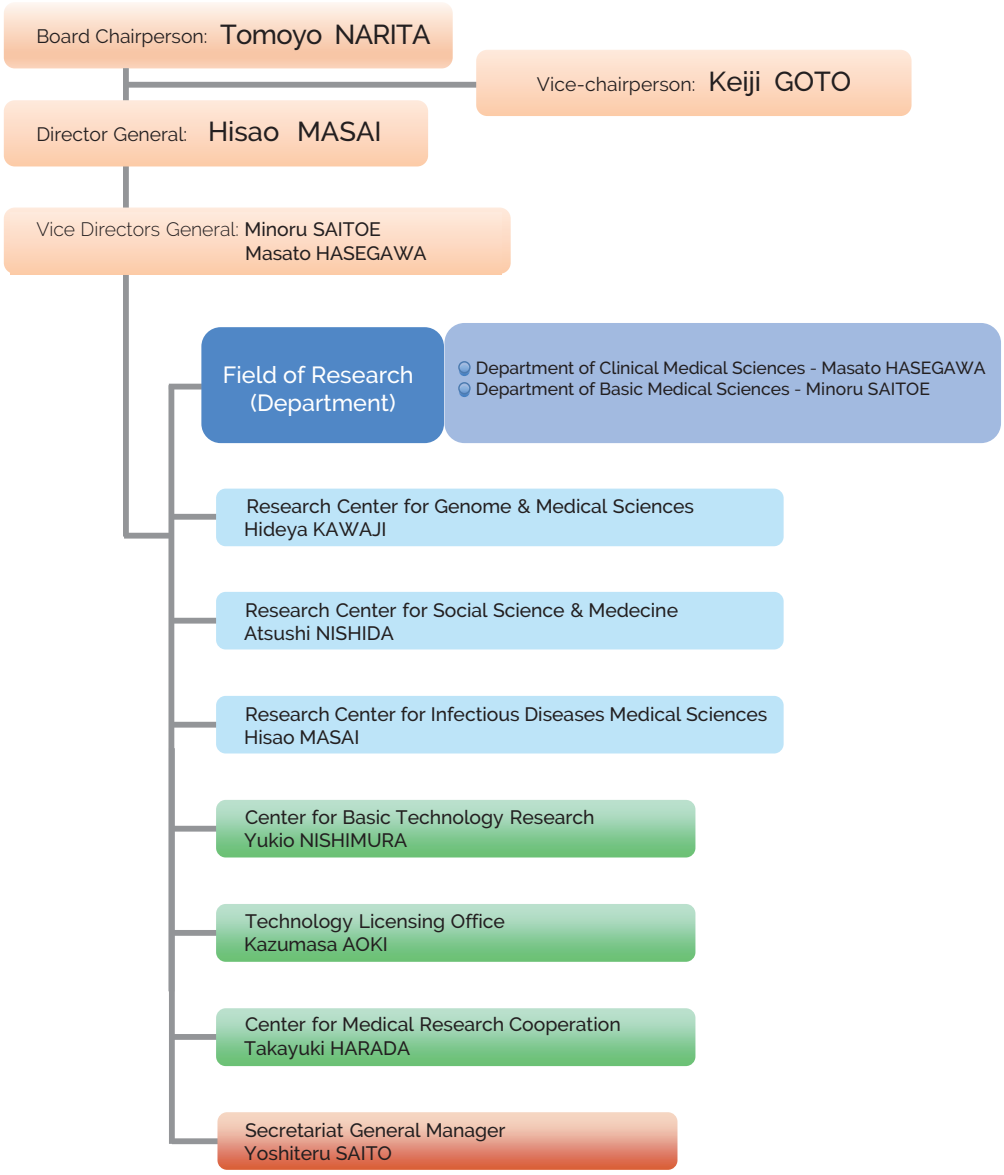
The world of DNA replication

When I met my mentor, the late Ken-ichi Arai, for the first time on April 6 of 1981, he suggested that I work on DNA replication, which he claimed is the most important issue in how life is maintained and inherited. I had no idea at that time that I would work in this field for the next 45 years. My scientific career evolved along with the development of the field of DNA replication. I was fascinated by the remarkably high signal-noise ratio of DNA replication assays in bacteria. I still remember the moment of deep joy I felt in the middle of the night in an empty lab, when the beeping of the Geiger counter on my glass fiber filter indicated that I had succeeded in replicating DNA in a test tube.
Studies of DNA replication started when the double helix structure of DNA was solved in 1953. Now, the entire process of DNA replication, from initiation to termination, has been reconstituted from purified proteins. DNA replication is central for the duplication and inheritance of genetic material, and is also intimately related to the maintenance and alteration of the epigenome, which leads to differentiation through asymmetric cell division. The process of DNA replication takes 6-8 hrs in human cells, and many events are coordinated with DNA replication to ensure faithful distribution of replicated chromosomes, repair of errors that occur during the process, and shuffling of genetic materials through recombination to increase the genetic diversity in the offspring. Temporal and spatial regulation of nuclear DNA replication during S phase is associated with higher-order chromatin architecture and potentially regulates early development processes and mutation rates. Evolution relies on rare but inevitable errors of DNA replication. At the individual level, errors during DNA replication are the major cause of diseased cells, including cancers. DNA replication is robust, but flexible and adaptive. The environment surrounding cells affects the process of DNA replication; cellular stresses perturb DNA replication and potentially increase mutation rates, and different tissues and organs may adopt distinct replication modes that best fit their functions. The birth of living species must have occurred when primordial genetic materials found a way to replicate.
With most, if not all, of the proteins involved in DNA replication identified, and a faithful replication system in hand, now is the time for truly important questions to be addressed; how does DNA replication regulate differentiation processes through asymmetric inheritance of epigenomic information? How does the mode of replication change in response to environmental cues, biological stresses, cellular senescence, or malignant transformation? How do higher-order chromatin structures shape replication profiles along chromosomes as well as within the nuclear space? What is the physiological significance of asymmetric synthesis of the two strands of DNA (leading vs. lagging strands)? How is the fidelity of DNA synthesis regulated; does it change depending on cellular environment or in different cell types? How was life with its ability to duplicate its genetic material created? How did it evolve? In the coming years, the true significance of DNA replication will be disclosed by addressing these key questions.

Outlook for 2026

At the Tokyo Metropolitan Institute of Medical Science, our mission is to conduct medical research that contributes to the improvement of the health, medical care, and welfare of Tokyo's citizens. Through the dissemination of innovative research outcomes, we aim to achieve discoveries that will bring transformative change to the health and medical care of the people of Tokyo, Japan, and the world.
2026, with all new projects fully in place, will be a pivotal year to further accelerate the Fifth-Term Project Program. One of the Institute's greatest strengths lies in the diversity of expertise among its researchers, spanning basic research at the molecular, cellular, and organismal levels, disease-oriented research, and social medical research that investigates the interaction between the society we live in and our health.
I hope you will enjoy reading our 2025 Annual Report, and I hope it will stimulate new collaborations between TMiMS and your institution.

Organizational Chart



Our People at a Glance

Position	Number
Researchers	140
Postdoctoral Fellows	69
Students	103
Visiting Scientists	127
Guest Scientists	114
Administrative Staffs	41
Total	594

February 1, 2026

Meet Our Scientists!

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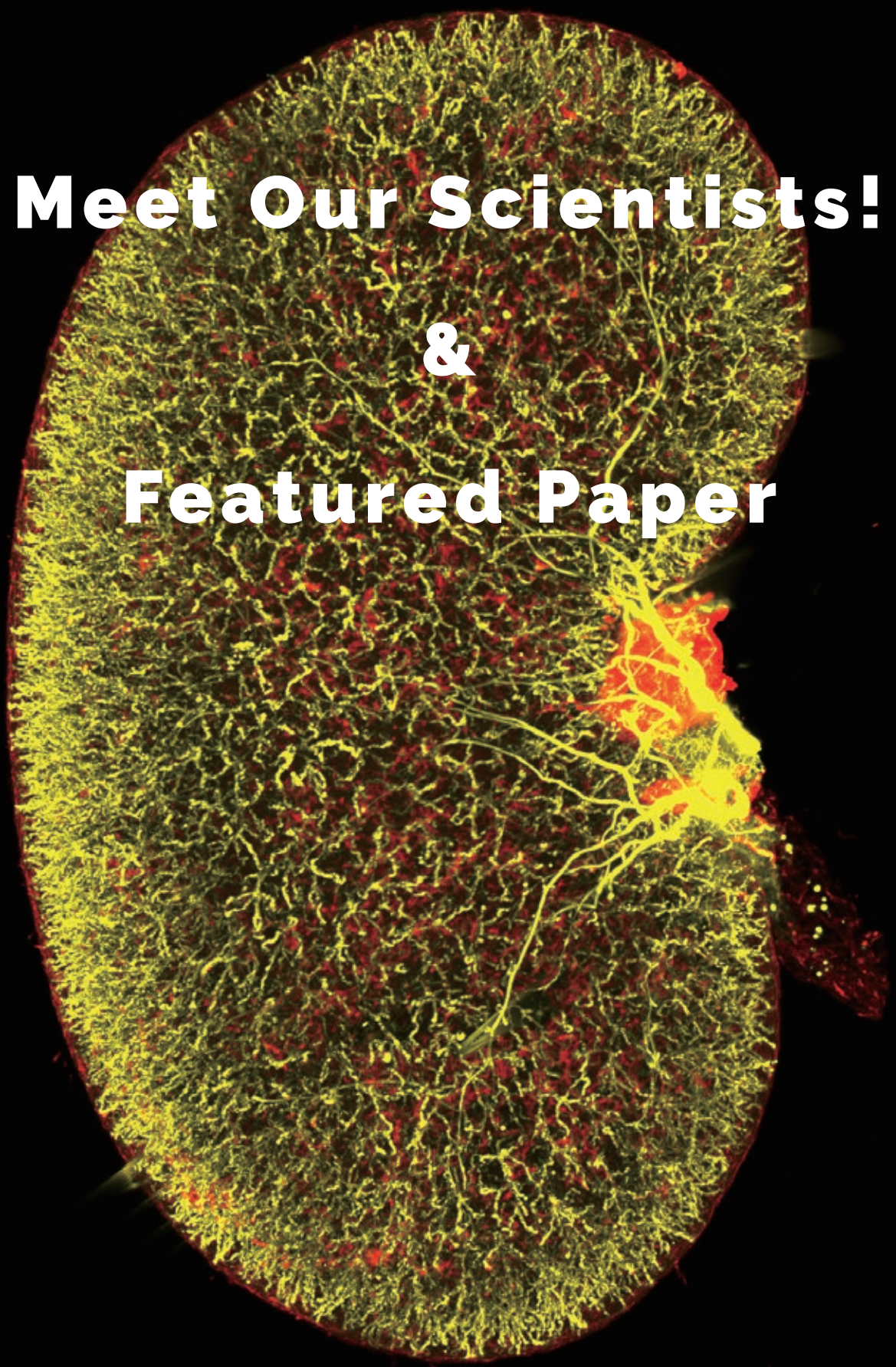
Featured Paper



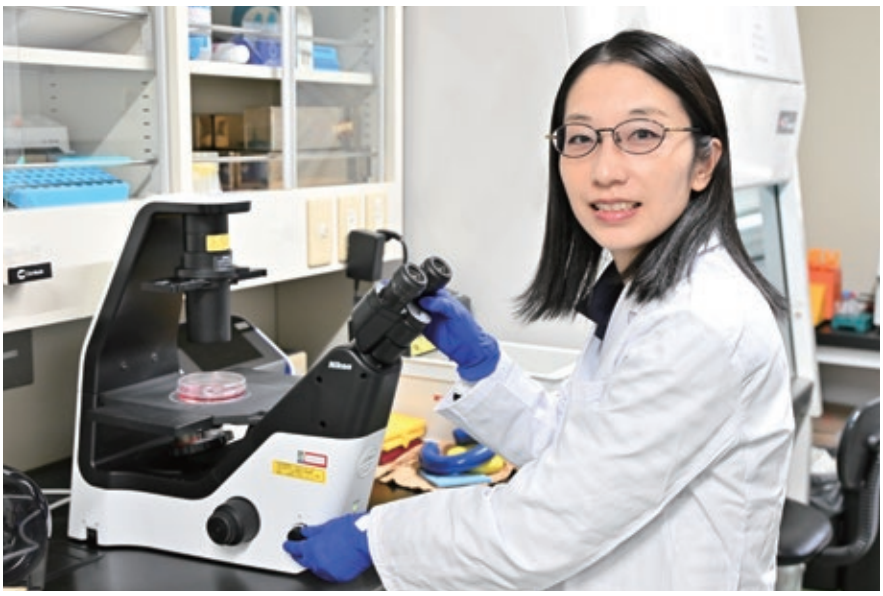
Three-dimensional imaging of a whole mouse kidney using light-sheet microscopy after tissue clearing. Sympathetic nerves that regulate kidney function are shown in yellow, and arteries that deliver blood to the kidney are shown in red.

Provided by Dr. Yukiteru NAKAYAMA (Stress-imprinted Immunity Project)

Meet Our Scientists!

Doctors have been using medicines to treat patients for thousands of years. However, different patients react differently to different medicines, reflecting the unique individuality of each patient. With the advent of whole-genome sequencing, it should theoretically become possible to map the differences between patients and tailor treatments to specific individuals. Saki Gotoh-Saito, a research scientist studying transcription at the Research Center for Genome and Medical Sciences, recently published a paper, Drug-induced cis-regulatory elements in human hepatocytes affect molecular phenotypes associated with adverse reactions, in Nature Communications. In this paper, Dr. Gotoh-Saito identifies variations in non-coding areas of the genome that affect our reactions to different medicines or drugs. Mutations in coding regions of our genomes (DNA sequences that are copied into mRNAs and translated into proteins) are well-known to produce altered proteins that affect different biological functions. However, mapping the effects of variations in regulatory regions (DNA regions that affect the amounts and types of mRNA transcripts made) on traits has been less common but is required for progress towards individualized medicine. We spoke to Dr. Gotoh-Saito about her work.

Saki Gotoh-Saito



How did you first become interested in research and biology?

To tell you the truth, I didn't like biology at all in High School, and I didn't study it much. But right after graduating, I happened to read a book on the human genome that blew my mind! This book described how DNA is composed of just four bases that are formed into long chains that encode genes, and how these genes are transcribed into messenger RNAs, which are then translated into proteins that do all the work in cells, and how this is the basis of all life on earth. It opened up a whole new world for me that I hadn't known existed! I was so amazed that I decided to major in Biology in college, and there, I realized that I really enjoy experiments.

Another major influence for me was studying abroad in the United States while I was in graduate school. The lab where I studied in Japan was very small, but during my time abroad, I had the opportunity to study nuclear receptors at a lab at NIH, which had great people and facilities. It was there that my interest in gene expression really deepened.

What do you enjoy most about research?

I enjoy the whole process! From thinking of a hypothesis that explains something, thinking of experiments to test that hypothesis, and obtaining results that tell me whether the hypothesis was correct or not. All of those steps are fascinating and fun!

How did you start your current work?

Dr. Kawaji, the head of the Research Center for Genome and Medical Sciences, allowed me to pursue any projects I wanted, so I decided to study the pregnane X receptor (PXR), which I'd studied when I was in the US. PXR is a ligand-activated transcription factor that belongs to the nuclear receptor superfamily. PXR has a flexible ligand-

binding pocket that allows it to bind to a wide range of prescription drugs. Once these drugs binds to PXR, PXR becomes active and induces expression of target genes involved in drug metabolism and transport. One documented adverse effect of several drugs that activate PXR is vitamin D deficiency, but the mechanism by which these drugs cause this deficiency had been unknown. I thought that by studying the cis-regulatory sequences (DNA sites) where PXR binds and identifying their target genes, I could understand why different people metabolize drugs differently, and why some become deficient for vitamin D.

Could you explain your paper in more detail?

Sure. We used a method called cap analysis of gene expression (CAGE) to determine where transcription is activated in the genome when cells are treated with a drug, rifampicin. Rifampicin acts as a high affinity ligand for the human PXR. This activates PXR and causes it to bind to specific DNA sites called cis-regulatory elements (CREs). These CREs are located within enhancers that boost transcription of their target genes. When PXR binds to CREs, it increases expression of downstream genes to make messenger RNAs. They also drive expression of noncoding RNAs from enhancers called enhancer RNAs or eRNAs. Thus, by using CAGE to determine where transcription increases, we identified rifampicin-activated promoters, and we also identified thousands of enhancers where PXR is likely to bind.

We combined our results with two other types of data from various previous studies. The first was data from mapping studies that identified sites that PXR binds to. From this, we were able to identify CREs that bind to PXR and increase activity in the presence of rifampicin. The second was genome-wide association studies (GWAS), which show linkages between traits such as drug-induced vitamin D deficiency and single nucleotide polymorphisms (SNPs). Basically, GWAS studies allow us to map traits to specific regions of DNA. By combining these data, we were able to identify PXR enhancers that were likely associated with traits such as drug-induced vitamin D deficiency.

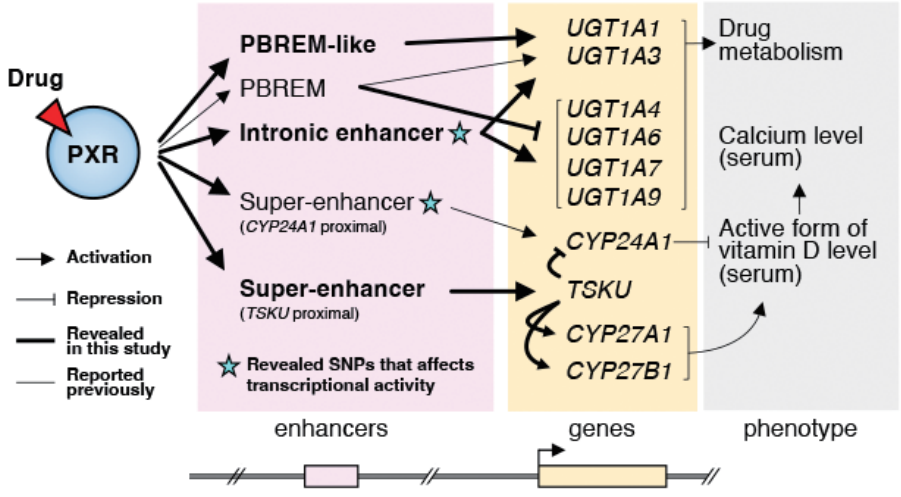
Finally, we were able to determine the function of our identified PXR enhancers by inhibiting or deleting them and measuring effects on their target genes.

Why is this work important?

People have different responses to drugs. For example, some people are susceptible to vitamin D deficiency when treated with certain drugs. A more serious case would be that some patients have an increased risk of neutropenia (an abnormally low number of neutrophils which increases the risk of serious infections) when treated with the anticancer drug irinotecan. We knew previously that these effects had something to do with PXR or genes associated with PXR, but not much more. Our work identifies the specific enhancers where PXR binds to regulate genes linked to a patient's susceptibility to neutropenia or vitamin D deficiency. Our work suggests that there are different variants of these enhancers that alter their binding affinity for PXR. This difference in binding directly affects gene expression, explaining why some people are more susceptible to severe side effects such as neutropenia or vitamin D deficiency than others. We haven't proven this, but I think this idea makes sense and it helps us to understand why different medicines have different effects on different patients.

What are your plans for the future?

Right now, I am studying the function of a drug-inducible non-coding RNA. Messenger RNAs get translated into proteins, so everyone knows their importance, but non-coding RNAs including eRNAs don't code for proteins so it's still a mystery why they are made. I don't think they are junk. They have a function and I'm currently studying one which binds to PXR. In any event, I really enjoy research so I'm planning on continuing to form hypotheses, conducting experiments, and obtaining results.



Drug-inducible and pregnane X receptor (PXR)-mediated enhancers and super-enhancers at the UGT1A1, CYP24A1, and TSKU loci. The novel and known enhancers, their regulatory targets, and the resulting phenotypes are schematically illustrated .

Meet Our Scientists!

