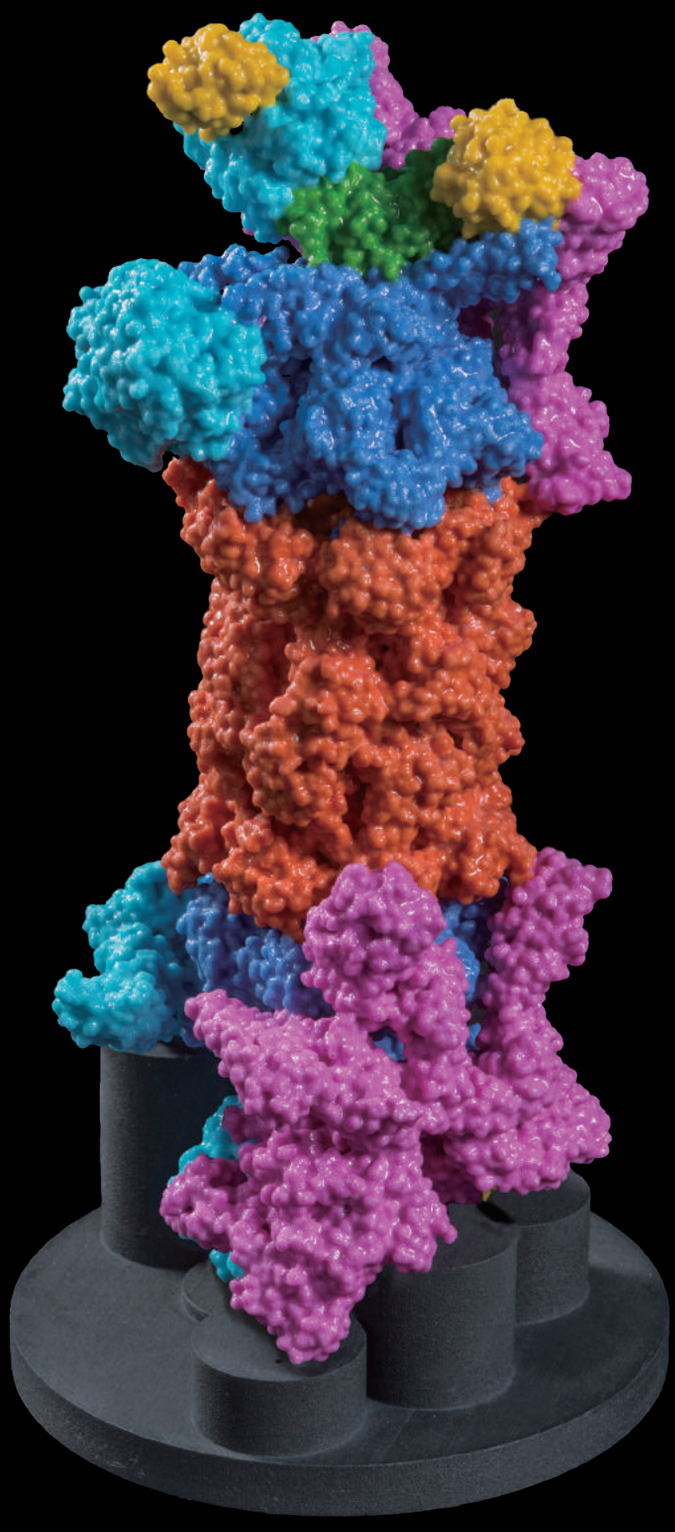
Tokyo Metropolitan Institute of Medical Science

TMiMS

2017



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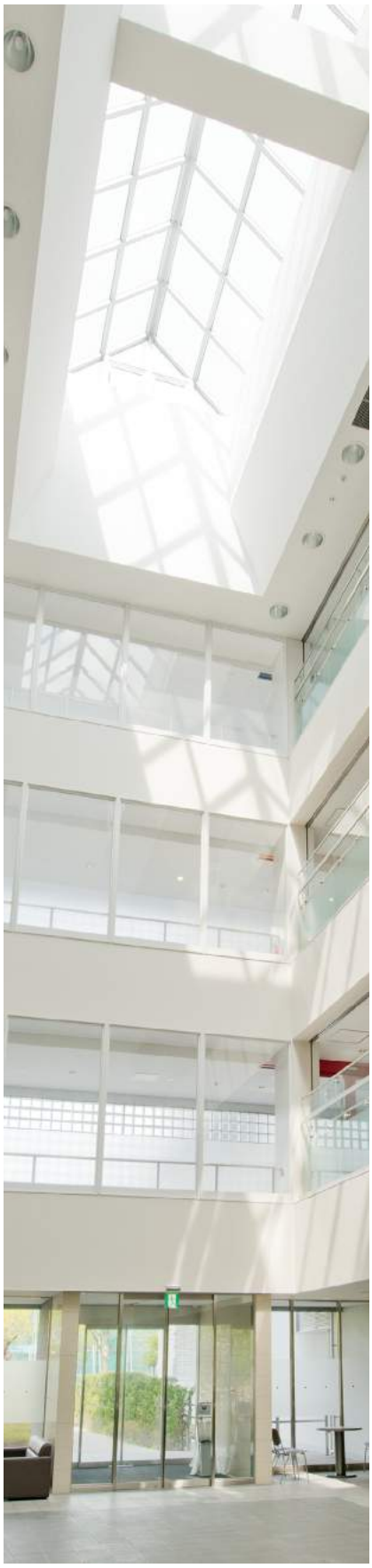
Message from Our Director

Director **Keiji Tanaka**



Metropolitan Tokyo is the center of Japan, and I believe that Tokyo's evolution into a healthy and welfare-spirited city will contribute significantly to the realization of a rich future for Japan. Our mission at the Tokyo Metropolitan Institute of Medical Science (TMiMS) is to contribute to the improvement of health, medicine, and welfare of the nation's capital by promoting life sciences research.

Unprecedented progress in the life sciences in our modern era has stripped away the veils hiding life's mysteries one by one. Even so, this does not mean that we have yet uncovered the full scope of the operating principles that generate life. Humanity, as it has acquired highly sophisticated biological systems that have evolved over long eons, has encountered various problems that have arisen due to that sophistication. Evolution on its own has not been sufficient to counter these problems, necessitating the study of basic and applied sciences.

While we admire the elegance of the mechanisms of life that our current wisdom is not yet fully able to elucidate, we know that the breakdown of these sophisticated mechanisms leads to various diseases. Furthermore, when we consider the inevitable and constant instances of new diseases that arise due to the randomness of gene mutation, we realize that humanity's fight against disease will be a permanent struggle. To overcome illnesses, it will be essential to determine the pathogenesis of complex diseases, and develop novel methods of manipulating biological pathways, including the immune-response system, the linchpin of our biological defense system. To do this, we need a full understanding of the basic biological mechanisms that give us life.

It is well-known that Japan has one of the world's most rapidly aging societies. Here in Tokyo—a microcosm of the entire nation—we have witnessed a steady increase in the rates of various illnesses such as cancer—our species' nemesis—, infectious diseases, and conditions that accompany aging, including brain and mental disorders. While overcoming these diseases is certainly one of humanity's common goals, and has been the target of a number of national level initiatives, Tokyo, as a global city, must also strive to take a leading role in this effort. Moreover, Tokyo is facing a growing number of challenges that affect large metropoles. For example, although research into rare diseases is generally not a top-priority, Tokyo is home to many people suffering from these diseases. TMiMS aims to protect the health of the capital's populace through proactive research into basic biological mechanisms, as well as research on diseases and other health-related problems affecting Tokyo.

When we examine the history of science, we see how the development of new technologies has transformed our world, most notably during the industrial revolution. In the latter half of the twentieth century, the advent of molecular biology radically altered our understanding of the biological sciences, leading to the birth of the new age of scholarship.

Science and technology are constantly advancing, and no matter how sophisticated, past technologies are soon surpassed by new innovations. It is through this constant progress that science has come to serve as a foundation buttressing social development. The growth of humanity and our inheritance of the results that have been achieved through original research provide the driving energy to lead us towards a prosperous future. Likewise, the sustainable transmission of excellent research and training to next-generation personnel, who will support future research, will guarantee our institute's future survival. If we were to avoid this challenge and stand idly by, the institute would lose the very foundation of its existence. What is essential is that we create an attractive institute that will be able to nourish the hopes and dreams of younger generations.

It is my own personal belief that research is a symbol of culture, and our aim at TMiMS is to bring together top scientists whose research will contribute to Tokyo's excellence, both academically and culturally. Academic research is often broadly divided into top-down translational research (applied research) and bottom-up basic research (which may not have immediate applications, but is carried out with an eye to the future). At TMiMS, we strive for a flexible style of organizational management that can benefit from the additive and synergistic effects of both of these strategies. These two strategies are not antithetical to one another and do not entail a trade-off that precludes collaboration and integration. In fact, throughout history, we find examples of research that at first glance seemed useless, but was quickly transformed into practical research through innovative thinking to seize the world's attention with a major contribution to society.

Medical researchers at TMiMS tackle ambitious research challenges around the clock to develop new methods to treat and prevent illnesses to "Ensure a Healthy Tomorrow." While they are also responsible for educating students and the general public, they simultaneously produce concrete research outcomes. To aid in this effort, we provide them with the latest state-of-the-art technologies, and support the life sciences at the broadest level, from basic to applied research. It is paramount that TMiMS grow as an institute that conforms to the world's highest standards and makes broad social contributions. The guidance and encouragement of the citizens of Tokyo and of our partners will be essential to TMiMS's successful development. I thank you for your current and future support.

History

The Tokyo Metropolitan Institute of Medical Science (TMiMS) was established in April 2011 as a result of the merger of three institutes; the Tokyo Metropolitan Institute for Neuroscience, the Tokyo Metropolitan Institute of Psychiatry, and the Tokyo Metropolitan Institute of Medical Science, all of which had been founded in early- to mid-1970s with the support of Tokyo Metropolitan Government and had been located at different locations in Tokyo. The scientists from three different disciplines got together in a new research building in a quiet residential area at Kamikitazawa in Setagaya-ku, about 15 minutes by train from Shinjuku. The institute is under the continuous support from the Tokyo Metropolitan Government, and our aim is to contribute to medical advances and improve the health and welfare of people living in the metropolises through collaborative research in basic life sciences, medical sciences, social medicine, and nursing.