Neurons are highly efficient at transmitting information through axonal processes that can extend over long distances. However, because neurons are highly specialized post-mitotic cells, damage to neurons or their axons is difficult to repair. Dr. Kazuhiko Namekata and colleagues at the Visual Research Project study axonal regeneration using the optic nerve as a model system. Previously, they identified several key factors important for axonal regeneration following injury. They showed that constitutive activation of the BDNF/TrkB signaling pathway enhances regeneration, and further identified activators of DOCK3, a downstream target of BDNF/TrkB, that also enhance regeneration. This past year, they published a paper in Science Advances entitled "Role of HAUS7 as a DOCK3 binding partner in facilitating axon regeneration." In this study, they build on their previous work to present a more coherent model of the steps involved in axonal regeneration. We spoke to Dr. Namekata about this work.

Kazuhiko Namekata

Could you give us some background on your DOCK3 work?
I've been interested in diseases associated with aging since I was a college student, and I've been studying DOCK3 for over 15 years because it is a protein associated with Alzheimer's disease. The DOCK proteins are a family of intracellular signaling molecules that activate Rho family GTPases to regulate processes such as cytoskeleton remodeling, cell migration, and neurite and axonal growth and regeneration. I've been studying DOCK3 in particular because it is expressed specifically in neurons, and we previously found that if we overexpress DOCK3 in retinal ganglion cells (the cells whose axons compose the optic nerve), we can enhance optic nerve regeneration [after damage]. We also screened for activators of DOCK3 and identified two molecules that enhance axonal regeneration when injected into the eye.

How does the BDNF/TrkB signaling pathway relate to DOCK3?
BDNF is a secreted extracellular signaling factor that regulates processes such as neuronal survival and differentiation. It is also important for axonal regeneration. It functions by binding to and activating the cell surface TrkB receptor, which is expressed on neurons. We previously found that expressing constitutively active TrkB in retinal ganglion cells enhances optic nerve regeneration. DOCK3 is a key mediator of TrkB-dependent axonal regeneration. So, a biochemical pathway that stimulates axonal regeneration after damage would be BDNF activating TrkB, resulting in activation of DOCK3 and Rac1, which increases actin cytoskeleton remodeling required for regeneration.

How does your current paper continue this story?
For axons to regenerate, you need microtubules to polymerize, but we don't have a connection to microtubules in our BDNF/TrkB/DOCK3 pathway. This current project started from the idea that DOCK3 is a large protein with multiple functions and multiple binding partners. We thought that there must be other important proteins that bind to DOCK3, and we identified HAUS7 as a novel DOCK3 binding partner. This is important because HAUS7 is a subunit of the augmin complex, and the augmin complex is important for microtubule branching.

Without the augmin complex, branching doesn't occur. Microtubules are critical cytoskeletal components of axons, but axons aren't composed simply of single, straight, unbranched microtubules. Microtubules are thought to elongate through polymerization and branching nucleation. So, if you are unable to branch, you should be unable to make the long microtubule structures needed to regenerate axons.

I envisioned axons as long graceful structures which contained long, graceful, straight, unbranched microtubules.

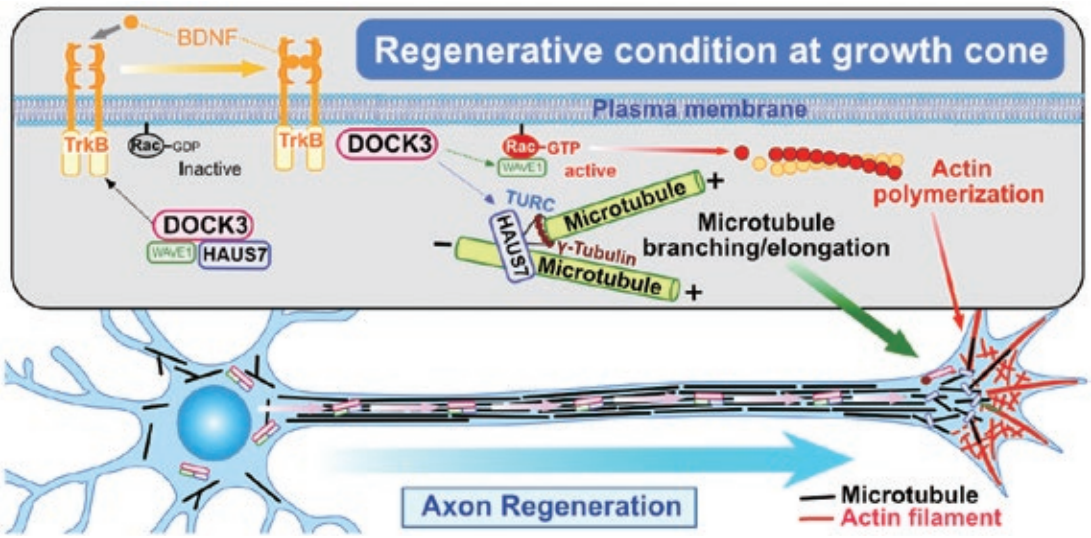
That was the model for a long time. But, if you think about it, if all microtubules were ultra-long, unbranched structures, that could be too restricting. If there were some problem at some place in the microtubule, you wouldn't be able to use it. On the other hand, if microtubules can branch and branches can extend, you have much more freedom. Also, if you have only long microtubules, do they have to last throughout your lifetime? Branching might allow you to repair different portions of the structure as they are damaged or get old.

What do you think is most significant about your recent paper?

I think our work is important because it links three processes, extracellular signaling from BDNF to actin skeleton remodeling through DOCK3 and Rac1 to microtubule extension and remodeling through HAUS7 and the augmin complex. Currently, our model is that HAUS7 and another protein, WAVE1, bind to DOCK3 and all three proteins are transported along microtubules to the growth cone at the end of regenerating axons. BDNF activation of TrkB induces the HAUS7-WAVE1-DOCK3 complex to move to the cell membrane at the growth cone where DOCK3 is phosphorylated. Phosphorylation of DOCK3 causes WAVE1 and HAUS7 to dissociate from DOCK3, freeing them to induce actin polymerization and microtubule assembly required for axonal regeneration.

Do you think there are any medical applications to your findings? What are your future plans?

The results from this study don't directly translate to medical treatments, since we didn't increase regeneration. Instead, we identified mechanisms that are important for regeneration. However, I think our future studies may be more relevant to medicine. In this study, we made Haus7 knockout mice [mice in which Haus7 is deleted]. Surprisingly, these mice are alive, and HAUS7 isn't a completely essential gene. It's possible that HAUS7 may not be an essential subunit of the augmin complex or that other microtubule nucleation pathways can compensate for augmin deficiencies. What we do know is that Haus7 knockout mice are alive but are deficient for axonal regeneration. We also know that Haus7 knockouts are defective for processes that require rapid cell proliferation, since cell division requires microtubules and microtubule branching. So, Haus7 KO mice are defective for processes such as spermatogenesis, thymic function, and microglial proliferation. Since immune responses require rapid responses and rapid proliferation of immune cells, I believe that inhibiting HAUS7 activity or augmin function might be a viable strategy for combating autoimmune diseases such as multiple sclerosis (MS), and I'm interested in pursuing these types of studies in the future. This strategy might also work as a possible cancer treatment, although I'm not actively pursuing that avenue now. Finally, I think that inhibiting HAUS7 activity might accelerate the onset and severity of diseases such as Alzheimer's disease and glaucoma. So, I believe that HAUS7, augmin, and altered microtubule structures could contribute to various diseases and I'm eager to study these connections in the future.



Under regenerative conditions, HAUS7 is transported along retinal ganglion cell (RGC) axons to the growth cone in a DOCK3-dependent manner, even in the absence of extracellular stimulation. Following BDNF signaling, the DOCK3–HAUS7 complex is recruited to the plasma membrane. Upon phosphorylation of DOCK3, HAUS7 dissociates and facilitates microtubule assembly, while WAVE1 concurrently induces actin polymerization at the growth cone.

Meet Our Scientists!

Syudo Yamasaki from the Research Center for Social Science and Medicine was a practicing clinical psychologist for years before joining the Research Center for Social Science and Medicine as a research scientist. He is interested in understanding the causes of mental health problems and depression in adolescents and developing effective treatments. Recently, he and other members of the Research Center collaborated with a group from King's College in London to publish a paper, Trajectories of depressive symptoms among young people in London, UK, and Tokyo, Japan: a longitudinal cross-cohort study, in Lancet Child and Adolescent Health. We spoke to him about his work.

Syudo Yamasaki

How did you first become interested in research?
Before coming to this institute, I worked as a practicing clinical psychologist for ten years, where I helped young patients with severe mental illnesses, such as psychoses and developmental disorders. A concern that I had during this time was that most patients waited a very long time, five or more years, until symptoms became extremely severe, before seeking treatment. I saw patients in their late twenties to early thirties, but I often learned that it was in their adolescence, when they were in junior high or high school, when their mental problems began. I realized that if we were able to understand and help patients during adolescence, we could have a greater effect on their future well-being and happiness.

So, your interest began from a desire to help people rather than from strictly scientific curiosity?
Well, of course, I also really like science. When I started working as a psychologist, clinical psychology wasn't evidence-based. Psychoanalysis was dominant. Japan

was behind other countries where evidence-based treatments such as cognitive behavioral therapy were being used.

What is cognitive behavioral therapy?

Depression and anxiety are emotional problems. Under similar aversive conditions, some people become depressed while others don't. People who are able to focus on things they enjoy are more likely to be able to bounce back from depressing situations. For people who can't bounce back, it can become a vicious cycle. So, people have different tendencies, and through discussions with psychologists, patients figure out what tendencies they have and how they should modify their behaviors to improve their emotions. By experimenting during therapy, they find out what treatments work for them. That is cognitive behavioral therapy (CBT). There are many randomized control trials that prove that CBT works. So, my interest in research started from my desire to integrate evidence-based therapies into Japanese psychological treatments.

So, you decided to move from clinical practice to research.

When I was a practicing psychologist, I worked with medical doctors and studied brain science, so in my mind, clinical practice and research weren't so separate. At the institute, now, I focus on adolescent cohort studies. I focus on big data from cohorts to identify what factors contribute to recovery from depression, and what factors function as barriers to recovery. I think this research will contribute to better clinical treatments.

Please tell us a little more about your current work.

One difficulty with mental health is that it is difficult to visualize the problems and identify their causes. For example, we know that depression is far more common in women compared to men, but we didn't know when these gender differences started and what their causes are. Depression is pretty low in children in general, and increases rapidly in adolescents, but there are few reliable studies in adolescents. We are dealing with this deficit by performing large scale longitudinal studies of teens in Tokyo. In this current study, we collaborated with a team doing similar studies in the UK to determine at what age gender differences start in adolescence. Our paper was likely accepted in Lancet Child and Adolescent Health because we used similar protocols and could reliably compare the results from two different societies. We found that in both countries, adolescent girls had more depression than adolescent boys and this difference increased by age. Interestingly, gender differences started slightly earlier in London (11-12 years of age) compared to Tokyo (between 11 and 14 years of age), and increased much more rapidly, 4 times as quickly, in London as in Tokyo. Our study found that gender differences in depression are caused by social factors, so they might be preventable through social and structural changes.

That's fascinating. How are you continuing this work?

We have a collaboration with King's College in London, and the Wellcome Trust is funding us for five years in a continuation project, Bridging Divides, to identify the causes of this gender mental health gap, by comparing Japan and London. What is special about this project is that we share our data with the young people we interviewed to obtain their viewpoints and interpretation in group discussions. We hear what the young people themselves are feeling and experiencing to develop hypotheses together that we can then test. Using this approach, we've identified several candidate mechanisms for gender differences in depression.

One is that girls are more concerned about how they are perceived, how their physical appearance is judged, and what body types they have compared to boys. This is intensified in the age of smartphones and Instagram and contributes to the mental health gap. Second, interpersonal relationships and social networks are more important to girls during adolescence and they are more sensitive to isolation and loneliness and this also contributes to the mental health gap.

What are your dreams for the future?

We will continue our cohort study to find out how our subjects change as they grow older. But we've gained a lot of data so we're now planning on moving onto the next step which for us is interventional studies. We're collaborating with the Tokyo Metropolitan Government and going to schools to try to decease depression by changing the environment at schools. School is a critical environment where adolescents spend about 15,000 hours. If that environment is terrible, of course teens will become depressed. And we've confirmed from our teen cohort studies that school is a very important factor influencing mental health, so I believe that interventions in school are a worthwhile endeavor. Thus, one of my plans for the future is to conduct interventional studies to alter the environment in schools to improve adolescent mental health.

Featured Paper

Advice about science and life from an Institute Project Leader
Hikari Yoshitane, Circadian Clock Project

Dr.Hikari Yoshitane (left)
and
Dr.Yuta Otobe (right)

You can't do research half-heartedly. You have to find the right question, the right theme that interests you.

The mammalian circadian clock is an amazing machine. When we study biochemistry in college, we learn that biological reactions tend to approach a state of equilibrium where reactants and products exist in a steady state. However, biological clocks don't follow this basic rule. Instead, they oscillate back and forth around the equilibrium without staying there. Harmonic oscillations have been explained in physics, but the basic principles underlying biological clocks are still unknown. Progress has been made, and negative feedback pathways involving key clock components have been identified. However, these findings still don't explain why biological clocks don't maintain a steady-state equilibrium. Dr. Hikari Yoshitane's goal is to understand how circadian clocks work.

Recently, Dr. Yoshitane and colleagues published a remarkable paper in Molecular Cell, entitled "A mouse circadian proteome atlas." It doesn't identify the core mechanism of clock function (he plans to publish findings in that area next year in an even higher-impact paper), but instead, it was a characterization the circadian activity of almost 19,000 proteins, covering approximately 74% of all mouse proteins. In this paper, Dr. Yoshitane and colleagues dissected 32 tissues from mice at 4-hr time points throughout a 24-hr day and analyzed proteins from these tissues using mass spectrometry. They identified proteins that show variations in amounts throughout a circadian day in different tissues, proteins that showed circadian variations in nuclear localization, and proteins that showed circadian variations in phosphorylation, which regulates activity. Overall, they found that more than half of all proteins exhibit rhythmic activity in various tissues, and they created an online resource that allows scientists to observe the circadian profiles of all the proteins they analyzed. We spoke to him about this work.

What interests you about circadian rhythms?

I'm interested in the basic question of how genes and proteins make an accurate clock. But I'm also fascinated by a particular aspect of the clock: its temperature independence. All biological reactions are highly dependent on temperature. They have a temperature where they work optimally, but if that temperature is raised or lowered even slightly, the reaction speed drops precipitously. That doesn't happen with the biological clock. Its rhythm stays constant. If you think about that a little, it's very curious. How do you build a clock or a machine that is temperature independent from components or reactions that are all highly temperature dependent? It's a mystery that I'm fascinated by.

What is it that you like most about research?

I'm most thrilled at the moment when an idea strikes. There are so many questions in the world that are fascinating, but just not answerable right now. And then

there are many questions that you can find the answers to, but the questions aren't particularly interesting. And finally, there are some questions that are fascinating that you can find the answers to if you are just creative and inspired enough. When I come up with an experiment that will clearly answer a question like that, that's fun. That's the part I enjoy most about research.

What was the motivation for your current paper?

My main interest is to identify the mechanism of the 24 hr circadian clock. But as a scientist who studies the clock, a question that comes up is: What is the purpose of the clock? And the answer is to organize the body's physiological functions. To regulate the rhythms of the whole body. Different biological functions need to occur at different times of the day. Some are needed at midday, some in the evenings, some at night. That's why the biological clock is important: it regulates the timing of biological functions. So, in order to understand the body's physiology, we need to know the daily activity profiles of various proteins. Recently, we'd obtained an amazing next-generation mass spectrometer that allowed us to analyze about 10,000 proteins at once. So, this paper resulted from the intersection of opportunity, ideas, technological ability, and effort. We realized that we could analyze the circadian profiles of massive numbers of proteins from different tissues, and publish a paper and make an online resource that would be enormously useful for chronobiologists, physiologists, and other scientists.

That must have been a tremendous amount of work.

I have to credit the first author, Yuta Otobe, who was pretty amazing. At first, I thought we could analyze circadian profiles in four or eight commonly studied organs for our study, but we realized that competitors and groups from other countries may also be doing similar work, and we wanted to produce a resource that would be useful for a long time. To do this, we needed to obtain high-quality, reliable data, analyze many proteins, and publish first. Otobe kun, from early on, was eager to expand the number of proteins we analyzed, so the number of tissues we analyzed went from four or eight to thirty-two. To encourage each other, we used to joke that we were aiming for the Guinness World Record for the most proteins analyzed. Our ultimate dream would be to characterize all proteins so that scientists wouldn't have to analyze individual proteins using Western blots ever again. They could just look up the data on our site.

We also realized that to create an online resource that people would use, we needed a simple user interface to make our data more accessible. We couldn't simply post raw mass spectrometer data or even data organized into Excel files. In the end, we worked with a professional website company to create a user-friendly interface that allows users to quickly search for proteins and displays protein amounts graphically. Even then, it took over nine months to work out all the bugs and get a working server running. Overall, I think it was worth it. If we didn't have a usable site running or if we only posted raw data, few people would access our data.

What impact has this paper had?

When we presented our work at conferences, our presentations were packed, and we received lots of offers for collaborations to see our data before publication. My lab is also gaining recognition for our ability to do large-scale protein analyses and our expertise in circadian biology from this work, so I've had lots of offers for collaborative work on that front as well. Personally, I'm also predicting that our work will have an impact on medicine. Medicines have different effects on patients depending on the time of day they are taken, but we don't really know why, and most knowledge about when a particular medicine is most effective is based on patient feedback. I think that if we analyze the rhythms of all the proteins affected by a drug, we will be able to determine when a drug will be most effective. Similarly, if we can analyze the proteins that drugs interact with that cause side effects, we should be able to determine when a drug is safest to take and when we need to be more cautious. I think patients and doctors will benefit from a comprehensive list of drugs and the optimal times to take them.

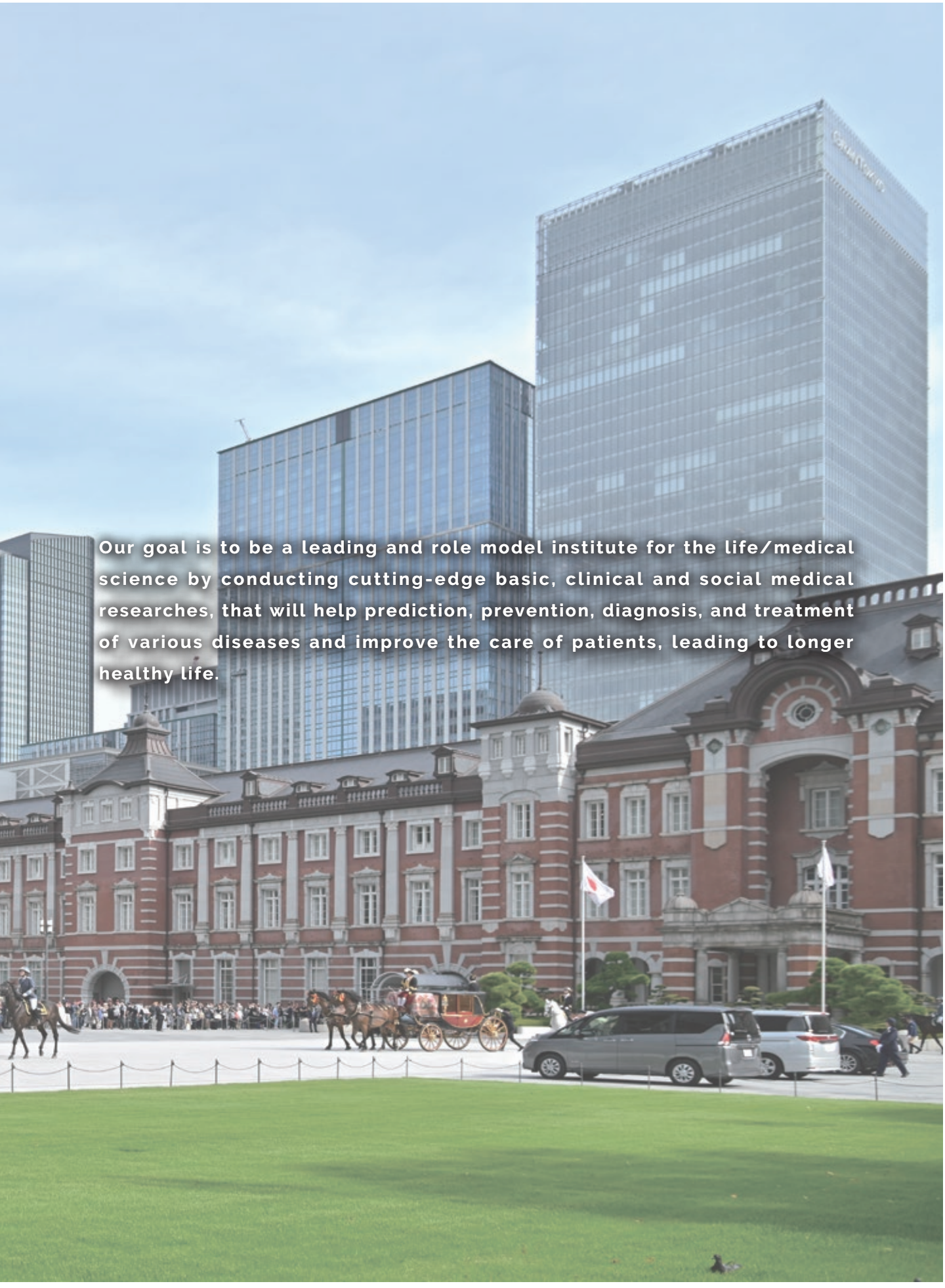
What are your plans for the future of this project?

Analyzing protein amounts is useful, but protein amounts on their own aren't enough to determine protein activity. For example, we showed that the nuclear localization of proteins may fluctuate in a circadian manner although the total protein amounts may remain the same. And even if the nuclear amounts of a protein are stable, the phosphorylation and activation of the protein may be rhythmic. So, to get an even more accurate idea of protein behavior and activity during a circadian day, we are planning to separate proteins into subcellular compartments before analyzing them by mass spectrometry. We're planning on separating tissue extracts into cytoplasmic, mitochondrial, lysosomal, Golgi, and endoplasmic reticulum fractions to analyze. In the brain, we're planning to separate different neuronal and glial cell types as well as separate cell body proteins from synaptic proteins. From this work, we should obtain a more comprehensive model for when and where individual proteins are made, transported, and active during the circadian day.

What is your advice to young people interested in research?

Find a theme or question that you can devote your life to pursuing. You can't do research half-heartedly. You have to find the right question, the right theme that interests you. I come from a generation when family computers and computer games were just becoming popular, and I was addicted to them as a child. I always wanted to know what comes next, what appears on the next level. I feel that way about research now. I work late nights and weekends because I'm excited by it. I want to continue the story and find out what comes next. As a scientist, you will be working with and competing against other people who have that passion, and you won't be able to keep up or excel unless you have the same or greater passion. So, immerse yourself and have fun!

Our Goal

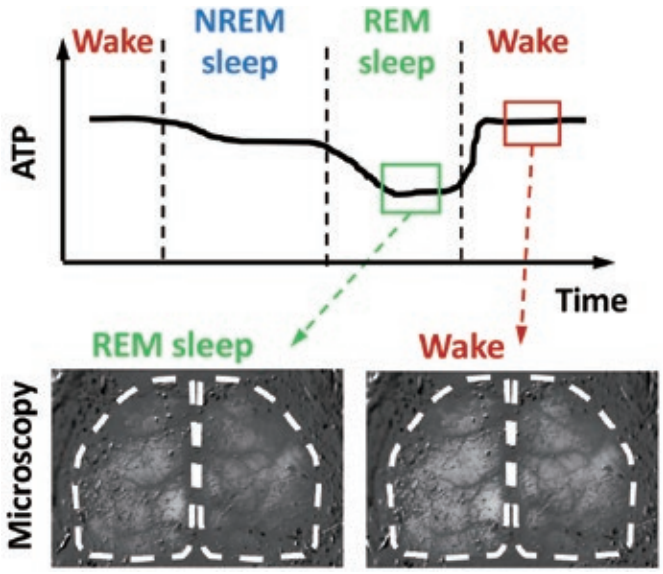


Our goal is to be a leading and role model institute for the life/medical science by conducting cutting-edge basic, clinical and social medical researches, that will help prediction, prevention, diagnosis, and treatment of various diseases and improve the care of patients, leading to longer healthy life.

Research Activities in 2025

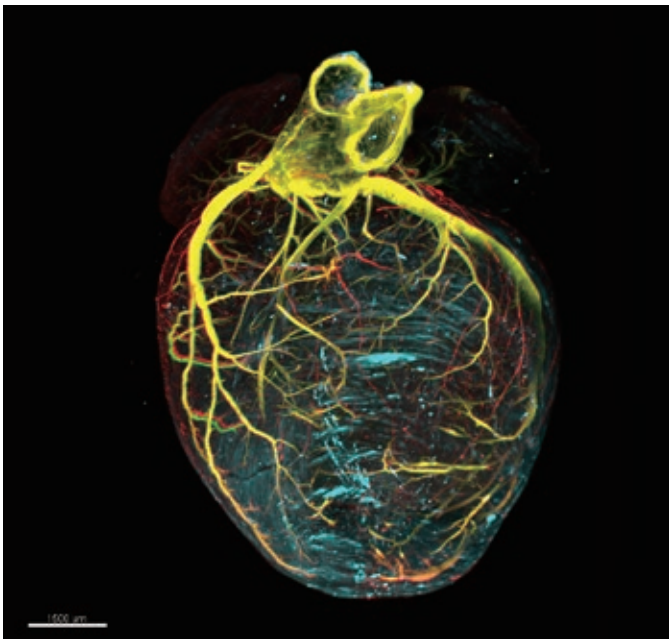
Three-color labeling of the embryonic chick pallium using iOn switch reporters. Cytoplasmic reporters and nuclear reporters were co-electroporated with piggyBac transposase into the chick pallium at embryonic day 4. Brains were collected at E14, cryosectioned, and imaged using a STELLARIS 5 confocal microscope. Different colors indicate cells with different linages.

Provided by Dr. Takuma KUMAMOTO (Developmental Neuroscience Project)



Transcranial macro-imaging of ATP in brain of Thy1-ATeam transgenic mice.

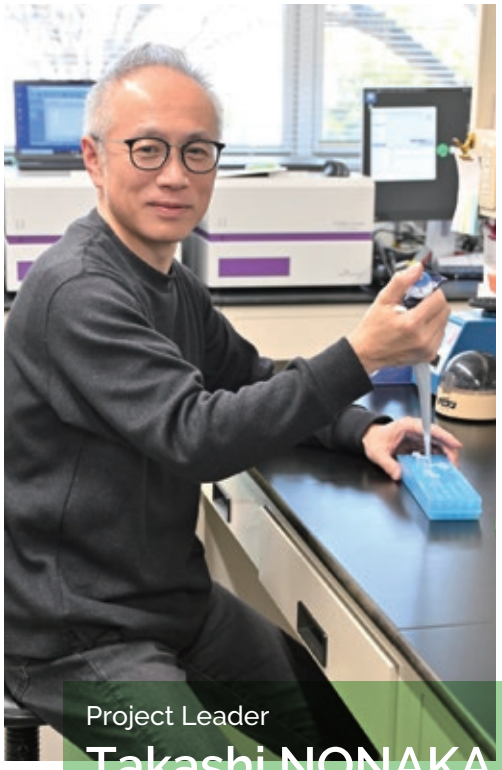
Provided by Dr. Akiyo NATSUBORI (Sleep Disorders Project)



Three-dimensional imaging of a whole mouse heart using light-sheet microscopy after tissue clearing. Coronary arteries that supply blood to the heart are shown in yellow, sympathetic nerves that regulate cardiac function in red, and macrophages—important immune cells in cardiac tissue—in cyan.

Provided by Dr. Yukiteru NAKAYAMA (Stress-imprinted Immunity Project)

Clinical Medical Sciences



Project Leader
Takashi NONAKA

Takashi Nonaka studies the molecular pathogenesis of neurodegenerative diseases. He started working on neurodegenerative diseases at Masato Hasegawa's lab in 2002, and found alpha-synuclein fibrils have prion-like seeding activity in vitro and in vivo. In 2006, Masato Hasegawa' group found that phosphorylated TDP-43 accumulates in frontotemporal dementias and amyotrophic lateral sclerosis. He has been studying the prion-like spread of neurodegenerative disease-associated proteins such as tau, alpha-synuclein and TDP-43. He also found that TDP-43 aggregates from brains of patients have prion-like activity. Recently, he collaborated with Dr. Benjamin Ryskeldi-Falcon, MRC UK, and found heteromeric amyroid filaments of ANXA11 and TDP-43 in brains of patients with frontotemporal lobe dementia.

Dementia Research

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

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Research Progress in 2025

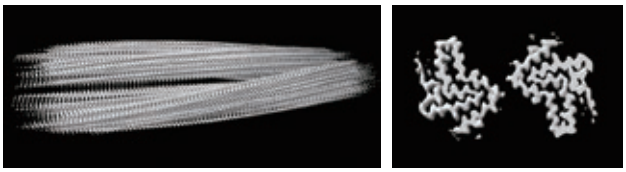
Background

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 2025

In 2025, we reported the enhanced secretion of misfolded TDP-43 mediated by the ER-ubiquitin specific peptidase USP19. This research highlights the role of the enzyme USP19 in the ER in promoting the secretion of misfolded TDP-43. We also found that cerebral hypoperfusion reduces tau accumulation likely through an increase in microglial phagocytic activity towards tau and an elevation in degradation through cathepsin D. This study contributes to understanding the relationship between tau pathology and cerebrovascular diseases in older people with multimorbidity. We are also analyzing protein fibril structures using cryo-electron microscopy. Several structures of protein fibrils determined by our group have been deposited in PDB database in 2025.



Recombinant alpha-synuclein mutant fibrils

Selected Publications

Papers in 2025

Picard F, Nonaka T, et al. Enhanced secretion of the amyotrophic lateral sclerosis ALS-associated misfolded TDP-43 mediated by the ER-ubiquitin specific peptidase USP19. ***Cell Mol Life Sci***. 2025 Feb 13;82(1):76.

Gheni G, et al. Cerebral hypoperfusion reduces tau accumulation. ***Ann Clin Transl Neurol***. 2025 Jan;12(1):69-85.

Masuda-Suzukake M, et al. Animal models of tau propagation in Alzheimer's disease. ***Neurosci Res.*** 2025 Sep 23;220:104960.

Key papers

Qi C, et al. Tau filaments from amyotrophic lateral sclerosis/parkinsonism-dementia complex adopt the CTE fold. ***Proc Natl Acad Sci U S A***. 2023 Dec 19;120(51):e2306767120.

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Schweighauser M, et al. Age-dependent formation of TMEM106B amyloid filaments in human brains. ***Nature***. 2022 May;605(7909):310-314.

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Hosokawa M, et al. Development of a novel tau propagation mouse model endogenously expressing 3 and 4 repeat tau isoforms. ***Brain***. 2022 Mar 29;145(1):349-361.

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

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

Project Leader
Yukio NISHIMURA

Neural Prosthetics

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

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

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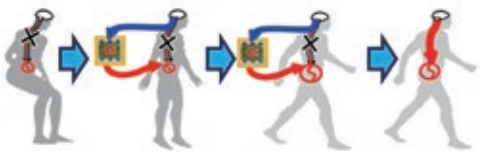
Research Progress in 2025

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.

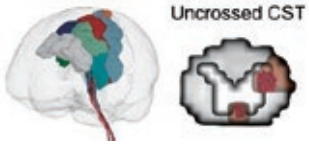
Depression often hinders, while motivation enhances, functional recovery after neuronal damage. Although increased motivation is known to boost motor performance, the neural substrates driving this psychological effect remain elusive. Our research seeks to identify these substrates by uncovering the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



Achievements in 2025

Gait disturbance after spinal cord injury (SCI) arises from loss of supraspinal input to lumbar locomotor centers. We developed a noninvasive, volition-controlled magnetic spinal stimulation paradigm, enabling paraplegic individuals to regain bilateral stepping control. Hand muscle activity triggered lumbar stimulation, producing start–stop, step length, and cadence control. Repeated closed-loop application improved stimulus-induced stepping and, with preserved descending pathways, stimulus-free stepping. This noninvasive approach bypasses spinal lesions, strengthens spared circuits, and shows promise for SCI gait rehabilitation (Brain 2025).

The uncrossed corticospinal tract (CST) has been proposed as a compensatory pathway for motor recovery after stroke. Using fibre tractography and diffusion-weighted magnetic resonance imaging in healthy adults, we found uncrossed CST primarily from the primary motor cortex, with additional contributions from somatosensory, premotor, and supplementary motor areas. Most streamlines descended through the dorsolateral funiculus, clarifying origins of the uncrossed CST relevant for post-stroke rehabilitation (Neurosci Res 2025).



Selected Publications

Papers in 2025

Tazoe T, et al. Non-invasive closed-loop spinal stimulation restores leg stepping control in humans with paraplegia. ***Brain***. 2025 Nov 26:awaf230.

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Nakayama Y, Yokoyama O, Hoshi E, Nishimura Y. Premovement neuronal activity in the primary motor cortex is associated with the initiation of ipsilateral hand movements in monkeys. ***Neurosci Res***. 2025 Apr;213:95-109.

Key papers

Umeda T, Yokoyama O, Suzuki M, Kaneshige M, Isa T, Nishimura Y. Future spinal reflex is embedded in primary motor cortex output. ***Sci Adv***. 2024 Dec 20;10(51):eadq4194.

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Kaneshige M, Obara K, Suzuki M, Tazoe T, Nishimura Y. Tuning of motor outputs produced by spinal stimulation during voluntary control of torque directions in monkeys. ***Elife***. 2022 Dec 13;11:e78346.

Kato K, Sawada M, Nishimura Y. Bypassing stroke-damaged neural pathways via a neural interface induces targeted cortical adaptation. ***Nat Commun***. 2019 Oct 16;10(1):4699.

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 infection-triggereded encephalopathy syndromes 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

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

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Research Progress in 2025

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 2025

We developed and validated a diagnostic prediction score for pediatric anti-NMDA receptor encephalitis using clinical and laboratory data, achieving high sensitivity and specificity. The score enhances early diagnosis accuracy and supports timely treatment for children with suspected autoimmune encephalitis. 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.

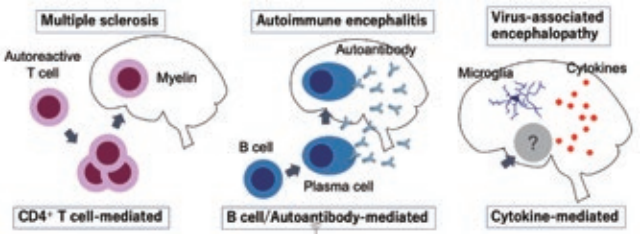

Figure Pathomechanisms of inflammatory and autoimmune neurological diseases
Multiple sclerosis has been regarded as CD4 T-cell mediated disease, in which autoreactive T cells are activated, proliferate, migrate into brain, and cause myelin damage. Autoimmune encephalitis is caused by autoantibodies against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

Selected Publications

Papers in 2025

Matsuda S, et al. Evidence-based diagnostic prediction score for pediatric NMDA receptor encephalitis. ***Eur J Paediatr Neurol***. 2025 Jan;54:50-57.

Nakai R, et al. CSF1R-Dependent Microglial Repopulation and Contact-Dependent Inhibition of Proliferation In Vitro. ***Brain Sci***. 2025 Jul 31;15(8):825.

Sakuma H, et al. International consensus definitions for infection-triggered encephalopathy syndromes. ***Dev Med Child Neurol***. 2025 Feb;67(2):195-207.

Key papers

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Horino A, et al. Intrathecal dexamethasone therapy for febrile infection-related epilepsy syndrome. ***Ann Clin Transl Neurol***. 2021 Mar;8(3):645-655.

Project Leader
Makoto ARAI

Schizophrenia Research

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

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.

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Research Progress in 2025

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 2025

In our recent studies, we identified glucuronic acid (GlcA) as a novel precursor of pentosidine (PEN). PEN is a type of advanced glycation end products (AGEs) known to accumulate in a subset of patients with schizophrenia. However, it remains unclear whether elevated GlcA levels directly contribute to the pathophysiology of schizophrenia, and the potential influence of medication has not been thoroughly examined. In this study, we investigated the relationship between GlcA levels and clinical characteristics in patients with schizophrenia. Specifically, we assessed symptom severity using the PANSS and analyzed its correlation with GlcA concentrations. Additionally, to evaluate the impact of antipsychotic and psychotropic medication dosages on this association, we conducted multiple regression analyses.

Table: Association between GlcA and PANSS scores, adjusted by age and psychotropic dosage.

	Unadjusted model			Adjusted model*		
	Standardized β [95% CI]	P-value†	Adjusted R^2	Standardized β [95% CI]	P-value†	Adjusted R^2
Positive symptom score	2.027 [−7.050, 11.105]	0.653	−0.028	0.691 [−8.439, 9.841]	0.879	0.042
Negative symptom score	13.906 [2.915, 24.956]	0.015*	0.142	13.906 [2.369, 25.443]	0.020*	0.131
General psychopathology score	18.790 [3.810, 33.771]	0.016*	0.140	19.437 [3.884, 34.990]	0.016*	0.146
Total score	34.753 [1.373, 68.134]	0.042*	0.093	34.054 [−0.517, 68.626]	0.053	0.104

- Plasma glucuronic acid (GlcA) levels in patients with schizophrenia were significantly correlated with duration of illness and the negative symptom score, general psychopathology score, and total score on the Positive and Negative Syndrome Scale (PANSS).

- The correlation between GlcA levels and negative symptom scores and total psychopathology scores remained even after adjusting for age and psychotropic medication dose, suggesting a role for GlcA in the pathophysiology of schizophrenia.

Future research will aim to elucidate the molecular mechanisms by which GlcA influences schizophrenia symptoms. Additionally, we seek to explore targeted therapeutic interventions aimed at modulating GlcA levels to mitigate symptom severity and improve patient outcomes.

Selected Publications

Papers in 2025

Tabata K, et al. Schizophrenia with hypozincemia: Clinical features and symptom severity. ***Schizophr Res***. 2025 Oct 17;286:9-15.

Toriumi K, et al. Association between plasma glucuronic acid levels and clinical features in schizophrenia. ***BJPsych Open***. 2025 Mar 31;11(3):e77.

Masada M, et al. Role of pentosidine accumulation in stress-induced social behavioral deficits. ***Neurosci Lett***. 2025 Mar 15;852:138180.

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***. 2025 Jan;79(1):12-20.

Key papers

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

Suzuki K, et al. Role of advanced glycation end products in the longitudinal association between muscular strength and psychotic symptoms among adolescents. ***Schizophrenia (Heidelb)***. 2022 Apr 27;8(1):44.

Miyashita M, et al. Fingertip advanced glycation end products and psychotic symptoms among adolescents. ***NPJ Schizophr***. 2021 Aug 12;7(1):37.

Toriumi K, et al. Vitamin B6 deficiency hyperactivates the noradrenergic system, leading to social deficits and cognitive impairment. ***Transl Psychiatry***. 2021 May 3;11(1):262.

Project Leader
Taku MIYAGAWA

Taku MIYAGAWA has been leading the Sleep Disorders Project since 2025. He conducted genetic studies on narcolepsy susceptibility under the supervision of Professor Katsushi Tokunaga and received his Ph.D. from the Graduate School of Medicine at the University of Tokyo in 2008. Afterward, he served as an Assistant Professor at the University of Tokyo, where he broadened his research to include the human genetics of other hypersomnias. In 2015, he joined the Tokyo Metropolitan Institute of Medical Science as a Research Scientist. His primary research interests include the identification of susceptibility genes for narcolepsy and idiopathic hypersomnia, elucidation of their pathophysiology, and the development of better biomarkers and therapeutic approaches for these conditions.

Sleep Disorders

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

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Research Progress in 2025

Background

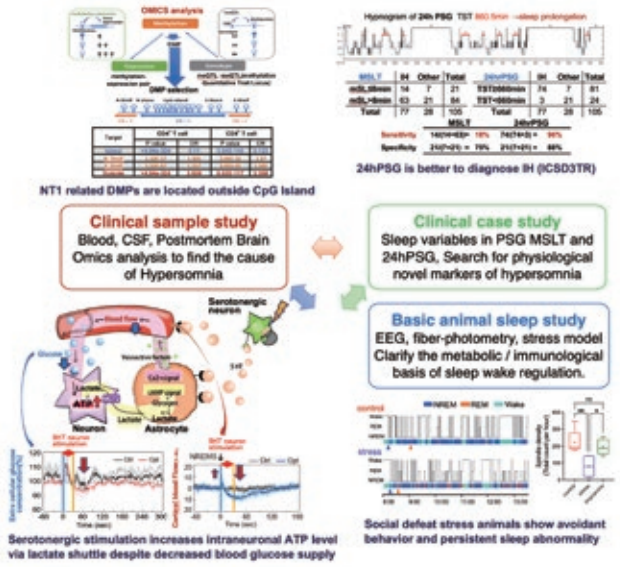
Narcolepsy (NT1) and idiopathic hypersomnia (IH) are believed to result from abnormal regulation of intrinsic sleep-wake brain centers but the pathogenesis remains unclear. Hypersomnia patients show cognitive dysfunction leading to severe impairments in daily and social life, however currently available therapies are symptomatic and inadequate. Understanding the underlying physiological and pathological regulation of sleep-wake cycles in hypersomnia is essential.