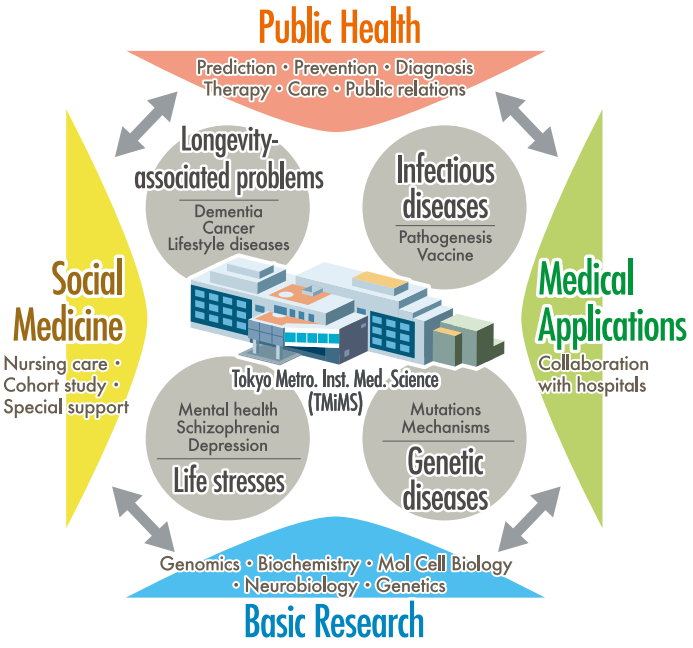
Our Mission

The mission of our institute is to pursue research that will lead to the development of solutions for health-related problems commonly observed in large urban areas and developed countries. Utilizing results from the forefront basic research on molecular and cellular mechanisms of biological pathways and disease pathology, we will collaborate with municipal hospitals and clinics to predict, prevent, and treat health problems. We will also identify causes of unsolved diseases and develop drugs and therapies for them. Our mission is also to provide help and care with those suffering from serious diseases such as ALS to better the patients' quality of life. It is also our mission to analyze the mental disturbances of the public and provide care and treatment.

Our Strategies

In a metropolis such as Tokyo, people suffer from various diseases and other health-related problems unique to urban life-styles. These include mental disturbances caused by stresses associated with daily life, diseases associated with longevity, and diseases caused by complicated genetic traits. We are studying these problems using a unique combination of disciplines, technology and expertise.

We conduct forefront basic research in various biological fields including genome and protein functions, genetic diseases, brain functions, neurobiology, neurodegeneration, stem cells and development, virus infection, allergy, schizo-phrenia, and depression. Using the state-of-art and newest technology and equipment, we are identifying molecules and mechanisms responsible for disease progression and biological phenomena. This knowledge and technology will be used to predict and prevent diseases, and develop new drugs and therapies that can be tailored to individual patients.

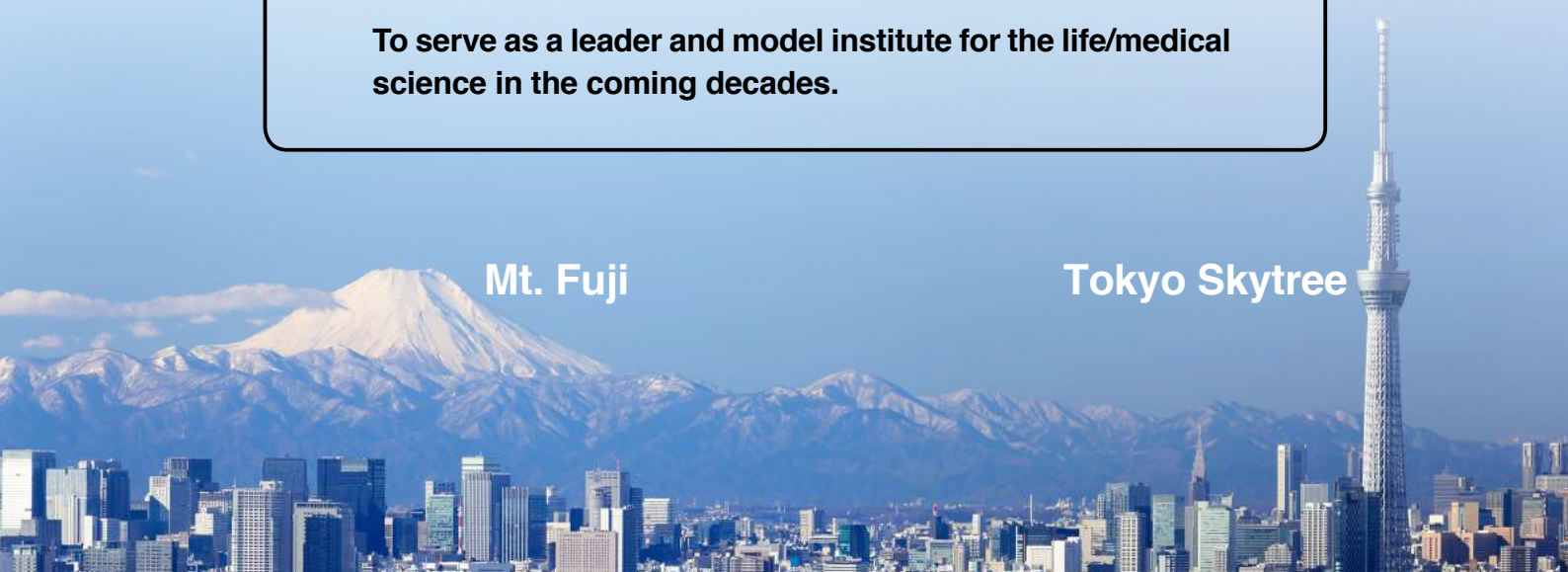


We are also combining sociomedical approaches with molecular and genomic approaches to discover unique and effective treatments for mental disorders. Our institute takes advantage of a multi-disciplinary structure to provide novel solutions to various health-related issues. Located in one of the biggest cities in the world, we hope to be a role model for medical research institutes in the coming decades.

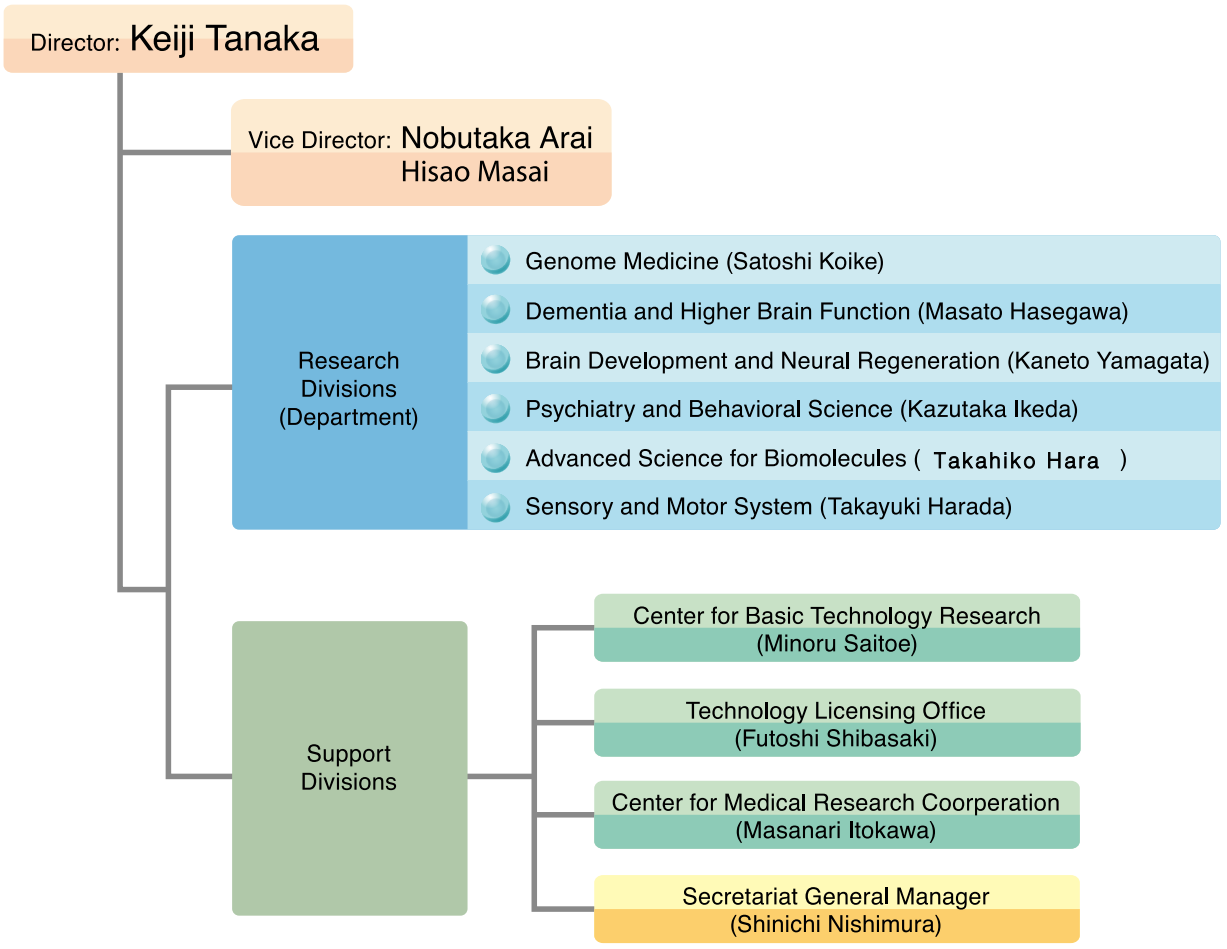
Our Goals

To pursue research that will help prediction, prevention, diagnosis, and treatment of various diseases and improve the care of patients, leading to longer healthy life.

To serve as a leader and model institute for the life/medical science in the coming decades.



Organizational Chart



Our People at a Glance

Position	Number
Researchers	169
Postdoctral Fellows	42
Students	105
Visiting Scientists	164
Guest Scientists	127
Administrative Staffs	28
Total	635

As of December 1, 2017

Laboratory Head **Keiji Tanaka** Protein Metabolism Laboratory

Protein Metabolism:
The Ubiquitin Proteasome System

All proteins of the cell continually are recycled with individually distinct life-span, which is fundamentally important to keep healthy cellular activities in eukaryotes. The proteasome, in collaboration with the ubiquitin system used for choice of target proteins, selectively degrades unnecessary proteins that must be eliminated from the cells. Indeed, the ubiquitin-proteasome system (UPS) plays a pivotal role in the control of a diverse array of basic cellular functions by catalyzing a number of reactions timely, rapidly, and irreversibly. The missions of our laboratory aim to elucidate the molecular mechanisms of the UPS and to integrate it into physiology and pathology.

Research Projects
The Proteasome

1. Structure and Assembly of Proteasomes

The 26S proteasome is a highly organized and sophisticated proteolytic nanomachine that degrades ubiquitylated proteins in an ATP-dependent fashion. (Fig. 1). One longstanding question is how the complex structure of the proteasome is organized with high fidelity. During the past decade, we have succeeded in structural analysis of the 20S and 26S proteasomes. Further, we identified approximately 10 proteasome-dedicated assembling chaperones (i.e., CP and RP chaperones) that assist in the efficient formation of 20S and 26S proteasomes. Of them, we have determined the tertiary structures of almost all CP and RP chaperones, displaying the mechanisms underlying proteasome assembly at the atomic levels. Based on these findings, we have established a model in which multiple dedicated chaperones govern proteasome assembly.