Achievements in 2025

We have continued recruiting clinical cases suspected of hypersomnia (more than 1,000 cases) with PSG-MSLT data and DNA samples. Through omics analyses, we identified fatty acid and other metabolic abnormalities in NT1, as well as global hypomethylation in NT1.

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

Animal sleep studies demonstrated that serotonergic stimulation increases intraneuronal ATP levels during wakefulness via two pathways. We also identified persistent sleep dysregulation in animals subjected to social defeat stress.



Selected Publications

Papers in 2025

Shimada M, et al. DNA methylation and multi-omics profiling of T cells uncovers chemotactic pathways and proliferation-linked hypomethylation in narcolepsy type 1. ***Sleep***. 2025 Sep 16:zsaf278.

Key papers

Shimada M, et al. Identification of region-specific gene isoforms in the human brain using long-read transcriptome sequencing. ***Sci Adv***. 2024 Jan 26;10(4):eadj5279.

Natsubori A, et al. Serotonergic regulation of cortical neurovascular coupling and hemodynamics upon awakening from sleep in mice. ***J Cereb Blood Flow Metab***. 2024 Sep;44(9):1591-1607.

Matsuda Y, et al. Physiological paradigm for assessing reward prediction and extinction using cortical direct current potential responses in rats. ***Sci Rep***. 2024 May 7;14(1):10422. doi: 10.1038/s41598-024-59833-7.

Natsubori A, et al. Serotonergic neurons control cortical neuronal intracellular energy dynamics by modulating astrocyte-neuron lactate shuttle. ***iScience***. 2023 Jan 5;26(1):105830.

Miyagawa T, et al. A rare genetic variant in the cleavage site of prepro-orexin is associated with idiopathic hypersomnia. ***NPJ Genom Med***. 2022 Apr 12;7(1):29.

Honda M, et al. Low carnitine palmitoyltransferase 1 activity is a risk factor for narcolepsy type 1 and other hypersomnia. ***Sleep***. 2022 Oct 10;45(10):zsac160.

Honda M, et al. Evaluation of pathological sleepiness by Multiple Sleep Latency Test and 24-hour polysomnography in patients suspected of idiopathic hypersomnia. ***Psychiatry Clin Neurosci***. 2021 Apr;75(4):149-151.

Natsubori A, et al. Intracellular ATP levels in mouse cortical excitatory neurons varies with sleep-wake states. ***Commun Biol***. 2020 Sep 7;3(1):491.

Shimada M, et al. Epigenome-wide association study of narcolepsy-affected lateral hypothalamic brains, and overlapping DNA methylation profiles between narcolepsy and multiple sclerosis. ***Sleep***. 2020 Jan 13;43(1):zsz198.

Shimada M, et al. Metabolome analysis using cerebrospinal fluid from narcolepsy type 1 patients. ***Sleep***. 2020 Nov 12;43(11):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

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

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Research Progress in 2025

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 2025

Postoperative nausea and vomiting (PONV) is a frequent and distressing complication after orthognathic surgery. To investigate genetic susceptibility under standard prophylaxis, researchers analyzed two single-nucleotide polymorphisms (SNPs)—CHRM3 rs2165870 and TACR1 rs3755468—in 121 Japanese patients. All patients received dexamethasone after intubation and ondansetron before the end of surgery. PONV severity was assessed using an 11-point numeric rating scale (NRS) and the need for metoclopramide rescue within 0–2 and 2–24 hours after anesthesia.

CHRM3 rs2165870 AA carriers showed significantly higher NRS scores ($P = 0.0340$) and required more metoclopramide ($P = 0.0248$) than GG or GA carriers, suggesting reduced responsiveness to ondansetron. TACR1 rs3755468 CC carriers also had significantly higher NRS scores ($P = 0.00997$) than CT or TT carriers, despite ondansetron administration.

A two-way ANOVA revealed a significant interaction between time and genotype ($P = 0.0439$). CHRM3 AA carriers showed a time-dependent response to ondansetron ($P = 0.0326$), while TACR1 CC carriers did not ($P > 0.05$). These findings suggest that CHRM3-related nausea is more responsive to ondansetron, which primarily acts outside the blood-brain barrier, whereas TACR1-related nausea may involve central mechanisms less affected by the drug.

This study highlights the qualitative differences in nausea pathways associated with CHRM3 and TACR1 and supports the development of genotype-guided PONV prevention strategies tailored to individual genetic risk profiles, potentially improving postoperative care and patient comfort (Mol Brain, 2025).

Selected Publications

Papers in 2025

Hagihara H, et al. Hyper-maturity and accelerated aging in the hippocampus of mouse models of neuropsychiatric disorders with anxiety-like behavior. ***Neuropsychopharmacology***. 2025 Oct 27.

Vinnakota C, et al. Effects of NMDA receptor antagonists on working memory and gamma oscillations, and the mediating role of the GluN2D subunit. ***Neuropsychopharmacology***. 2025 May 15.

Kang Y, et al. Differential effects of antiemetic serotonin receptor antagonist Ondansetron on nausea associated with CHRM3 rs2165870 and TACR1 rs3755468 single-nucleotide polymorphisms. ***Mol Brain***. 2025 Jul 21;18(1):64.

Hayashi M, et al. rs1051931 Nonsynonymous Polymorphism of Platelet-Activating Factor Acetylhydrolase Gene PLA2G7 Is Associated with Dysesthesia and Pain Severity After Surgery. ***Int J Mol Sci***. 2025 Apr 22;26(9):3931.

Key papers

Ide S, et al. Distinct Roles of Opioid and Dopamine Systems in Lateral Hypothalamic Intracranial Self-Stimulation. ***Int J Neuropsychopharmacol***. 2017 May 1;20(5):403-409.

Kashii H, et al. Tsc2 mutation rather than Tsc1 mutation dominantly causes a social deficit in a mouse model of tuberous sclerosis complex. ***Hum Genomics***. 2023 Feb 2;17(1):4.

Project Leader
Takayuki HARADA

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

Visual Research

HP: https://www.igakuken.or.jp/english/project/detail/retina1.html

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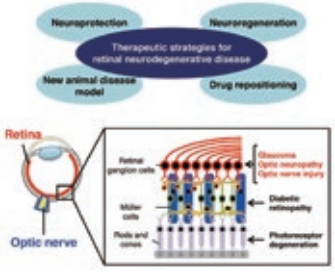
Jun KANDA

Research Progress in 2025

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 2025
Our group has discovered a novel mechanism that promotes neuronal protection and regeneration. We previously found that DOCK3, a protein activated by BDNF/TrkB signaling, is essential for optic nerve regeneration (Namekata et al., PNAS, 2010). In our recent study, we identified HAUS7, a subunit of the augmin complex that promotes microtubule branching, as a novel DOCK3-binding partner (Kiyota et al., 2025). HAUS7 associates with DOCK3 and is transported along axons to the growth cone, where it facilitates microtubule branching necessary for axonal elongation. Suppression of DOCK3 via shRNA markedly impaired HAUS7 transport and reduced axonal growth. Furthermore, BDNF stimulation induced DOCK3 phosphorylation at Y562, promoting HAUS7 dissociation, indicating a dynamic regulation of DOCK3/HAUS7 interaction.
To investigate the in vivo role of HAUS7, we generated Haus7-deficient mice. Electron microscopy revealed a significant reduction in axonal microtubules, and these mice exhibited markedly impaired optic nerve regeneration following injury. Additionally, gene expression analysis in a glaucoma model showed reduced levels of Haus7 and Dock3. Conversely, regenerative gene therapy increased Haus7 expression in retinal ganglion cells.
Taken together, these findings demonstrate that HAUS7, as a DOCK3-binding protein, is essential for axonal regeneration, promoting microtubule stability within axons, and contributing to optic nerve repair. Furthermore, HAUS7 dysfunction may underlie visual impairment in glaucoma, suggesting its potential as a therapeutic target.

Selected Publications

Papers in 2025

Kiyota N, Shinozaki Y, Guo X, Kimura A, Kawamura K, Nishijima E, Honda S, Harada C, Nakazawa T, Namekata K, Harada T. Role of HAUS7 as a DOCK3 binding partner in facilitating axon regeneration. ***Sci Adv***. 2025 Jul 25;11(30):eadq7105.

Noro T, Guo X, Kikuchi R, Sato K, Namekata K, Shinozaki Y, Harada C, Yurimoto T, Hashimoto N, Moriya-Ito K, Nakano T, Sasaki E, Harada T. Age-related decline in retinal function in marmosets. ***Sci Rep***. 2025 Jul 1;15(1):22374.

Noro T, Guo X, Namekata K, Shinozaki Y, Hashimoto N, Moriya-Ito K, Harada C, Nakano T, Harada T. Valproic acid prevents NMDA-induced retinal degeneration in marmosets. ***Neurosci Lett***. 2025 Apr 23;855:138197.

Seki E, Guo X, Namekata K, Komori T, Hayashi H, Arai N, Harada T. ASK1 activation in glial cells in post-mortem multiple sclerosis tissue. ***Neuropathology***. 2025 Feb;45(1):20-29.

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. Vision protection and robust axon regeneration in glaucoma models by membrane-associated Trk receptors. ***Mol Ther***. 2023 Mar 1;31(3):810-824.

Guo X, Kimura A, Namekata K, Harada C, Arai N, Takeda K, Ichijo H, Harada T. ASK1 signaling regulates phase-specific glial interactions during neuroinflammation. ***Proc Natl Acad Sci U S A***. 2022 Feb 8;119(6):e2103812119.

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

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

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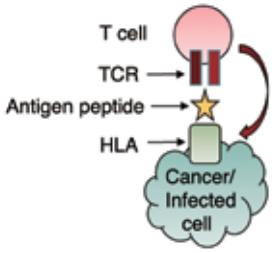
Research Progress in 2025

Background

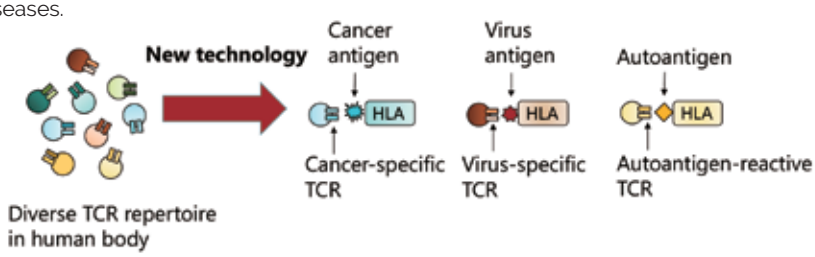
T cells play a critical role in adaptive immunity. They express an enormous repertoire of TCRs on their surfaces. Using these TCRs, T cells recognize antigen-HLA complexes presented by pathogenic cells and eliminate them. Therefore, elucidating the interactions between TCRs and antigen-HLA complexes 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 2025

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.

Selected Publications

Papers in 2025

Aoki K, et al. Isolation of a Monoclonal Human scFv Against Cytomegalovirus pp71 Antigen Using Yeast Display. ***Antibodies (Basel)***. 2025 Jul 10;14(3):57.

Key papers

Tanno H, et al. A facile technology for the high-throughput sequencing of the paired VH:VL and TCRβ:TCRα repertoires. ***Sci Adv***. 2020 Apr 22;6(17):eaay9093.

Tanno H, et al. Determinants governing T cell receptor α/β-chain pairing in repertoire formation of identical twins. ***Proc Natl Acad Sci U S A***. 2020 Jan 7;117(1):532-540.

Project Leader
Yukiteru NAKAYAMA

Yukiteru Nakayama is a cardiovascular immunologist and physician-scientist whose research explores how cardiac stress and heart failure imprint long-lasting changes on the hematopoietic and immune systems. He graduated from the Faculty of Medicine at the University of Tokyo in 2004 and obtained his Ph.D. from the Graduate School of Medicine, the University of Tokyo, in 2013. Following more than a decade of clinical practice as a cardiologist at the University of Tokyo Hospital, he kicked off the Stress-imprinted immunity Project at the Tokyo Metropolitan Institute of Medical Science in October 2025. His research centers on stress-imprinted immunity—how sympathetic neural remodeling and altered bone marrow niches influence hematopoietic stem cells and drive chronic inflammation in heart failure.

Stress-imprinted Immunity

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

Research Progress in 2025

Background

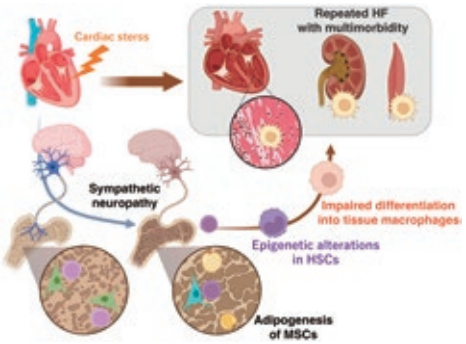
The prevalence of heart failure (HF) is rapidly increasing worldwide due in part to the graying of society. Despite significant medical advances in recent decades, HF mortality rates remain high. Chronic inflammation has emerged as a key contributor to the development of cardiovascular diseases, including HF. However, results of more recent clinical trials evaluating drugs targeting inflammation and cytokines have been mixed and conflicting. This highlights the complex regulatory mechanisms underlying inflammation in HF.

We recently reported that hematopoietic stem cells (HSCs) in bone marrow can carry an innate immune memory of cardiac stress that exacerbates HF and predisposes other organs to pathology. HF causes epigenetic alterations in HSCs, which not only shifts their differentiation trajectory toward myeloid cells but also affects differentiation of monocytes to macrophages. The progeny monocytes from HF-experienced HSCs more frequently give rise to proinflammatory macrophages than to mature cardiac tissue resident macrophages.

As tissue resident macrophages are essential for the maintenance of cardiac homeostasis and proper adaptive responses to cardiac stress, perturbations to cardiac macrophage homeostasis by HF-experienced HSC-derived cells likely induce cardiac dysfunction and remodeling. Similarly, systemic changes to tissue-resident and monocyte-derived macrophages recruited upon insult likely contribute to the increased vulnerability of the kidneys and skeletal muscles by biasing stress responses toward inflammation and remodeling.

Achievements in 2025

We have focused our research on the concept of central innate immune memory induced by cardiac stress. Our work revealed that changes in the hematopoietic niche—such as altered phenotypes of bone marrow mesenchymal stromal cells and reduced sympathetic nervous activity—serve as key triggers of this immune memory. Building on these findings, We are now extending his research to elucidate how autonomic neural remodeling during heart failure orchestrates multi-organ immune dysregulation.



Selected Publications

Papers in 2025

Sugita J, et al. Cardiopulmonary neuro-immune reflex: From afferent stress signaling to peripheral myeloid memory. ***J Cardiol***. 2025 Aug 29:S0914-5087(25)00217-5.

Hasumi E, et al. Heart failure monitoring with a single lead electrocardiogram at home. ***Int J Cardiol***. 2025 Aug 1;432:133203.

Nakayama Y, Fujiu K. Innate immune memory in macrophage differentiation and cardiovascular diseases. ***Inflamm Regen***. 2025 Jun 3;45(1):17.

Awaji K, et al. Impact of Fli1 deletion on B cell populations: A focus on age-associated B cells and transcriptional dynamics. ***J Dermatol Sci***. 2025 Feb;117(2):19-29.

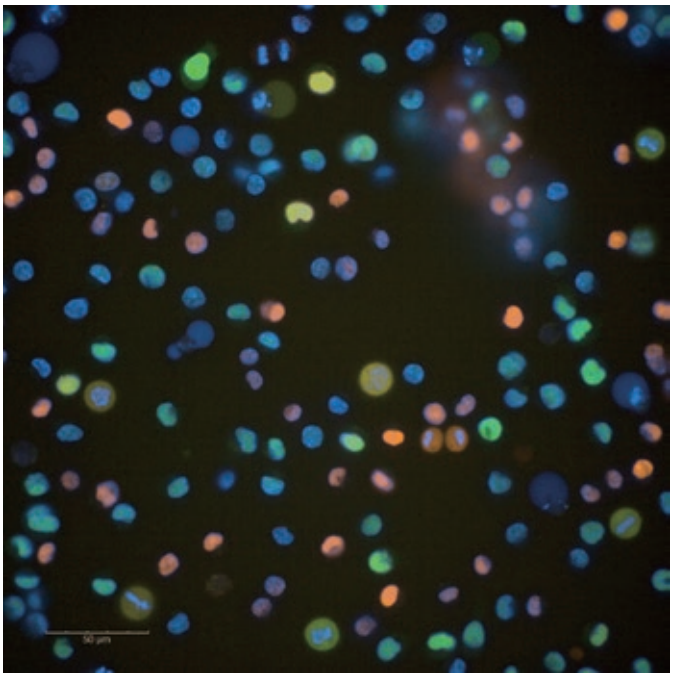
Key papers

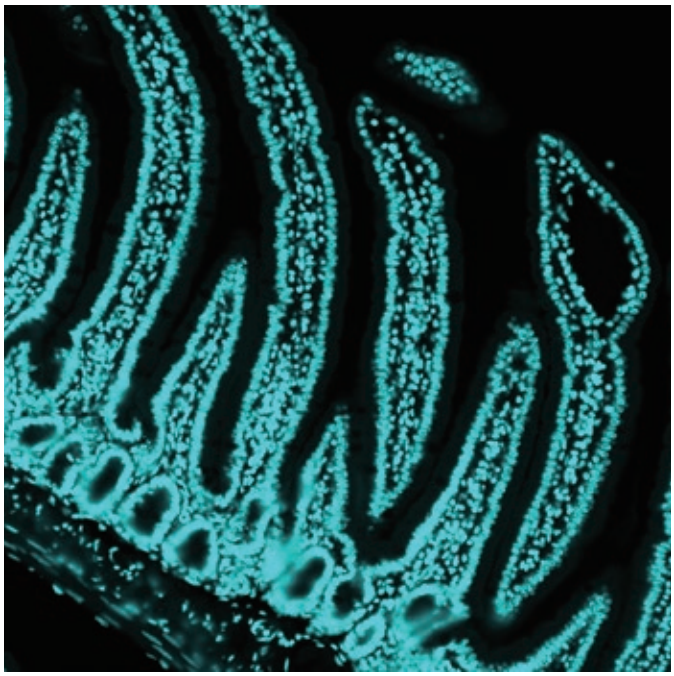
Nakayama Y, et al. Heart failure promotes multimorbidity through innate immune memory. ***Sci Immunol***. 2024 May 24;9(95):eade3814.

Sugita J, et al. Cardiac macrophages prevent sudden death during heart stress. ***Nat Commun***. 2021 Mar 26;12(1):1910.

Nakayama Y, et al. A long noncoding RNA regulates inflammation resolution by mouse macrophages through fatty acid oxidation activation. ***Proc Natl Acad Sci U S A***. 2020 Jun 23;117(25):14365-14375.

Visualization of Cell Cycle Progression with Fluorescent Probes in human B cells. Red, green and yellow cells represent those in G1, S and G2/M phases of cell cycle, respectively.
Provided by Dr. Kenji KITAJIMA
(Genome Dynamics Project)





Nuclear Staining of the Mouse Small Intestine.
Provided by Mr. Leo NOVOKRESHCHENOV
(Genome Dynamics Project)

Basic Medical Sciences

Project Leader
Hiroyuki SASANUMA

Genome Dynamics

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.

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Research Progress in 2025

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 2025

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 tumorigenesis caused by genome instability

Selected Publications

Papers in 2025

Biller M, et al. REV7 associates with ATRIP and inhibits ATR kinase activity. ***Nucleic Acids Res***. 2026 Jan 14;54(2):gkaf1527.

Hirai H, et al. TORC2 inactivation promotes heterochromatin formation in rDNA and prolongs viability of quiescent fission yeast cells. ***Commun Biol***. 2025 Nov 19;8(1):1606.

Çelik Ç, et al. Water-soluble cationic porphyrins with enhanced phototoxicity to cancer cell lines for G4-targeting photodynamic therapy. ***RSC Med Chem***. 2025 Oct 1;17(1):225-235.

Tanaya Y, et al. Evaluation of the effects of G4 ligands on the interaction between G-quadruplexes and their binding proteins. ***Chem Commun*** (Camb). 2025 Jul 31;61(63):11790-11793.

Tanegashima K, et al. CXCL14 is an essential modulator of TLR9 agonist-induced antitumor immune responses. ***J Immunol***. 2025 Aug 1;214(8):2076-2086.

Saito R, et al. Expression cloning of cell surface receptors for the CpG oligodeoxynucleotide/CXCL14 complex. ***Biochem Biophys Res Commun***. 2025 Jul 1;768:151954.

Kim S, et al. Marcet-Ortega M, Xu J, Eng DY, Feeney L, Petrini JHJ, Keeney S. Mouse MRE11-RAD50-NBS1 is needed to start and extend meiotic DNA end resection. ***Nat Commun***. 2025 Apr 16;16(1):3613.

Yone H, et al. Light-controlled Spo11-less meiotic DNA breaks by MagTAQing lead to chromosomal aberrations. ***Nucleic Acids Res***. 2025 Apr 10;53(7):gkaf206.

Fracassi A, et al. Natural and Synthetic LDL-Based Imaging Probes for the Detection of Atherosclerotic Plaques. ***ACS Pharmacol Transl Sci***. 2025 Feb 4;8(2):578-591.

Key papers

Zheng Z, et al. Reconstitution of SPO11-dependent double-strand break formation. ***Nature***. 2025 Mar;639(8055):784-791.

Ogawa A, et al. SLFN11-mediated ribosome biogenesis impairment induces TP53-independent apoptosis. ***Mol Cell***. 2025 Mar 6;85(5):894-912.e10.

Iguchi T, et al. Loss of a single Zn finger, but not that of two Zn fingers, of GATA3 drives skin inflammation. ***Genes Cells***. 2024 Dec;29(12):1173-1189.

Charlton SJ, et al. The fork protection complex promotes parental histone recycling and epigenetic memory. ***Cell***. 2024 Sep 5;187(18):5029-5047.e21.

Yamazaki K, et al. Homologous recombination contributes to the repair of acetaldehyde-induced DNA damage. ***Cell Cycle***. 2024 Feb;23(4):369-384.

Shibata T, et al. Homology recognition without double-stranded DNA-strand separation in D-loop formation by RecA. ***Nucleic Acids Res***. 2024 Mar 21;52(5):2565-2577.

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

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

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

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Hiroko BEPPU

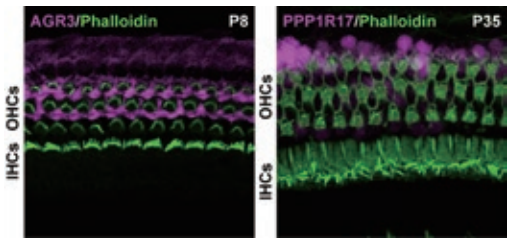
Research Progress in 2025

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. One of our research targets is the development and aging of outer hair cells (OHCs) in the cochlea. This is because many aspects remain unclear regarding the morphogenesis of the V-shaped structure of OHC stereocilia and the mechanisms of OHC death associated with aging, and these processes are deeply implicated in the onset of hearing loss.

Achievements in 2025

There are two types of hair cells in the mammalian cochlea: inner hair cells (IHCs) and outer hair cells (OHCs). OHCs are responsible for sound amplification, and their degeneration leads to hearing loss (e.g., *Hear Res*, 2020; *Biomedicines*, 2022). To investigate the molecular consequences of OHC loss and to identify genes specifically expressed in OHCs, we previously established an OHC-specific toxin receptor–mediated conditional cell ablation (TRECK) system using transgenic mice that express the human diphtheria toxin receptor under the control of the prestin promoter (*Sci Rep*, 2019). In this study, we performed bulk RNA sequencing followed by differential expression analysis using cochleae from neonatal (postnatal day 1) and mature (postnatal day 28) mice before and after OHC-TRECK treatment. As expected, the expression of many OHC-specific genes was markedly reduced after OHC ablation; however, the functions of several OHC-enriched genes remained unknown. Among these, anterior gradient 3 (AGR3) and protein phosphatase 1 regulatory subunit 17 (Ppp1r17) were expressed in Deiters' cells, the supporting cells adjacent to OHCs. Immunohistochemical analysis revealed that AGR3 was localized in the cytoplasm, while PPP1R17 was detected in both the cytoplasm and nucleus of Deiters' cells, with expression increasing during OHC maturation. Both AGR3 and PPP1R17 proteins were diminished following OHC ablation, suggesting that OHC loss affects gene expression in neighboring supporting cells. However, *Ppp1r17* knockout mice showed no detectable auditory or morphological abnormalities, and the physiological function of PPP1R17 in the cochlea remains to be elucidated.



Localization of the AGR3 and PPP1R17 in the Deiters' cells. Stereocilia in the inner hair cells (IHCs) and outer hair cells (OHCs) are visualized using phalloidin staining.

Selected Publications

Papers in 2025

Cao L, et al. *Cdkl5* Knockout Mice Recapitulate Sleep Phenotypes of CDKL5 Deficient Disorder. ***Int J Mol Sci***. 2025 Apr 16;26(8):3754.

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***. 2025 Apr 20;74(2):251-263.

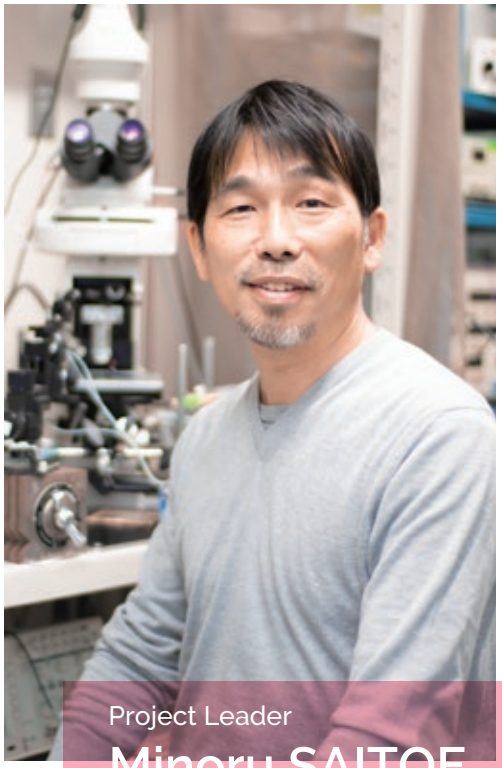
Mutai H, et al. Genetic landscape in undiagnosed patients with syndromic hearing loss revealed by whole exome sequencing and phenotype similarity search. ***Hum Genet***. 2025 Jan;144(1):93-112.

Key papers

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

Yasuda SP, et al. Two Loci Contribute to Age-Related Hearing Loss Resistance in the Japanese Wild-Derived Inbred MSM/Ms Mice. ***Biomedicines***. 2022 Sep 7;10(9):2221.

Matsuoka K, et al. OHC-TRECK: A Novel System Using a Mouse Model for Investigation of the Molecular Mechanisms Associated with Outer Hair Cell Death in the Inner Ear. ***Sci Rep***. 2019 Mar 27;9(1):5285.



Project Leader
Minoru SAITOE

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

Higher Brain Function

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

Staff

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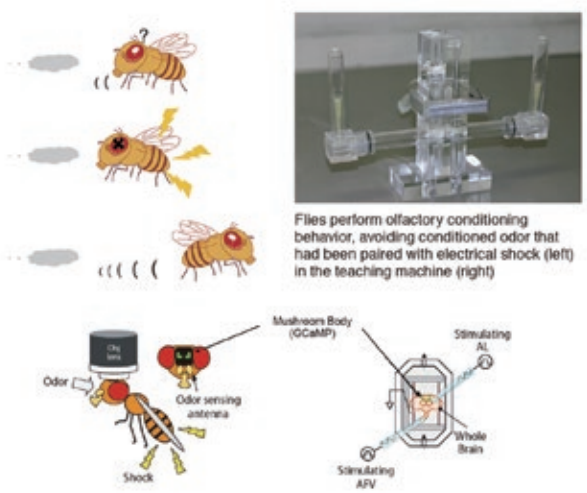
Research Progress in 2025

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 2025

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



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

Selected Publications

Key papers

Miyashita T, et al. Glia transmit negative valence information during aversive learning in Drosophila. ***Science***. 2023 Dec 22;382(6677):eadf7429.

Ueno K, et al. Carbon Monoxide, a Retrograde Messenger Generated in Postsynaptic Mushroom Body Neurons, Evokes Noncanonical Dopamine Release. ***J Neurosci***. 2020 Apr 29;40(18):3533-3548.

Ueno K, et al. Coincident postsynaptic activity gates presynaptic dopamine release to induce plasticity in Drosophila mushroom bodies. ***Elife***. 2017 Jan 24;6:e21076.

Hirano Y, et al. Shifting transcriptional machinery is required for long-term memory maintenance and modification in Drosophila mushroom bodies. ***Nat Commun***. 2016 Nov 14;7:13471.

Matsuno M, et al. Long-term memory formation in Drosophila requires training-dependent glial transcription. ***J Neurosci***. 2015 Apr 8;35(14):5557-65.

Yamazaki D, et al. Glial dysfunction causes age-related memory impairment in Drosophila. ***Neuron***. 2014 Nov 19;84(4):753-63.

Hirano Y, et al. Fasting launches CRTC to facilitate long-term memory formation in Drosophila. ***Science***. 2013 Jan 25;339(6118):443-6.

Miyashita T, et al. Mg(2+) block of Drosophila NMDA receptors is required for long-term memory formation and CREB-dependent gene expression. ***Neuron***. 2012 Jun 7;74(5):887-98.

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

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

Staff

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Senri DOI

Research Progress in 2025

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 2025

We previously demonstrated that subplate neurons (SpNs) regulate the migration pattern of developing cortical neurons, converting it from a multipolar to a bipolar mode (Science, 2018). In 2025, we applied Visium spatial transcriptomics to identify region-specific molecular markers in the developing cerebrum (Fig.1). This analysis revealed embryonic markers distinct from those found in the adult brain, underscoring the utility of spatial transcriptomics for investigating regional differentiation during brain development (Sci.Rep., 2025).

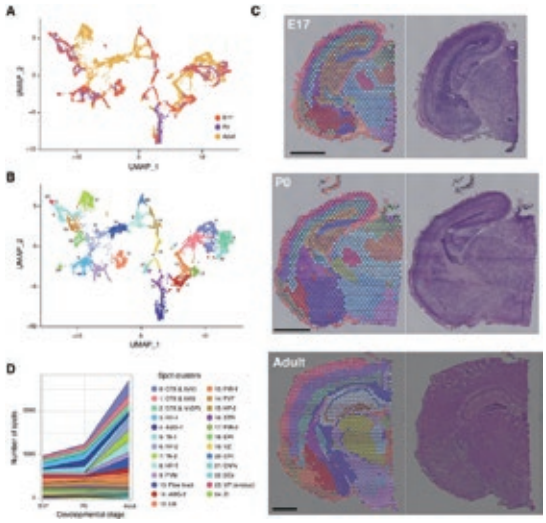

Fig.1 Spatial transcriptomic landscape during mouse brain development

Selected Publications

Papers in 2025

Tsurugizawa T, et al. A Cross-Species Brain Magnetic Resonance Imaging and Histology Database of Vertebrates. ***Sci Data***. 2025 Jul 12;12(1):1206.

Hara Y, et al. The spatial transcriptome of the late-stage embryonic and postnatal mouse brain reveals spatiotemporal molecular markers. ***Sci Rep***. 2025 Apr 10;15(1):12299.

Key papers

Kaneko N, et al. ADAMTS2 promotes radial migration by activating TGF-β signaling in the developing neocortex. ***EMBO Rep***. 2024 Jul;25(7):3090-3115.

Katayama R, et al. Thalamic activity-dependent specification of sensory input neurons in the developing chick entopallium. ***J Comp Neurol***. 2024 Jun;532(6):e25627.

Kumamoto T, Ohtaka-Maruyama C. Visualizing Cortical Development and Evolution: A Toolkit Update. ***Front Neurosci***. 2022 Apr 12;16:876406.

Ohtaka-Maruyama C. Subplate Neurons as an Organizer of Mammalian Neocortical Development. ***Front Neuroanat***. 2020 Mar 19;14:8.

Kamimura K, et al. The HSPG Glypican Regulates Experience-Dependent Synaptic and Behavioral Plasticity by Modulating the Non-Canonical BMP Pathway. ***Cell Rep***. 2019 Sep 17;28(12):3144-3156.e4.

Ohtaka-Maruyama C, et al. Synaptic transmission from subplate neurons controls radial migration of neocortical neurons. ***Science***. 2018 Apr 20;360(6386):313-317.

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 research focus is to engineer human induced pluripotent stem (iPS) cells to cure genetic disorders by disease modeling, cell transplantation therapy, and direct genetic manipulation in patients' cells. He aims to improve the accuracy and predictability of genome editing for these therapeutic applications. He is also interested in the application of polyploid iPS cells generated by cell fusion.

Regenerative Medicine

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

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Moe SATO

Research Progress in 2025

Background

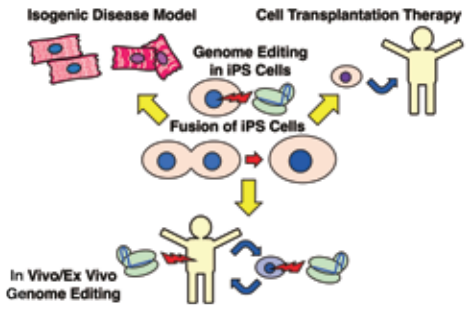
Genome editing allows us to rewrite the genetic information in any species and cell type, including human cells. In addition, cell fusion can produce polyploid cells. We focus on human iPS cells, a type of pluripotent stem cell that can be generated from patients' cells by the introduction of specific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

Achievements in 2025

Genome editing activates two 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). However, quantification of HDR and NHEJ induced in individual cells has been challenging, especially in human iPS 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, and found that identical genetic modifications, including insertions and deletions with different lengths, tend to be bi-allelically induced in single human iPS cells (Stem Cell Res Ther 2025).

Furthermore, we established tetraploid human iPS cells (4N-iPS cells) by cell fusion and differentiated them into cardiomyocytes. These 4N-iPS cell-derived cardiomyoctes exhibited more matured phenoyptes compared to the conventional diploid iPS cell-derived cardiomyocytes such as increased mitochondria, less mitotic gene expression, stronger and faster contraction, and enhanced drug resistance (bioRxiv 2025.06.23.661005). Our results demonstrate that cell fusion is a valuable approach to engineer iPS cells.



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. 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. Cell fusion can produce polyploid iPS cells, which can be used to model organs and tissues that are naturally polyploid in the human body.

Selected Publications

Papers in 2025

Takahashi G, et al. High-throughput robotic isolation of human iPS cell clones reveals frequent homozygous induction of identical genetic manipulations by CRISPR-Cas9. ***Stem Cell Res Ther***. 2025 Jun 7;16(1):295.

Key papers

Kato-Inui T, et al. Fusion of histone variants to Cas9 suppresses non-homologous end joining. ***PLoS One***. 2024 May 13;19(5):e0288578.

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

Takahashi G, et al. Genome editing is induced in a binary manner in single human cells. ***iScience***. 2022 Nov 17;25(12):105619.

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

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

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Haruka YASUMOTO
Utaro NAKAMURA
Takashi SHIMOMURA
Takeru SATO
Saya GOTO
Kana ENDO
Yuria OZEKI

Research Progress in 2025

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.

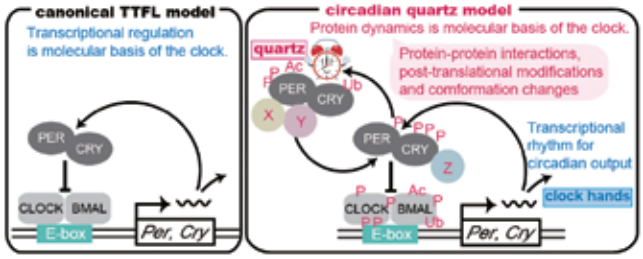
Achievements in 2025

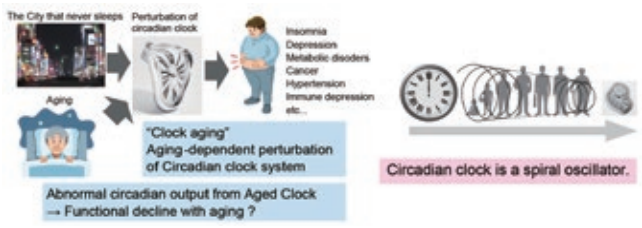
<objective 1. circadian quartz>

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.





Selected Publications

Papers in 2025

Okazaki T, et al. Membrane topology inversion of GGCX mediates cytoplasmic carboxylation for antiviral defense. ***Science***. 2025 Jul 3;389(6755):84-91.

Otobe Y, Yoshitane H. Phosphorylation of CLOCK and BMAL1-a key regulatory mechanism in the mammalian circadian clockwork. ***FEBS Lett***. 2025 Oct 18.

Key papers

Otobe Y, et al. Phosphorylation of DNA-binding domains of CLOCK-BMAL1 complex for PER-dependent inhibition in circadian clock of mammalian cells. ***Proc Natl Acad Sci U S A***. 2024 Jun 4;121(23):e2316858121.

Abe YO, et al. Rhythmic transcription of Bmal1 stabilizes the circadian timekeeping system in mammals. ***Nat Commun***. 2022 Aug 23;13(1):4652.

Masuda S, et al. Mutation of a PER2 phosphodegron perturbs the circadian phosphoswitch. ***Proc Natl Acad Sci U S A***. 2020 May 19;117(20):10888-10896.

Imamura K, et al. ASK family kinases mediate cellular stress and redox signaling to circadian clock. ***Proc Natl Acad Sci U S A***. 2018 Apr 3;115(14):3646-3651.

Terajima H, et al. ADARB1 catalyzes circadian A-to-I editing and regulates RNA rhythm. ***Nat Genet***. 2017 Jan;49(1):146-151.

Project Leader

Koji YAMANO

Koji Yamano received his Ph.D. in Science from Nagoya University in 2009. Following his doctoral studies, he undertook a research fellowship at the National Institutes of Health (NIH) in the United States, where his work focused on the mitochondrial quality control system implicated in Parkinson's disease.
Returning to Japan in 2014, Dr. Yamano joined the Tokyo Metropolitan Institute of Medical Science. Since then, he has continued his pioneering research into mitochondrial quality control mechanisms while expanding his interests including the molecular mechanisms of autophagy and intracellular vesicular trafficking. This has led him to the cutting edge of science, identifying novel factors and exploring their connections to human disease.
After serving as an associate professor at Tokyo Medical and Dental University (now Institute of Science Tokyo) from 2022 to 2024, Dr. Yamano returned to TMIMS. In April 2025, he launched the Quality Control Project as a project leader. In this capacity, he is now driving forward research into the relationship between intracellular quality control systems and human health.

Intracellular Quality Control

HP: https://www.igakuken.or.jp/iq_control/e-index.html

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Haruhiro SANO

Research Progress in 2025

Background

Our cells contain distinct structures with specialized functions, known as organelles. Like any complex system, organelles are susceptible to damage from stress and aging. Therefore, maintaining them in optimal condition is essential for preserving cellular homeostasis.

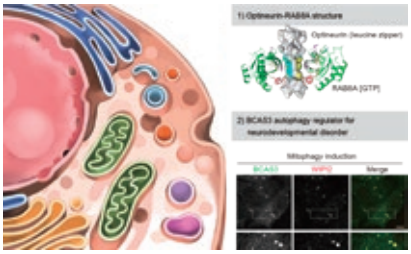
Much like a manufacturing plant relies on quality control to inspect defective products and replace old machinery, cells possess their own sophisticated mechanisms for continuous organelle surveillance. This system works to repair or dismantle and recycle damaged or weakened organelles. Collectively, this critical process is termed Intracellular Quality Control (IQC).