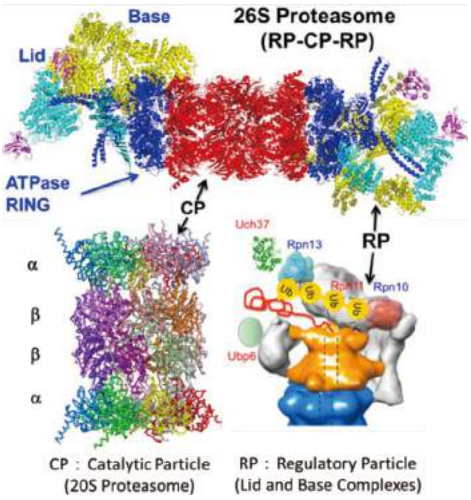


Figure 1. The 26S proteasome
The 26S proteasome consisting of a 20S core/catalytic particle (CP) and one or two 19S regulatory particles (RP). The CP (alias 20S proteasome) is composed of four heptameric rings, which are made up of seven structurally related a and b subunits, displaying an $\alpha_{1\text{-}7}\beta_{1\text{-}7}\beta_{1\text{-}7}\alpha_{1\text{-}7}$ organization. The RP recognizes ubiquitylated proteins, deubiquitylates for recycling of ubiquitin, and then unfolds and translocates them into the interior of the CP for degradation.

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Protein Metabolism

2. Roles of Specialized Proteasomes in Cell-mediated Immunity

The proteasome has acquired diversity of the catalytic β subunits, which have evolved during the acquisition of adaptive immunity. To date, we have discovered the vertebrate-specific alternative 20S CP, which we named the "immunoproteasome" and the “thymoproteasome” (Fig. 2). Whereas the immunoproteasome plays a specialized role as a professional antigen-processing enzyme in cell-mediated immunity, the thymoproteasome is involved in the development of $CD8^+$T cells in thymus; i.e., it has a key role in the generation of MHC class I-restricted $CD8^+$T cell repertoire during thymic selection called positive selection.

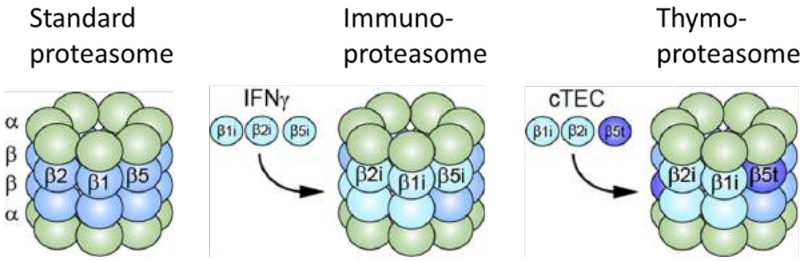


Figure 2.
The immuno- and thymo-proteasomes
The immunoproteasome has catalytic subunits β1i, β2i, and β5i replacing β1, β2, and β5 and enhances production of MHC-I ligands. The thymoproteasome contains thymus-specific subunit β5t in place of β5 or β5i and plays a pivotal role in positive selection of $CD8^+$ T cells.

3. Spatio-temporal Dynamisms of the Proteasome

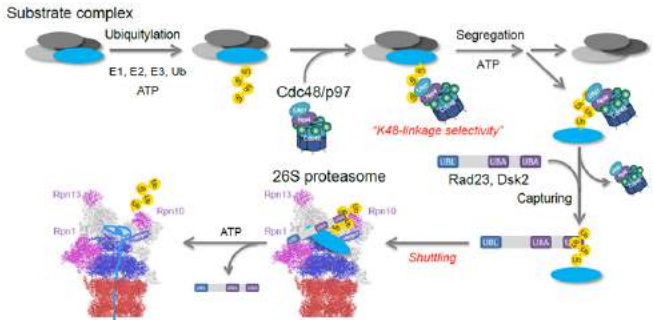
Little is known about the molecular dynamics of the proteasomes in living cells. We measured the absolute concentration, dynamics, and complex formation of the proteasome by quantitative live-cell imaging and quantitative proteomics analyses. We found that the 26S proteasome is a highly mobile complex and enriches in the nucleus. The 26S proteasome appears to complete its assembly process in the cytoplasm and then translocates as a holoenzyme into the nucleus. Furthermore, we also found that the proteasome dynamically changes its subcellular localization and its cofactors under various stresses. This might be a novel cellular response for adapting to stress by regulating protein homeostasis.


Yasushi Saeki

The Ubiquitin System

1. Developing Methods to Decipher the Ubiquitin Code

Ubiquitylation is involved in numerous important cellular processes such as proteasomal degradation, DNA repair, protein sorting, and signal transduction. The ubiquitin function is relied on eight structurally distinct ubiquitin chains of different lengths, but our knowledge of the relationship between their topology and functional outcomes is still insufficient. To understand the ubiquitin code, it is essential to develop new methods for analyzing linkage types, chain lengths, and complexity of ubiquitylation.




Hikaru Tsuchiya

Figure 3.
The Cdc48/p97-RAD23 axis is a major route to the proteasome
Proteasomal degradation is mainly regulated by indirect substrate sorting pathway by the ubiquitin-selective chaperone Cdc48/p97 and the shuttling factors Rad23 and Dsk2.

We have developed a highly sensitive MS/MS-based quantification method for ubiquitin chains. The method allows us to analyze linkage-type selectivity of ubiquitin decoder proteins at endogenous experimental setting. We recently identified the main pathway targeting the K48-linked ubiquitylated substrates for proteasomal degradation (Fig. 3). We are further analyzing the decoder proteins throughout the ubiquitin-mediated pathways to reveal the ubiquitin network.