Our project is dedicated to elucidating the mechanisms by which our cells maintain a healthy state. Specifically, we are identifying novel stress response pathways that challenge cellular function, along with the key proteins involved in these processes, to better understand how IQC safeguards cellular health.

Achievements in 2025

1) We identified RAB8A, a small RAB GTPase that controls vesicular trafficking, as an interacting factor with optineurin (OPTN), a known autophagy adaptor. We determined the crystal structure of the OPTN–RAB8A complex at 1.83 Å resolution and elucidated the specific interaction mechanism between these proteins. This work revealed the functional role of OPTN in regulating both vesicular trafficking and selective autophagy (Okatsu et al. 2025 Genes Cells).

2) Our previously identified autophagy regulator, the BCAS3-PHAF1 complex, was recently reported to be the causative factor for the neurodevelopmental disorder HEMARS. Investigating the link between autophagy and this neurological disorder, we found that disease-associated BCAS3 mutations impeded the interactions with PHAF1, which impaired autophagy activity. Moreover, the loss of BCAS3 and PHAF1 in Drosophila melanogaster leads to the accumulation of autophagic cargo in vivo, impaired tissue remodeling, and a shortened lifespan. Our findings, therefore, provide new insights into the pathogenesis of HEMARS by highlighting, at both the molecular and organismal levels, the critical roles of BCAS3 and PHAF1 in autophagy regulation (Kojima et al. 2025 submitted).



Selected Publications

Papers in 2025

Okatsu K, et al. Functional and Structural Insights Into Complex Formation Between OPTN Leucine Zipper Domain and RAB8A. ***Genes Cells***. 2025 Sep;30(5):e70043.

Endo A, et al. Ubiquitination-activated TAB-TAK1-IKK-NF-B axis modulates gene expression for cell survival in the lysosomal damage response. ***Elife***. 2025 Sep 24;14:RP106901.

Watanabe A, et al. The reaction mechanism for glycolysis side product degradation by Parkinson's disease-linked DJ-1. ***J Cell Biol***. 2025 Aug 4;224(8):e202411078.

Key papers

Hsu MC, et al. Mitochondrial YME1L1 governs unoccupied protein translocase channels. ***Nat Cell Biol***. 2025 Feb;27(2):309-321.

Endo R, et al. TBK1 adaptor AZI2/NAP1 regulates NDP52-driven mitochondrial autophagy. ***J Biol Chem***. 2024 Oct;300(10):107775.

Yamano K, et al. Optineurin provides a mitophagy contact site for TBK1 activation. ***EMBO J***. 2024 Mar;43(5):754-779.

Hayashida R, et al. Elucidation of ubiquitin-conjugating enzymes that interact with RBR-type ubiquitin ligases using a liquid-liquid phase separation-based method. ***J Biol Chem***. 2023 Feb;299(2):102822.

Kojima W, et al. Mammalian BCAS3 and C16orf70 associate with the phagophore assemb ly site in response to selective and non-selective autophagy. ***Autophagy***. 2021 Aug;17(8):2011-2036.

Yamano K, et al. Critical role of mitochondrial ubiquitination and the OPTN-ATG9A axis in mitophagy. ***J Cell Biol***. 2020 Sep 7;219(9):e201912144.

Laboratory Head
Yukiko YOSHIDA

Laboratory of Protein Metabolism

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

Research Assistants
Naoko Ishibashi
Meari OKADA
Chikage TAKAHASHI

Research Progress in 2025

Background

Protein recycling is essential for our health. All proteins in our bodies have distinct lifespans after which they are recycled. Old and defective proteins recognized by the ubiquitin system are tagged with K48-linked ubiquitin chains and degraded by the proteasome. In contrast, K63-linked ubiquitin chains trigger distinct outcomes such as signal transduction and membrane trafficking.

Defects in the ubiquitin system have been implicated in the pathogenesis of various diseases including cancers, neurodegenerative diseases, and genetic disorders. Our laboratory studies mechanisms of ubiquitin signaling and proteasomal degradation to understand cellular proteostasis and the pathogenesis of these diseases.

Achievements in 2025

We previously identified ubiquitin-mediated endosomal stress of early endosomes and its responsive signaling pathways (JCB, 2024). In the endosomal stress response, the TAB–TAK1 pathway is activated by K63-linked ubiquitin chains that accumulate on defected endosomes. This induces expression of NF-B target genes for inflammation. The finding prompted further exploration into the potential role of the identical signaling pathways in the distinct organelle stress response. We have found that the TAB–TAK1–IKK–NF-B axis is activated by K63-linked ubiquitin chains in damaged lysosomes (Figure). This leads to the expression of various transcription factors and cytokines that promote anti-apoptosis and intercellular signaling. The results suggest that the ubiquitin system plays multiple roles in the removal of damaged lysosomes by lysophagy and in activating cellular signaling for cell survival (eLife, 2025). It has been reported that NF-B undergoes LUBAC-mediated activation through stressed mitochondria and Golgi. In the organelle stress response, the K63Ub–TAB–TAK1–IKK–NF-B axis, in cooperation with LUBAC-mediated M1 ubiquitination, may serve as a universal signaling pathway for target gene expression and subsequent cellular functions that maintain homeostasis.

Selected Publications

Papers in 2025

Endo A, et al. Ubiquitination-activated TAB-TAK1-IKK-NF-B axis modulates gene expression for cell survival in the lysosomal damage response. ***Elife***. 2025 Sep 24;14:RP106901.

Morita M, et al. Combinatorial ubiquitin code degrades deubiquitylation-protected substrates. ***Nat Commun***. 2025 Mar 24;16(1):2496.

Key papers

Yoshida Y, et al. Sugar-mediated non-canonical ubiquitination impairs Nrf1/NFE2L1 activation. ***Mol Cell***. 2024 Aug 22;84(16):3115-3127.e11.

Endo A, et al. USP8 prevents aberrant NF-B and Nrf2 activation by counteracting ubiquitin signals from endosomes. ***J Cell Biol***. 2024 Mar 4;223(3):e202306013.

Yoshida Y, et al. Loss of peptide:N-glycanase causes proteasome dysfunction mediated by a sugar-recognizing ubiquitin ligase. ***Proc Natl Acad Sci U S A***. 2021 Jul 6;118(27):e2102902118.

Head researcher,
independent research group

Shinobu HIRAI

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.

Frontier Research Laboratory

Brain Metabolism Group

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

Staff

Shinobu HIRAI
Shoko TAMURA
Hiroko SHIMBO
Mai KAWAGUCHI
Ririko YAMAMOTO
Yumiko OJIMA
Kyoko OFUSA
Yayoi ONODERA
Kayoko HIROKADO
Sena UCHIDA
Nobuyuki ARUGA

Research Progress in 2025

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 developing adeno-associated virus (AAV)–based gene therapies for conditions such as GLUT1 deficiency syndrome, with the ultimate goal of clinical translation. 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 2025

Adeno-associated virus (AAV) vectors are among the most promising platforms for gene therapy and are already in clinical use for several neurological disorders. However, most existing AAV capsids preferentially target neurons, and efficient delivery to other brain cell types remains a challenge. This is problematic because astrocytes, the most abundant glial cells, are essential for metabolic homeostasis, synaptic regulation, and blood–brain barrier support. Their dysfunction contributes to diverse neurological and psychiatric diseases, yet conventional AAVs cannot target them with sufficient efficiency or specificity.

To address this, we engineered AAV-AST (Astrocyte-Tropic), a novel AAV9-derived capsid with a rationally designed seven–amino acid insertion that enhances blood–brain barrier penetration and astrocyte transduction. Across mice, non-human primates, and a human in vitro blood–brain barrier model, AAV-AST consistently showed markedly higher astrocytic transduction than AAV9.

This innovation enables direct manipulation of astrocytes in vivo, opening new avenues for disease modeling and therapy. By moving beyond neuron-centric strategies, astrocyte-targeted delivery may correct metabolic and homeostatic dysfunctions underlying epilepsy, neurodegeneration, and psychiatric disorders. A patent application for AAV-AST has been filed, and preclinical studies are underway toward clinical translation.

Selected Publications

Key papers

Tanaka T, et al. Minocycline prevents early age-related cognitive decline in a mouse model of intellectual disability caused by ZBTB18/RP58 haploinsufficiency. ***J Neuroinflammation.*** 2024 Oct 12;21(1):260.

Park J, et al. Impact of feeding age on cognitive impairment in mice with Disrupted-In-Schizophrenia 1 (Disc1) mutation under a high sucrose diet. ***Behav Brain Res***. 2025 Jan 5;476:115291.

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

Hirai S, et al. High-sucrose diets contribute to brain angiopathy with impaired glucose uptake and psychosis-related higher brain dysfunctions in mice. ***Sci Adv***. 2021 Nov 12;7(46):eabl6077.

Head researcher,
independent research group

Teruhiko SUZUKI

Dr. Teruhiko Suzuki received his Ph.D. in 2006 from Graduate School of Pharmaceutical Sciences, University of Tokyo. After a five-year postdoctoral fellowship at NIH, he became a researcher at Tottori University, and in 2012, he was appointed to our institute. In 2025, he established Immunomedicine group as an independent researcher. His group is now working on establishing gene-humanized model animals to contribute to the development of novel immunomedicines.

Frontier Research Laboratory
Immunomedicine Group

HP: https://www.igakuken.or.jp/frontier02/

Staff

Research Assistants
Mana YAMAKAWA
Saki AN
Fuyuko YOSHIDA
Yayoi WAKITA

Research Progress in 2025

Background

Our group is developing novel genome engineering technologies by applying chromosome engineering and genome editing techniques. Utilizing these novel technologies, we are actively tackling research challenges that were previously difficult to address with existing methods.

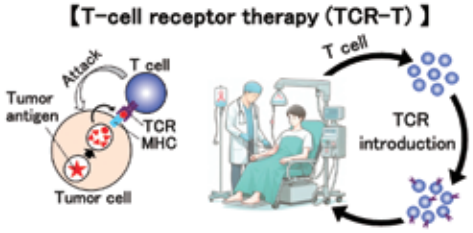
Human/mouse artificial chromosomes (HAC/MACs), which are chromosome-type gene delivery vectors, allow for the introduction of large sequences or multiple gene expression cassettes into target animal cells, as they have no limitation on the size of the DNA sequence that can be carried. Although HAC/MACs are considered highly useful tools because they are stably maintained as independent chromosomes within animal cells, the major challenge has been how to efficiently load multiple genes onto HAC/MACs. To overcome this problem, we have successfully developed a method for simultaneous integration of multiple genes into HAC/MACs using recombinase (SIM method) and significantly improved the utility of HAC/MACs.

We also recently developed all-in-one conditional knockout (cKO) system, which enables one-step cKO and simultaneous epitope tagging and reporter gene knock-in in mouse embryonic stem cells. This system enables detailed functional analysis of various genes, including those essential for cell survival.

Achievements in 2025

Utilizing our all-in-one cKO system, we successfully demonstrated the generation of RNA helicase DDX1 cKO cells even in U2OS cells that possess four genomic loci of DDX1 due to polyploidy. Efficient generation of cKO cell lines with our system in common cancer cell lines should greatly contribute to the analysis of gene functions.

Our group is now dedicated to creating model animals that recapitulate human-type antigen presentation, which were previously considered challenging to generate, by employing genome engineering technologies. If such model animals recapitulating human-type antigen presentation can be successfully generated, they are expected to become an extremely useful drug discovery platform for the research and development of immunotherapies, including TCR-T therapy that leverages cancer antigen-specific T cell receptors.



Selected Publications

Papers in 2025

Kishima N, Moriwaki T, Uno N, Suzuki T, Abe S, Sugawara M, Nagashima Y, Kazuki K, Endo T, Yamazaki K, Nakagawa W, Yuno R, Moriguchi Y, Matsukura S, Tomizuka K, Kazuki Y. Generation of transchromosomic mice harboring HLA-A/B/C and human B2M via mouse artificial chromosome and triple BAC integration. ***Sci Rep***. 2025 Jul 30;15(1):27852.

Tanegashima K, Esashi E, Ishida K, Kotaki A, Iwase R, Hasebe M, Takahashi R, Saito R, Kazuki Y, Suzuki T, Hara T. CXCL14 is an essential modulator of TLR9 agonist-induced antitumor immune responses. ***J Immunol***. 2025 Aug 1;214(8):2076-2086.

Suzuki T, Takagi S, Funada J, Egawa Y, Yamakawa M, Hara T. DDX1 is required for non-spliceosomal splicing of tRNAs but not of XBP1 mRNA. ***Commun Biol***. 2025 Jan 20;8(1):92.

Egawa M, Uno N, Komazaki R, Ohkame Y, Yamazaki K, Yoshimatsu C, Ishizu Y, Okano Y, Miyamoto H, Osaki M, Suzuki T, Hosomichi K, Aizawa Y, Kazuki Y, Tomizuka K. Generation of Monosomy 21q Human iPS Cells by CRISPR/Cas9-Mediated Interstitial Megabase Deletion. ***Genes Cells***. 2025 Jan;30(1):e13184.

Key papers

Uno N, Satofuka H, Miyamoto H, Honma K, Suzuki T, Yamazaki K, Ito R, Moriwaki T, Hamamichi S, Tomizuka K, Oshimura M, Kazuki Y. Treatment of CHO cells with Taxol and reversine improves micronucleation and microcell-mediated chromosome transfer efficiency. ***Mol Ther Nucleic Acids***. 2023 Jul 15;33:391-403.

Suzuki T, Katada E, Mizuoka Y, Takagi S, Kazuki Y, Oshimura M, Shindo M, Hara T. A novel all-in-one conditional knockout system uncovered an essential role of DDX1 in ribosomal RNA processing. ***Nucleic Acids Res***. 2021 Apr 19;49(7):e40.

Suzuki T, Kazuki Y, Oshimura M, Hara T. Highly Efficient Transfer of Chromosomes to a Broad Range of Target Cells Using Chinese Hamster Ovary Cells Expressing Murine Leukemia Virus-Derived Envelope Proteins. ***PLoS One***. 2016 Jun 7;11(6):e0157187.

Group Leader
Shoji HATA

Calpain Group

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

Shoji Hata leads the Calpain Group. As a graduate student, he investigated the role of calpains, a family of intracellular calcium-dependent cysteine proteases, in gastrointestinal function. He received his Ph.D. from the Graduate School of Agricultural and Life Sciences at the University of Tokyo in 2001. After continuing his research as a postdoctoral fellow at the University of Tokyo, he joined the Tokyo Metropolitan Institute of Medical Science as a research scientist in 2004. His current research focuses on elucidating the molecular mechanisms by which calpains contribute to the pathogenesis of various diseases.

Staff

Researchers
Chihiro HISATSUNE
Fumiko SHINKAI-OUCHI
Aya NOGUCHI

Research Progress in 2025

Background
Calpains constitute a family of calcium-dependent cysteine proteases that mediate the limited proteolysis of specific substrate proteins. Fifteen calpain isoforms have been identified in humans, each with distinct expression patterns and physiological roles. Defects in calpain function are implicated in a wide range of pathological conditions, including limb-girdle muscular dystrophy, cancers, impaired wound repair, and abnormalities in cellular growth and motility. These findings highlight calpains as critical regulators of tissue integrity and organismal health.
Our research aims to address key questions regarding the biological roles of calpains: why they cause limited proteolysis, how their activity is precisely controlled within cells, and what molecular and physiological consequences arise when calpains are absent, mutated, or dysregulated. By elucidating these mechanisms, we seek to clarify the fundamental significance of calpain-mediated proteolysis, provide novel insights into disease processes, and ultimately develop strategies to restore pathological conditions associated with calpain malfunction.

Achievements in 2025
We focused on the physiological roles of calpain 3 (CAPN3) and calpain 15 (CAPN15). CAPN3 is predominantly expressed in the skeletal muscle and is responsible for limb-girdle muscular dystrophy type R1 (LGMDR1), while CAPN15 is the causative gene product of the congenital disorder oculogastrointestinal neurodevelopmental syndrome (OGIN). By studying these enzymes, we aim to understand how they maintain muscle and brain health, and how their dysfunction leads to disease.
We developed an antibody specific for activated CAPN3 to investigate its spatiotemporal activation in cultured skeletal myotubes. Under resting conditions, CAPN3 was primarily localized at the M-line of the sarcomere. Treatment with the cardiotonic steroid, ouabain, which induces a gradual and modest increase in intracellular Ca^2, led to CAPN3 activation and translocation from the M-line to the cytoplasm. We further identified the cytoskeletal proteins spectrin and talin as potential physiological substrates of CAPN3.
We performed proteomic and metabolomic analyses of *Capn3* KO mice, a model of LGMDR1, and observed trends toward reduced glycogen and lipid content in the liver, suggesting that systemic metabolic alterations may occur prior to disease onset. These findings offer a new perspective on LGMDR1 pathophysiology, highlighting changes in systemic energy balance and suggesting that circulating metabolites, such as lipids, could serve as potential diagnostic markers.
We also found that CAPN15 is a protease that targets ubiquitinated proteins, but interestingly is not part of the proteasome. CAPN15 cleaves ubiquitinated E-cadherin and regulates its cell surface levels, thereby modulating cell adhesion. In *Capn15* KO mice, which exhibited congenital ocular and brain abnormalities similar to OGIN, we observed elevated E-cadherin expression. These findings suggest that dysregulation of E-cadherin contributes to the congenital defects observed in diseases such as OGIN.

Selected Publications

Papers in 2025
Nambu Y, et al. N-Terminal Fragment of Urine Titin Is Not a Product of Degradation by Calpain 3. ***Muscle Nerve***. 2025 Mar;71(3):442-445.

Shinkai-Ouchi F, et al. Distinct systemic metabolic features in limb-girdle muscular dystrophy type R1 mouse models as a potential early pathogenic signature. ***Biochim Biophys Acta Mol Basis Dis***. 2025 Oct;1871(7):167983.

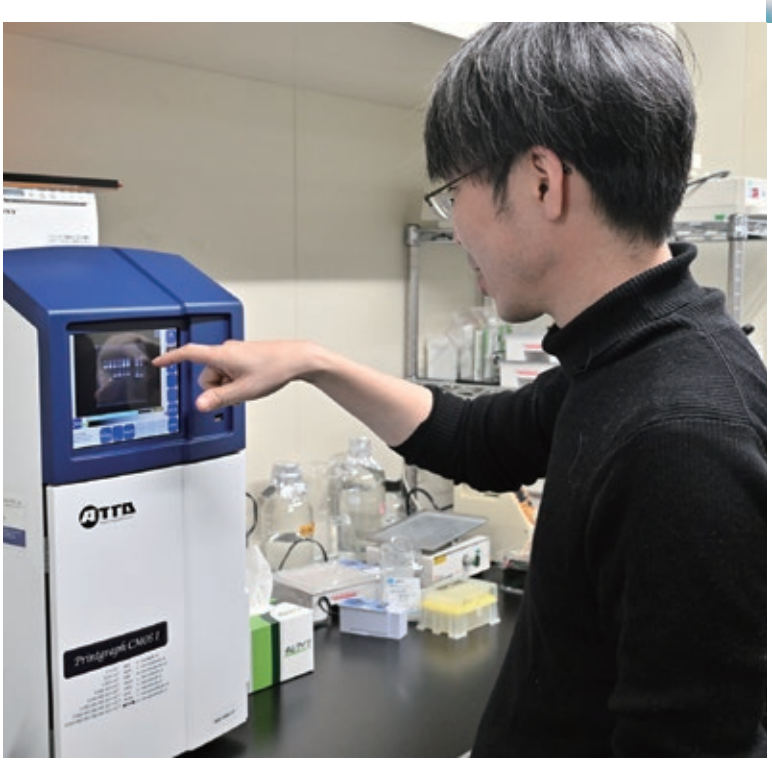
Hisatsune C, et al. In situ detection of activation of CAPN3, a responsible gene product for LGMDR1, in mouse skeletal myotubes. ***J Biol Chem***. 2025 Jun;301(6):108536.

Noguchi A, et al. (2025) "CAPN15 is a non-proteasomal, ubiquitin-directed calpain protease that regulates cell adhesion by cleaving E-cadherin." ***J. Biol. Chem***. in press.

Key papers
Shinkai-Ouchi F, et al. Calpain-2 participates in the process of calpain-1 inactivation. ***Biosci Rep***. 2020 Nov 27;40(11):BSR20200552.

Hata S, et al. A muscle-specific calpain, CAPN3, forms a homotrimer. ***Biochim Biophys Acta Proteins Proteom***. 2020 Jul;1868(7):140411.

Research Centers



Director
Hideya KAWAJI

Genome & Medical Sciences

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

Hideya Kawaji has led the Center for Genome and Medical Sciences since 2020. He earned his Ph.D. in Engineering Science from Osaka University in 2003. He began his career developing computational methods to identify functional motifs in protein sequences and later joined RIKEN, where he focused on transcriptional regulations, particularly mapping transcription start sites at base-pair resolution. After serving as a research scientist, unit leader, and coordinator at RIKEN, he assumed his current role. His research explores the regulatory logic encoded in the human genome that controls gene expression and influences health and disease.

Staff

Researcher
Nobumasa WATANABE
Naoko YOSHIZAWA
Toyoaki NATSUME
Saki SAITO

Research Assistant
Ryoko WADA
Naomi IDA

Research Progress in 2025

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.

Our research focuses on understanding how genes are switched on and off in human cells. We study key genomic regions, called cis-regulatory elements (such as promoters and enhancers), that control gene activity both near and far from their target genes. We also investigate how RNA molecules vary among cell types to better understand genome and cell functions. To address these questions, we combine cutting-edge experimental techniques with advanced computational analysis, and collaborate with other research projects and hospitals by applying the genomics technologies.

Achievements in 2025

- We identified drug-responsive cis-regulatory elements (CREs) that shape transcriptional responses in human hepatocytes and link them to molecular phenotypes associated with adverse drug reactions. This work revealed how drug-inducible CREs modulate gene expression involved in pharmacogenomic variability and toxicity (Gotoh-Saito et al., Nat Commun 2025).
- We conducted a clinical transcriptomic study investigating giant cell arteritis with Tokyo metropolitan hospitals and clarified participation of tissue-remodeling molecules to the pathogenesis. The findings advance our understanding of immune-mediated vascular diseases (Watanabe et al., Rheumatology (Oxford) 2025).
- We built a spatiotemporal transcriptomic atlas of the developing mouse brain, mapping molecular markers across late embryonic and postnatal stages, in collaboration with the Developmental Neuroscience Project in TMiMS. (Hara et al., Sci Rep 2025).
- We also updated the FANTOM web resource, enhancing its functionality for studying the noncoding genome. This update provides upgraded resource for exploring enhancer activities and transcriptome regulation (Nobusada et al., Nucleic Acids Res 2025).

Selected Publications

Papers in 2025

Gotoh-Saito S, et al. Drug-induced cis-regulatory elements in human hepatocytes affect molecular phenotypes associated with adverse reactions. ***Nat Commun***. 2025 Apr 29;16(1):3851.

Watanabe N, et al. Tissue degrading and remodelling molecules in giant cell arteritis. ***Rheumatology (Oxford)***. 2025 May 1;64(5):3095-3103.

Hara Y, et al. The spatial transcriptome of the late-stage embryonic and postnatal mouse brain reveals spatiotemporal molecular markers. ***Sci Rep***. 2025 Apr 10;15(1):12299.

Nobusada T, et al. Update of the FANTOM web resource: enhancement for studying noncoding genomes. ***Nucleic Acids Res***. 2025 Jan 6;53(D1):D419-D424.

Key papers

Pardo-Palacios FJ, et al. Systematic assessment of long-read RNA-seq methods for transcript identification and quantification. ***Nat Methods***. 2024 Jul;21(7):1349-1363.

Abugessaisa I, et al. FANTOM enters 20th year: expansion of transcriptomic atlases and functional annotation of non-coding RNAs. ***Nucleic Acids Res***. 2021 Jan 8;49(D1):D892-D898.

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Forrest, A.R.R., Kawaji H, et al. A promoter-level mammalian expression atlas. ***Nature***. 2014 Mar 27;507(7493):462-70.

Director Unit Leader
Atsushi NISHIDA

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

Mental Health Promotion

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

Staff

Researchers
Syudo YAMASAKI
Junko NIIMURA
Satoshi YAMAGUCHI

Research Progress in 2025

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 2025

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

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

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

Selected Publications

Papers in 2025

Narita ZC, Knowles G, Yamasaki S, Kasai K, Nishida A. The silent crisis in girls' mental health. ***Nat Hum Behav***. 2025 Sep 30.

Niimura J, Yamasaki S, Nakanishi M, Yamaguchi S, Baba K, Nakajima N, Miyashita M, Stanyon D, Knowles G, DeVylder J, Hiraiwa-Hasegawa M, Ando S, Kasai K, Nishida A. Investigating the association between the number of interpersonal supporters during first-time pregnancy and postpartum depression symptoms. ***Epidemiol Psychiatr Sci***. 2025 Jun 27;34:e34.

Narita ZC, Miyashita M, Furukawa TA, Nishida A. Key Considerations in Mediation Analysis for Psychiatric Research. ***JAMA Psychiatry***. 2025 Jul 1;82(7):634-636.

Knowles G, Stanyon D, Yamasaki S, Miyashita M, Gayer-Anderson C, Endo K, Usami S, Niimura J, Nakajima N, Baba K, Richards TS, Kitisu J, Hashi A, Clement-Gbede KS, Tettey N, Davis S, Lowis K, Buckley V, Moreno-Agostino D, Putzgruber E, Crudgington H, Woodhead C, Priestley K, Keyes KM, Dyer J, Ando S, Kasai K, Hiraiwa-Hasegawa M, Morgan C, Nishida A; Tokyo Teen Cohort Young Persons Advisory Group. Trajectories of depressive symptoms among young people in London, UK, and Tokyo, Japan: a longitudinal cross-cohort study. ***Lancet Child Adolesc Health***. 2025 Apr;9(4):224-233.

Nakanishi M, Yamasaki S, Stanyon D, Miyashita M, Nakashima T, Miyamoto Y, Ogawa A, Ando S, Nishida A. Associations among age at menopause, depressive symptoms, and cognitive function. ***Alzheimers Dement***. 2025 Apr;21(4):e70063.

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.

HP: 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 2025

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. Developing of safe nursing care techniques based on basic and clinical research findings
2. Improving of environments and support systems
3. Creating 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 with 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 2025

Building on the foundation of the Rare Disease Care Registry, we are advancing specific research themes focusing on clinical and physiological aspects of ALS. Ongoing studies include investigations of pulmonary pathologies in patients on tracheostomy invasive ventilation (TIV), revealing diverse lung changes associated with long-term TIV and emphasizing the importance of individualized respiratory management. Longitudinal analyses are also examining opioid use patterns according to respiratory management types and exploring autonomic regulation functions. These efforts aim to refine evidence-based care strategies and further enhance the quality of life for individuals living with ALS.

Selected Publications

Papers in 2025

Matsuda C, Nakayama Y, Haraguchi M, Morishima R, Itagaki Y, Bokuda K, Kimura H, Takahashi K, Shimizu T. Patients' choices regarding ventilatory support affect opioid use in amyotrophic lateral sclerosis. ***Amyotroph Lateral Scler Frontotemporal Degener.*** 2025 Aug;26(5-6):409-416.

Warita H, Urushitani M, Atsuta N, Izumi Y, Kano O, Shimizu T, Nakayama Y, Narita Y,Nodera H, Fujita T, Mizoguchi K, Morita M, Aoki M. Addendum to the 2023 Clinical Practice Guidelines for Amyotrophic Lateral Sclerosis in Japan: Approval and Integration of Novel Disease-Modifying Therapies. ***Rinsho Shinkeigaku*** (Clin Neurol) 2025 in Press.

Key papers

Nakayama Y, Shimizu T, Matsuda C, Haraguchi M, Hayashi K, Bokuda K, Nagao M, Kawata A, Takahashi K. Body Weight Gain Is Associated with the Disease Stage in Advanced Amyotrophic Lateral Sclerosis with Invasive Ventilation. ***Metabolites***. 2022 Feb 19;12(2):191.

Nakayama Y, Shimizu T, Matsuda C, Haraguchi M, Hayashi K, Bokuda K, Nagao M, Kawata A, Ishikawa-Takata K, Isozaki E. Body weight variation predicts disease progression after invasive ventilation in amyotrophic lateral sclerosis. ***Sci Rep***. 2019 Aug 22;9(1):12262.

Nakayama Y, Shimizu T, Matsuda C, Haraguchi M, Hayashi K, Mochizuki Y, Nagao M, Kawata A, Isozaki E. Non-motor manifestations in ALS patients with tracheostomy and invasive ventilation. ***Muscle Nerve***. 2018 May;57(5):735-741.

Unit Leader
Fumihiko YASUI

Infection Control Unit

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.

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

Staff

Researchers
Michinori KOHARA
Takahiro SANADA
Kenzaburo YAMAJI
Naoki YAMAMOTO
Ahmad faisal AMIRY

Research Assistants
Asako TAKAGI
Risa KONO
Ryusei FURUSAWA
Midori NAGAI
Yoko SUZUKI
Chizuru NAKAJIMA

Research Progress in 2025

Background

Emerging infectious diseases, caused by previously unknown pathogens, and re-emerging infectious diseases, which have begun to spread again have occurred around the world, pose major public health problems worldwide. To combat the spread of unpredictable viruses, we must deepen our understanding by conducting a wide range of research activities, including epidemiological surveys and basic research. Our focus is on two distinct categories: "priority infectious diseases" feared to cause enormous damage, and "intractable infectious diseases" for which control methods have not been fully established. Currently, our efforts are concentrated on liver disease, acute viral pneumonia, dengue fever, and Mpox. We are conducting large-scale epidemiological surveys (such as antibody measurements), analyzing disease mechanisms using cultured cells, and examining pathology and developing control methods in relevant animal models.

Achievements in 2025

1. We identified two hepaciviruses and one pegivirus in northern tree shrews, which are hepatitis models. Genomic analysis showed the hepaciviruses share liver-tropism traits with HCV and are highly prevalentre. These findings reveal that laboratory tree shrews carry natural viral infections, emphasizing the necessity of viral screening to characterize these pathogens and ensure the stability of tree shrews as experimental animals.(*Infect Genet Evol*, 2025)
2. We evaluated an intranasal Hepatitis B vaccine combining dual antigens with carboxyl-vinyl polymer (CVP) excipients in mice. The addition of CVP significantly improved antigen stability and enhanced both humoral and cell-mediated immune responses, including increased IgG production and neutralizing antibody titers. CVP demonstrates significant potential as an effective excipient for improving the immunogenicity and stability of intranasal HBV vaccines. (*Vaccines (Basel)*, 2025)
3. In a joint research project with The University of Tokyo, we conducted a comprehensive immunological evaluation of an attenuated vaccinia virus LC16m8 in mice, non-human primates, and humans. (*EBioMedicine*, 2025).
4. We developed recombinant H5N1 vaccines using attenuated vaccinia vectors (LC16m8 and DIs). Both candidates conferred rapid and long-term protection in mice; furthermore, LC16m8 provided protection in macaques against heterologous clades. Notably, the replication-deficient rDIs vaccine showed efficacy comparable to LC16m8, even in animals with prior vaccinia immunity. These results indicate that both vectors are effective, highlighting rDIs as a promising pre-pandemic vaccine candidate against H5N1 avian influenza. (*Vaccines (Basel)*, 2025)

Selected Publications

Papers in 2025

Sanada T, et al. Genomic characterization of hepaciviruses and pegivirus in the northern tree shrew (Tupaia belangeri). ***Infect Genet Evol***. 2025 Aug;132:105778.

Rashid MHO, et al. Immunogenicity of an Intranasal Dual (Core and Surface)-Antigen Vaccine Against Hepatitis B Virus Enhanced by Carboxyl-Vinyl Polymer Excipients. ***Vaccines (Basel)***. 2025 Apr 25;13(5):464.

Kobiyama K, et al. Immunological analysis of LC16m8 vaccine: preclinical and early clinical insights into mpox. ***EBioMedicine***. 2025 May;115:105703.

Yasui F, et al. Single Dose of Attenuated Vaccinia Viruses Expressing H5 Hemagglutinin Affords Rapid and Long-Term Protection Against Lethal Infection with Highly Pathogenic Avian Influenza A H5N1 Virus in Mice and Monkeys. ***Vaccines (Basel)***. 2025 Jan 15;13(1):74.

Key papers

Sanada T, et al. Serologic Survey of IgG Against SARS-CoV-2 Among Hospital Visitors Without a History of SARS-CoV-2 Infection in Tokyo, 2020-2021. ***J Epidemiol***. 2022 Feb 5;32(2):105-111.

Ishigaki H, et al. An attenuated vaccinia vaccine encoding the severe acute respiratory syndrome coronavirus-2 spike protein elicits broad and durable immune responses, and protects cynomolgus macaques and human angiotensin-converting enzyme 2 transgenic mice from severe acute respiratory syndrome coronavirus-2 and its variants. ***Front Microbiol***. 2022 Nov 18;13:967019.

Unit Leader
Daisuke YAMANE

Daisuke YAMANE leads research focused on host–virus interactions, aiming to uncover the molecular mechanisms underlying diseases associated with viral infections. He obtained his Ph.D. in Veterinary Medicine from the University of Tokyo, and subsequently completed a postdoctoral fellowship at the University of North Carolina at Chapel Hill under the mentorship of Dr. Stanley Lemon. In 2016, he was appointed Senior Scientist at the Tokyo Metropolitan Institute of Medical Science, where he initiated research on host factors influencing the replication of a diverse array of clinically significant human viruses, including hepatotropic viruses, neurotropic flaviviruses, and enteroviruses.

Immunity Control Unit

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

Staff

Researchers
Kyousuke KOBAYASHI
Tomoko HONDA
Satoshi KOIKE

Research Assistants
Masako UKAJI
Marie URANO
Aya KOSEKI
Karin MARUYAMA
Koyuki SHINODA

Students
Kotomi SHINOZAKI

Research Progress in 2025

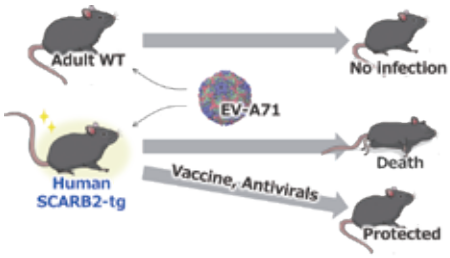
Background

Pathogenic viruses have evolved mechanisms to evade the host immune response and establish infection following the initial battle with host innate immunity. The host defense system comprises multiple layers; however, how these mechanisms are maintained or functionally activated in response to infection remains largely uncharacterized. Our aim is to (i) identify host signal transduction and metabolic pathways that play functional roles in restricting viral replication, (ii) uncover innate immune mechanisms involved in the clearance of pathogenic viruses and in enhancing vaccine efficacy, and (iii) develop antiviral compounds that mimic the mode of action of endogenous host antiviral effectors.

Our laboratory also focuses on the pathogenesis and replication mechanisms of picornaviruses, including enterovirus A71 (EV-A71), a major causative agent of hand-foot-and-mouth disease (HFMD) that can occasionally lead to neurological complications. Using a mouse model expressing the human receptor for EV-A71 identified by our group, we aim to develop prophylactic vaccines and antiviral therapeutics based on a detailed understanding of how the virus exploits host cellular factors.

Achievements in 2025

- We discovered a previously unrecognized cross-talk between apolipoproteins that redundantly regulate both triglyceride turnover and virion secretion of a hepatotropic virus.
- We identified new entry receptors for Saffold virus, a picornavirus that causes acute respiratory and gastrointestinal illnesses, as well as HFMD.
- Using cell culture and mouse models, we characterized host factors and EV-A71 genetic variants that influence the frequency of neuropathogenesis.
- We identified host factors that link constitutive and inducible antiviral defense mechanisms.



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.

Selected Publications

Papers in 2025

Shinozaki K, et al. Impaired ApoB secretion triggers enhanced secretion of ApoE to maintain triglyceride homeostasis in hepatoma cells. ***J Lipid Res***. 2025 May;66(5):100795.

Okuwa T, Himeda T, Kobayashi K, et al. Saffold virus exploits integrin αvβ8 and sulfated glycosaminoglycans as cooperative attachment receptors for infection. ***Nat Commun***. 2025 Dec 15.

Shimizu T, et al. Bile acid-FXR signaling facilitates the long-term maintenance of hepatic characteristics in human iPSC-derived organoids. ***Cell Rep***. 2025 May 27;44(5):115675.

Key papers

Matsumoto M, Shinozaki K, et al. CSNK2B modulates IRF1 binding to functional DNA elements and promotes basal and agonist-induced antiviral signaling. ***Nucleic Acids Res***. 2023 May 22;51(9):4451-4466.

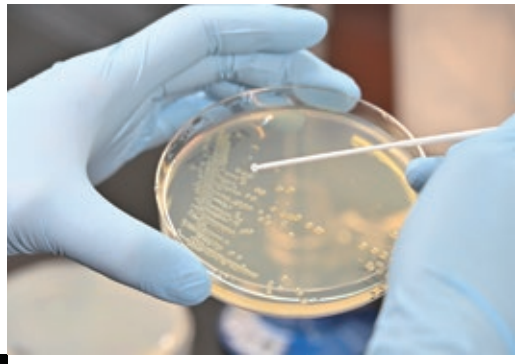
Yamane D, et al. FADS2-dependent fatty acid desaturation dictates cellular sensitivity to ferroptosis and permissiveness for hepatitis C virus replication. ***Cell Chem Biol***. 2022 May 19;29(5):799-810.e4.

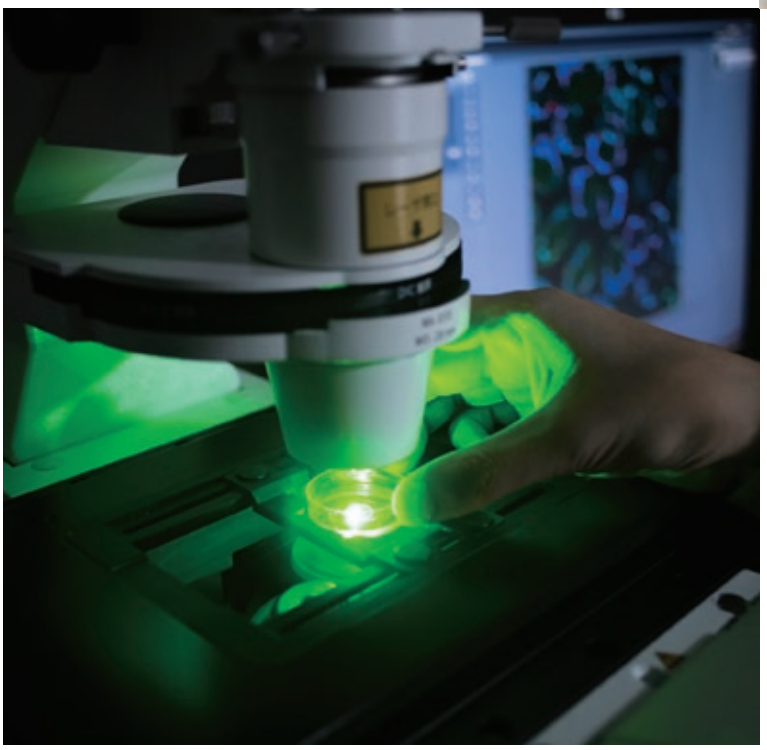
Kobayashi K, et al. Virulence of Enterovirus A71 Fluctuates Depending on the Phylogenetic Clade Formed in the Epidemic Year and Epidemic Region. ***J Virol***. 2021 Nov 9;95(23):e0151521.