2. Roles of Novel Ubiquitin Codes

Using quantitative mass spectrometry, we recently identified multiple chemical modifications of ubiquitin itself. Acetylation of ubiquitin inhibits the elongation of particular ubiquitin chains, whereas phosphorylation of S65 ubiquitin stimulates ubiquitin chain synthesis for mitophagy. More recently, we identified more complexed ubiquitin chains branched at K48 and K63. The K48/K63 branched chains act as a unique coding signal that specifically affects recognition by downstream reader proteins to enhance NF-κB signaling. These novel ubiquitin codes greatly expand ubiquitin functions. We further explore additional roles and regulatory mechanisms of these novel ubiquitin codes.

Fumiaki Ohtake

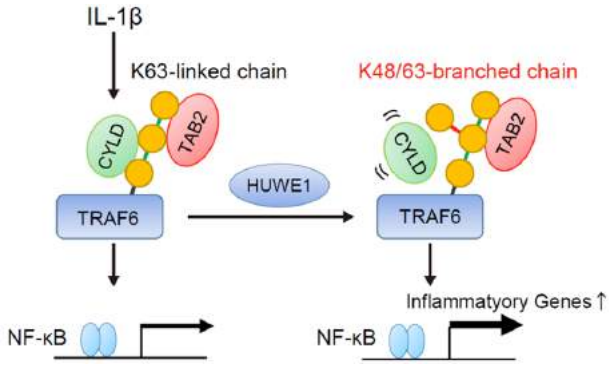


Figure 4.
The K48/K63 branched ubiquitin chains regulate NF-κB signaling pathway

Upon IL-1β stimuli, two ubiquitin ligases, TRAF6 and HUWE1 cooperatively assemble K48/K63 branched chains to amplify NF-κB signaling.

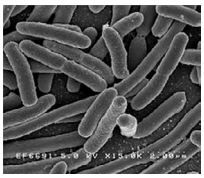
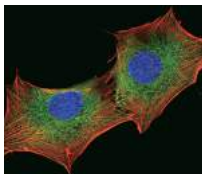
On-going Projects

1. **Regulations of the proteasome to adapt to environmental stress**
2. **Exploring proteasome cofactors as therapeutic targets**
3. **Generation of mouse models of proteasome-related diseases**
4. **Developing methods to analyze ubiquitin chain architecture**
5. **Roles of the branched ubiquitin chains in protein degradation and signaling**

Project Leader **Hisao Masai** Genome Dynamics Project

Genome Replication and Maintenance:
In search for unexplored message of the genome

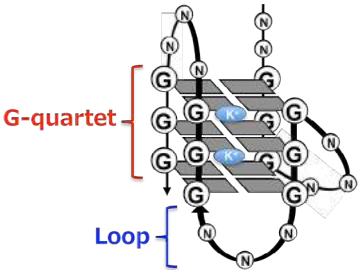
Precise duplication of genetic materials is central to the stable maintenance of genomes through generations. Defects in the genome copying processes would generate genomic instability which could ultimately result in various diseases including cancer. The goal of our studies is to understand the molecular basis of how the huge genomes are accurately replicated and the precise copies of the genetic materials are inherited to the next generation. Three billion base pairs of the human genome (2 meter long) are replicated with almost no errors during the 6-8 hr time span of the cell cycle. This requires an extreme level of coordination of temporal and spatial arrangements of chromatin organization and signaling events for initiation of DNA replication.

"We are trying to decipher 'unexplored message' of the genome that may play crucial roles in shaping the chromosomes, copying and reading out the information, and even in causing detrimental diseases."

We recently discovered novel and crucial roles of non-standard DNA structures in regulation of DNA replication and transcription. Notably, we found that G-quadruplex structures, which are widely present on genomes (more than 370,000 on the human genome), regulate organization of chromatin architecture and initiation of DNA replication. Our major goal is to establish a novel principle of the genome by elucidating the fundamental and universal functions of G-quadruplex and other non-B type DNA structures in regulation of various genome functions.

Through these efforts, we will also explore the possibility that mutations found in various diseases including cancer are related to alteration of these non-B DNA structures, which are likely to be essential components of genomes but somehow have been disregarded in the past.



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Genome Dynamics

Cdc7 kinase as a modulator of chromosome transactions

Dbf4/ASK

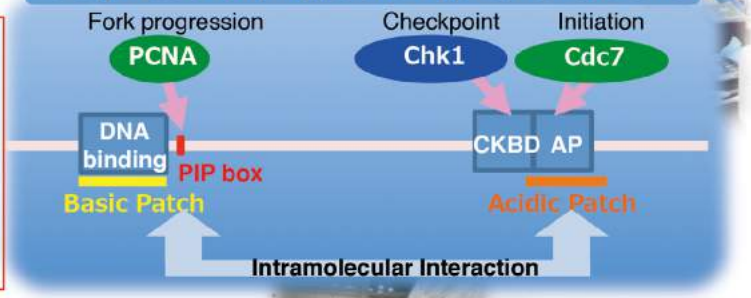
Cdc7

- Mcm: Replication initiation
- Claspin/Mrc1: Replication Checkpoint
- Rad18: Trans-lesion DNA synthesis/ repair
- Mer2: Meiotic recombination
- Rec8: Lsr4: Meiotic cell division
- HP1: Heterochromatin formation
- H3 T45: Histone modification
- Caf1: Chromatin reconstruction
- Mrc1, Ams2, Eco1: Protein degradation
- Top2A: Centromere regulation
- TDP43: Protein aggregation
- Mus4-Mus81: Homologous recombination

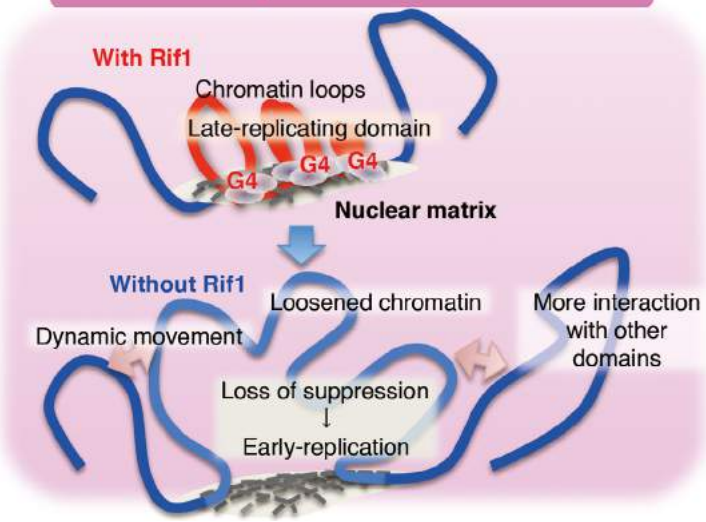
Our Major Projects

1) Universal mechanisms of DNA replication
2) Cellular responses to replication stress
3) Unusual DNA structures (G-quadruplex etc.)
4) DNA replication and development
5) Novel drugs and therapies for cancer

Claspin as a landing pad for replication proteins



Rif1 and G4 as organizers of chromatin architecture



Genome Dynamics

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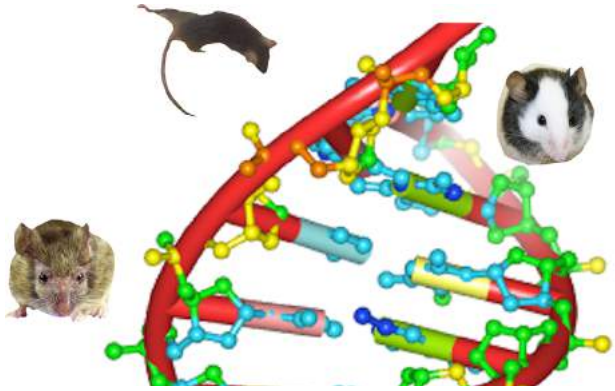
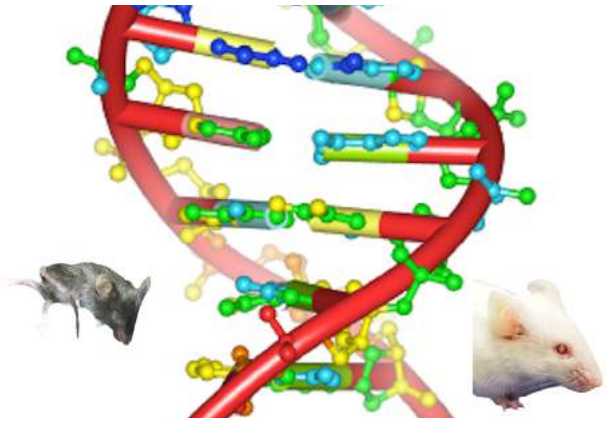
Project Leader **Yoshiaki Kikkawa** Mammalian Genetics Project

Gene Discovery: Phenotype- and gene-driven approaches to discovering disease-associated genes in mice

Mouse disease models were contributed the identification of the causes of pathogenic mechanisms. Their demand will be increased because generic factors and molecular mechanisms of the most genetic disease of human are still unknown in the most genetic disease. In particularly, mouse disease models are important tools for discovering the genes that are responsible for genetic diseases, allowing the processes that regulate the onset of genetic diseases, and evaluation of the effectiveness of a new drug; therefore, the establishment is essential study. We aim the establishment of novel mouse disease models for phenotypic analysis of genetic diseases in human and identification of the causes of pathogenic mechanisms by approaches of the forward and reverse genetics.



"We identify genes associated with human diseases from mutant mice and develop new mouse models for human diseases."



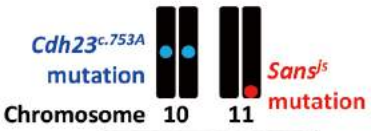
Mammalian Genetics

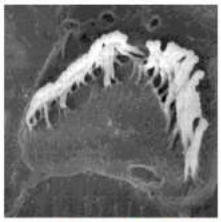
Main project: Genetics of deafness

Hearing loss is the most common sensory disease in the human population and severely affects the quality of life. We continues to make very significant advances in the understanding of the development, transduction and homeostasis of the auditory system, employing the mouse mutants. We utilize the similarities between the mouse and human genomes, and between the physiology and anatomy of their auditory systems, for the discovery and characterization of genes involved in deafness.

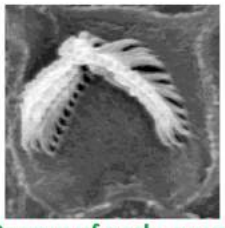
Current topic

Identification of a modifier gene for progressive hearing loss





Development of early-onset degeneration of stereocilia

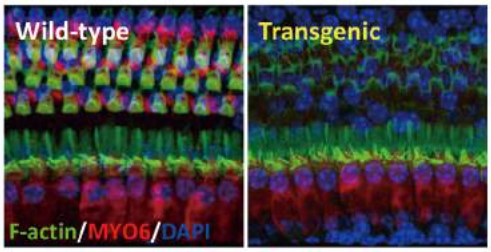


Rescue of early-onset degeneration of stereocilia

Yuki Miyasaka

Epistasis between the homozygous *Cdh23*$^{c.753A}$ and heterozygous *San*^{js} mutation in early-onset degeneration of stereocilia, and phenotypic rescue by knock-in (KI) via genome editing of *Cdh23*$^{c.753A}$ mutation.