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

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

Research Supports





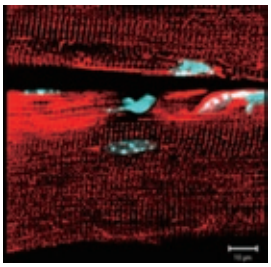
Director
Yukio NISHIMURA

Basic Technology Research

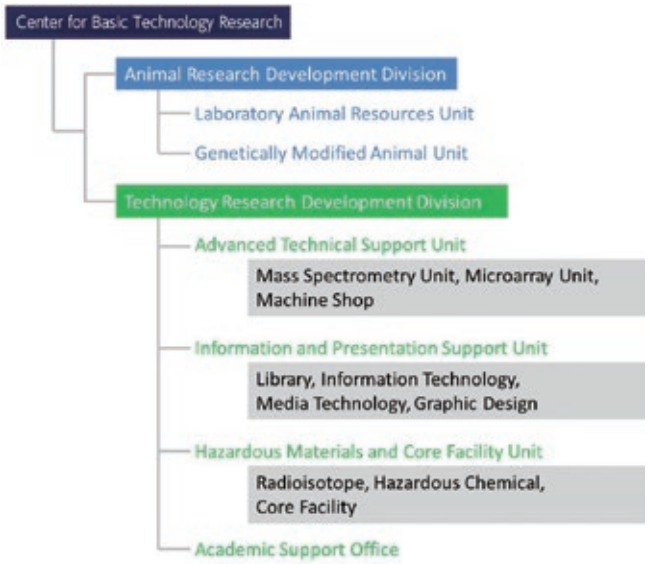
HP: https://www.igakuken.or.jp/english/center/basic/basictech.html

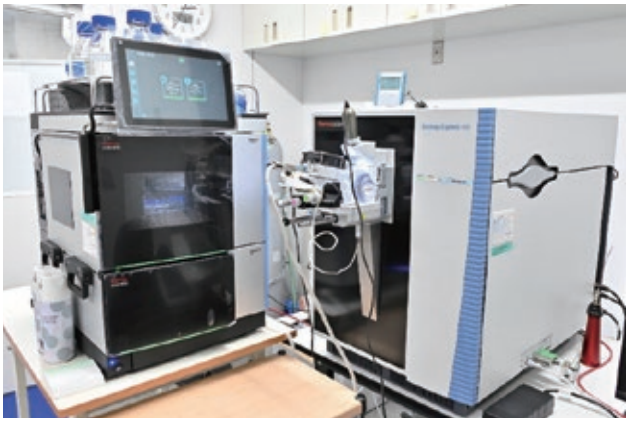
The Basic Technology Research Center provides resources that enable scientists to conduct their research efficiently by offering state-of-the-art technologies for biomedical and life science research and maintaining shared research facilities. The Center is organized into two divisions: **the Animal Research Development Division,** headed by Hiroshi Shitara, and **the Technology Research Development Division,** headed by Takahiko Hara.

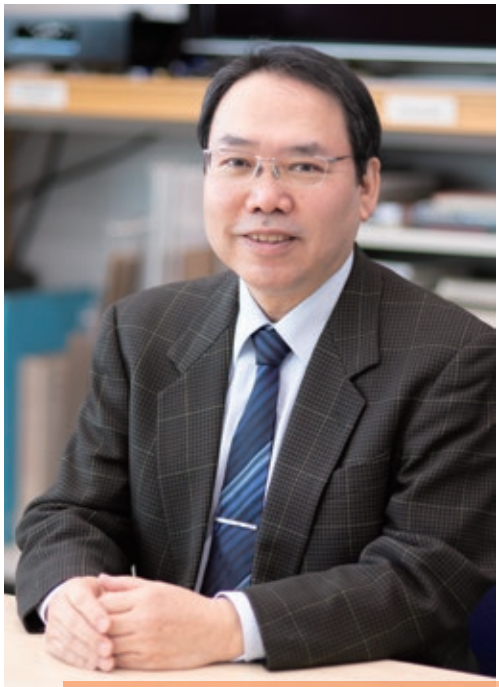
The Animal Research Development Division supports animal-based research by maintaining animal research facilities and ensuring the care and welfare of animals used in research. The Division assists researchers in the generation of genetically modified animals, including transgenic and knockout/knockin models, and maintains sperm and embryos from a wide range of mutant animal lines. It comprises two units: the Laboratory Animal Resources Unit, which oversees animal care, husbandry, and facility management, and the Genetically Modified Animal Unit, which provides technical support for the production, maintenance, and preservation of genetically modified animals.



The Technology Research Development Division supports cutting-edge biomedical and life science research by providing advanced technical services, shared research infrastructure, and specialized expertise. It comprises four units. The Advanced Technical Support Unit provides state-of-the-art technologies and facilities for biomedical research, including mass spectrometry, flow cytometry, microarray analysis, confocal and electron microscopy, histology, and other advanced experimental techniques. The Information and Presentation Support Unit comprises the library, the information technology section, the media technology laboratory, and the public relations office, supporting researchers in literature and information searches, computer systems management, media production, and public communication. The Hazardous Materials and Core Facility Unit manages radioisotope laboratories, hazardous chemical control rooms, and shared core facilities, ensuring safe operation and compliance with safety standards. The Academic Support Office provides consultation to improve the quality and impact of scientific manuscripts.



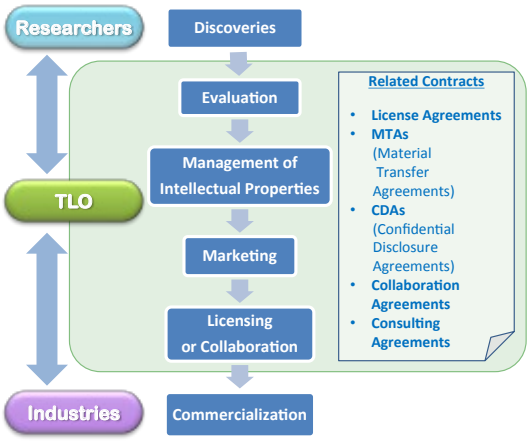




Technology Licensing Office

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

General Manager
Kazumasa AOKI



Who we are

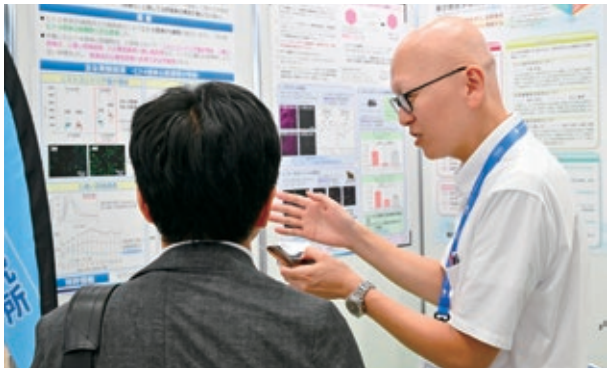
- The Technology Licensing Office (TLO) facilitates the conversion of scientific discoveries to innovative technologies with the ultimate goal of improving public health and welfare.
- We evaluate basic research findings (seeds) as intellectual property assets, and license promising candidates to industries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

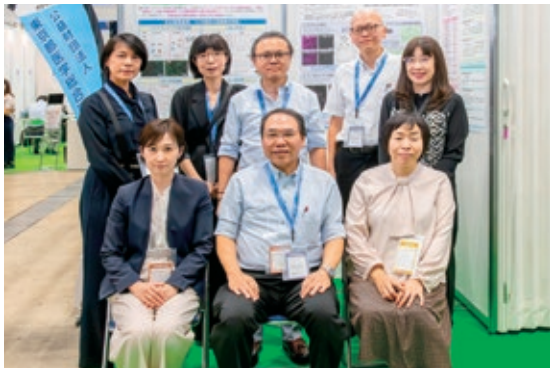
What we do

- 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 2025

- License agreements: 55
- Joint research agreements: 71





Medical Research Cooperation

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

Director

Takayuki HARADA

Staff

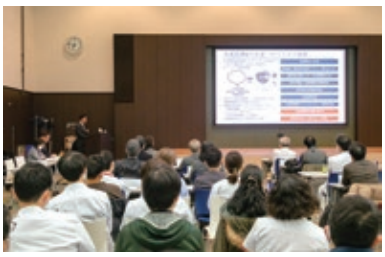
Kenji TOYAMA
Chikako ISHIDA
Keisuke OBOKI
Hiroko KOUSAKA

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

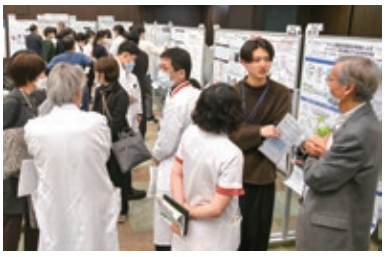
We facilitate collaboration between basic scientists at research institutes and healthcare professionals at Tokyo Metropolitan Hospitals. Our office promotes partnerships by:

- Matching medical doctors and other hospital staff with researchers at our institute.
- Providing seed funding (up to 500,000 yen) for collaborative clinical studies with hospital physicians.
- Organizing research exchange meetings to enhance communication and foster new collaborations.

Through these activities, we aim to create an ecosystem where hospital needs and scientific expertise converge, accelerating the translation of discoveries into better medical care.

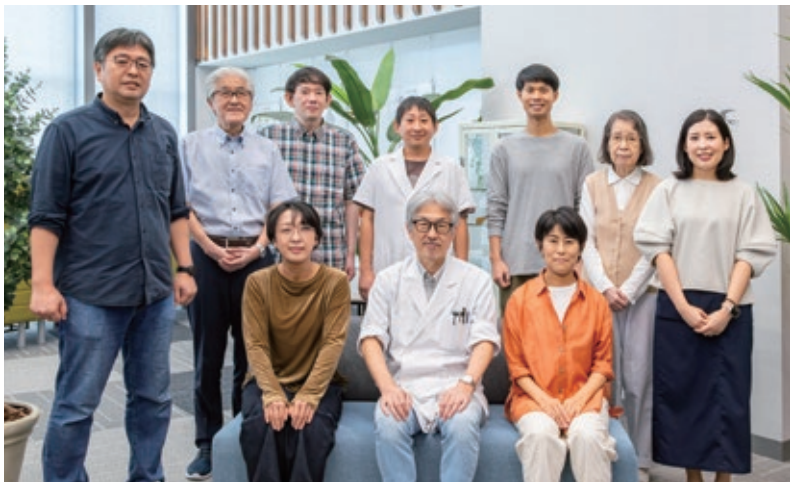


Conference with researchers and medical doctors



A young scientist discussing with researchers and medical doctors in conference

Molecular Pathology and Histology



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

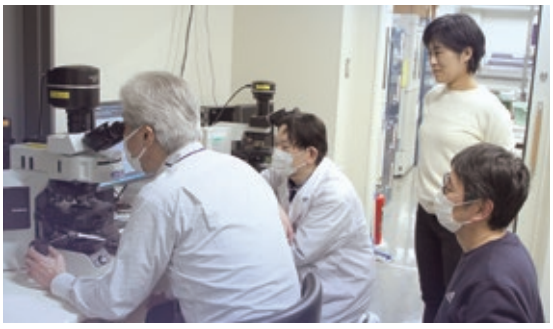
Translational Research using human materials and Management of Database for Essential Brain Anatomy & Neuropathology

Staff

Researchers
Masato HASEGAWA
Aki SHIMOZAWA
Kazunari SEKIYAMA
Rika KOJIMA
Kyohei MIKAMI
Yoshinobu IGUCHI
Emiko KAWAKAMI

Technicians
Erika SEKI
Kentaro ENDO

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 health and welfare. In 2025, lectures were conducted in a hybrid format combining online and in-person sessions. Lecture topics included dementia, avian influenza, the biological clock, liver cancer, addiction and others.

Early Detection and Treatment of Mental Illness
- Masafumi MIZUNO (Asaka Hospital)
- Kazutaka IKEDA (TMIMS)

Avian Influenza and Our Way of Life: What We Need to Know
- Yoshihiro SAKODA (The School of Veterinary Medicine, Hokkaido University)
- Fumihiko YASUI (TMIMS)

Revolutionizing Science and Society with Luminous Proteins!
- Takeharu NAGAI (The Institute of Scientific and Industrial Research Osaka University)
- Hikari YOSHITANE (TMIMS)

New Initiatives for Dementia 2025
- Hiroshi MORI (Tamiya Hospital, Nagaoka Sutoku University)
- Masato HASEGAWA (TMIMS)

Evidence-Based and Sustainable Support for Pregnant Women
- Kaori BABA (The Graduate School of Nursing Science St. Luke's International University)
- Atsushi NISHIDA (TMIMS)

Basic Researches and Drug Discovery
- Sayuri WATANABE (Janssen Pharmaceutical K.K.
- Takashi NONAKA (TMIMS)

How Can We Eliminate Liver Cancer for Healthy Liver?
- Tetsuro SHIMAKAMI (Graduate School of Medical Sciences,Kanazawa University)
- Daisuke YAMANE (TMIMS)

Super-Personalized Medicine Using Nucleic Acid Drugs
- Hiroya KUWAHARA (Department of Neurology and Neurological Science, Institute of Science Tokyo)
- Hideya KAWAJI (TMIMS)



Science café

In the past 16 years, we have had 51 special science presentations geared toward the general public. The "science cafes" provide people of all ages with the opportunities to learn, experience, and enjoy science first hand in a casual setting. In 2025, we had three science cafes on fragrance, light and other topics. The participants enjoyed various activities including on-site experiences of scientific experiments.

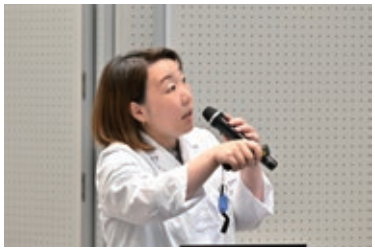
The Science of Fragrance
- Tomoe NISHIMURA / Kohji KASAHARA (TMIMS)

The Science of Light and Vision
- Kohji KASAHARA (TMIMS)

How the Human Body Works: Lessons from a Pediatrician
- Hiroshi SAKUMA (TMIMS)








Institutional seminars (Igakuken Seminars)

We have institutional seminars on a regular basis. In 2025, we had 26 seminars (18 in face to face, and 8 on a hybrid format). Seminars were held by domestic and foreign scientists including many scientists participating from overseas (US, UK and others). We were particularly excited to be able to invite world-prominent scientists to the Igakuken Seminars.

Understanding the Molecular Mechanisms of Human Germ Cell Development Using an In Vitro Reconstitution System
.....Shihori YOKOBAYASHI (RIKEN)

Pattern Formation and Function of Vascular Networks - From the Perspective of Mathematical Modeling -
.....Takashi MIURA
(Faculty of Medical Sciences Kyushu University)

Life Science Researches Using Micro-Compartmentalized Culture Units
.....Kazuki HATTORI
(Research Center for Advanced Science and Technology The University of Tokyo)

Engineering Cortical Plasticity in Primate Brain
.....Azadeh Yazdan-Shahmorad
(Departments of Bioengineering and Electrical and Computer Engineering, the University of Washington)

Therapies Targeting Splicing Abnormalities in Cancer
.....Akihide YOSHIMI
(National Cancer Center Japan Research Institute)

How ATPase Motors Unfold Proteins, Unwind DNA Double Helix, and Resolve DNA G4 Structures - a Molecular Level Perspective
.....Huilin Li
(Department of Structural Biology, Van Andel Institute, USA)

Genomic Polymorphism Information and Its Database for Experimental Mice Supporting Disease Researches
.....Toyoyuki TAKADA
(RIKEN BioResource Research Center)

Development and Eevolution of Thalamocortical Connectivity
.....Zoltán Molná
(Department of Physiology, Anatomy & Genetics, University of Oxford)

How to Promote Academic Researches Using Intellectual Property and Technology Transfer
.....Keiko HONDA (TODAI TLO, Ltd.)

Transient Circuits in the Developing Brain
.....Zoltán Molná
(Department of Physiology, Anatomy & Genetics, University of Oxford)

Evolutionary Developmental Biology of the Mammalian Cerebral. Cortex
.....Zoltán Molná
(Department of Physiology, Anatomy & Genetics, University of Oxford)

A Unified Model of Gene Expression Control by Cohesin and CTCF
.....Takeo NARITA
(Department of Proteomics, The Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen)

Circadian Rhythm Theory of Health
.....Satchidananda Panda
(Salk Institute for Biological Studies)

Fast, Synchronous Exocytosis: the Dyad Model.
.....Cameron Baldwin Gundersen
(Department of Molecular & Medical Pharmacology UCLA School of Medicine)

Evolution of DNA replication: Chlamydomonas reinhardtii as a Model System
.....Amy IKUI
(Brooklyn College, Brooklyn, NY Graduate Center at The City University of New York, New York, NY,USA)

Functional Characterization and Therapeutic Targeting of Gene Regulatory Elements
.....Nadav Ahituv
(University of California San Francisco)

(Partial Excerpt)

TMIMS International Symposium

In 2025, we held an international symposium titled "Principles of Neocortical Development and Evolution II." This symposium, a follow-up of the international symposium held in 2019, aimed to deepen our understanding of the principles governing the construction of the cerebral cortex and the mechanisms of its evolution. Leading researchers from Japan and abroad presented and discussed cutting-edge research findings.The symposium enjoyed highly stimulating in-person presentations and lively discussions with 18 renowned scientists from Japan and abroad.

Joint programs with universities

Many scientists at TMIMS have joint appointments as visiting professors or lecturers at various universities. In 2025, we held an "Open Lab" event combining online and in-person formats for undergraduate students who may be interested in doing researches at TMIMS, attracting 176 participants (16 in face to face, and 160 online). We currently have 70 students from affiliated universities and other schools, who conduct their research at our institute. The scientists at TMIMS conduct lectures for students at the universities.

Support for students and young scientists

Research Associate Fellowships

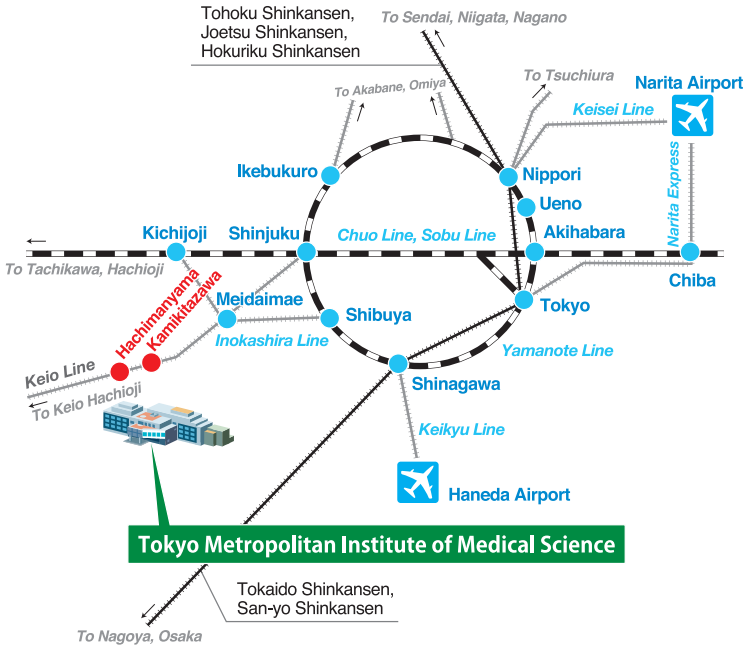
We provide graduate students who conduct their masters/Ph.D. research at TMIMS with research associate fellowships that allow them to concentrate on their studies and research.

Travel support for young scientists attending international meetings

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

Access Map

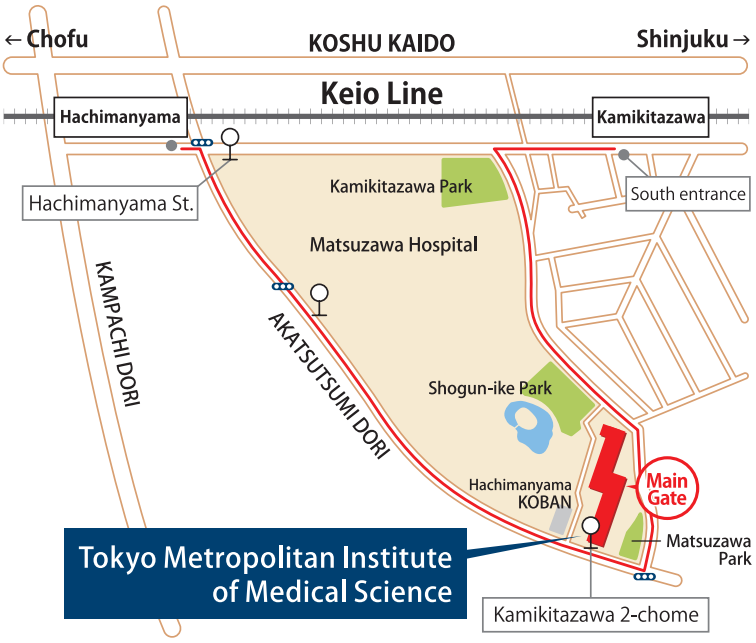
Tokyo Metropolitan Institute of Medical Science	
Address	2-1-6 Kamikitazawa, Setagaya-ku, Tokyo, 156-8506, Japan
Tel	+81-3-5316-3100
Fax	+81-3-5316-3150



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

TMiMS

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As of March 1, 2026