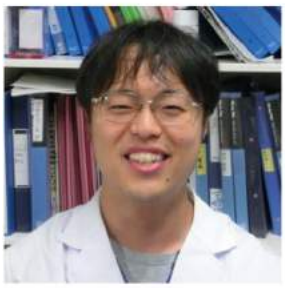
Projects in progress

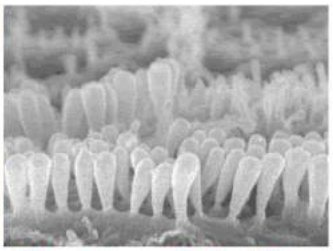


Selective ablation of outer hair cells

Kunie Matsuoka

Establishment of novel mouse models for human deafness

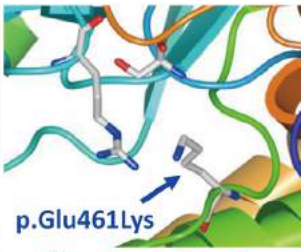




Short stereocilia in *Whrn* mutant mouse

Shumpei Yasuda

Elucidation of mechanisms for stereociliary shortness in Whrlin (*Whrn*) mutation



Novel mutation in myosin VI gene

Yuta Seki

Functional analysis of novel mutations associated with hearing loss

Mammalian Genetics

Project Leader **Fumihiko Yasui** Viral Infectious Diseases Project

Control of viral infectious diseases: Virology, immunology, vaccinology and therapy

Our project studies the virology, immunology, vaccinology and therapy of incurable viral diseases. We currently focus on liver diseases, influenza and dengue fever. However, the lack of suitable infection models in in vitro and in vivo has hampered the clarification of pathogenesis by these virus infections. To overcome the problems, we have been developing various animal models including transgenic mice, humanized mice with human liver cells, monkeys and tree shews. We also investigate the precise mechanisms by which host factors regulate viral growth.

"We are studying to clarify the mechanisms underlying development of severe acute inflammation and establishment of chronic infection by viruses through the development of suitable animal models that are capable of infecting viruses."

Hepatitis

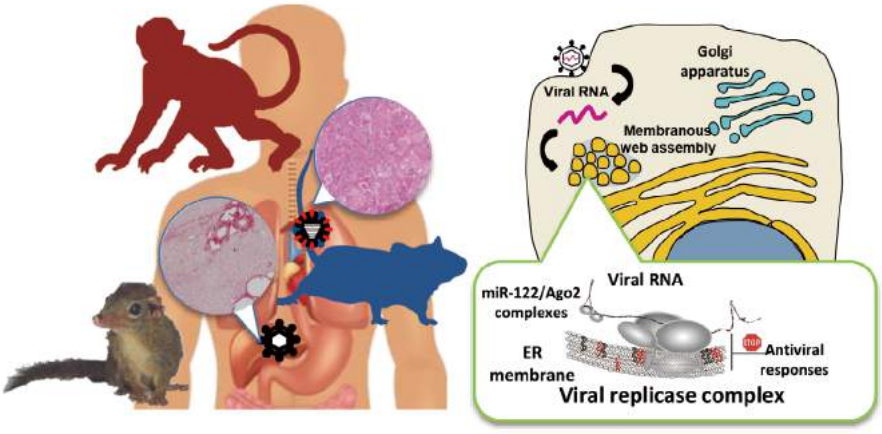
- Identification of host factors regulating virus growth.
- Elucidation of the mechanisms underlying pathogenesis caused by hepatitis virus infection.
- Development of therapeutic vaccine and drug for chronic HBV/HCV infection and other liver diseases.

Influenza

- Elucidation of the mechanisms by which highly pathogenic Flu causes severe pneumonia.
- Development of novel vaccine and therapeutic drug against highly pathogenic Flu and seasonal Flu.

Dengue fever

- Development of suitable animal models to study vaccine efficacy and pathogenesis of dengue fever.
- Development of novel vaccine for all serotypes of DENV.



Tokunaga Y., Osawa Y., Ohtsuki T., Hayashi Y., Yamaji K., Yamane D., Hara M., Munekata K., Tsukiyama-Kohara K., Hishima T., Kojima S., Kimura K., Kohara M. (2017) Selective inhibitor of Wnt/β-catenin/CBP signaling ameliorates hepatitis C virus-induced liver fibrosis in mouse model. ***Sci Rep.*** 7, 325.

Sanada T., Hirata Y., Naito Y., Yamamoto N., Kikkawa Y., Ishida Y., Yamasaki C., Tateno C, Ochiya T, Kohara M. (2016) Transmission of HBV DNA mediated by ceramide-triggered extracellular vesicles. ***Cell Mol Gastroenterol Hepatol.*** 3, 272-283.

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Sanada T, Tsukiyama-Kohara K, Yamamoto N, Ezzikouri S, Benjelloun S, Murakami S, Tanaka Y, Tateno C, Kohara M. (2016) Property of hepatitis B virus replication in Tupaia belangeri hepatocytes. ***Biochem Biophys Res Commun.*** 469, 229-235.

Yamamoto N, Sato Y, Munakata T, Kakuni M, Tateno C, Sanada T, Hirata Y, Murakami S, Tanaka Y, Chayama K, Hatakeyama H, Hyodo M, Harashima H, Kohara M. (2016) Novel pH-sensitive multifunctional envelope-type nanodevice for siRNA-based treatments for chronic HBV infection. ***J Hepatol.*** 64, 547-555.

Ohtsuki T., Kimura K., Tokunaga Y., Tsukiyama-Kohara K., Tateno C., Hayashi Y., Hishima T., Kohara M. (2015) ***J. Virol.*** 90:300-307.

Viral Infectious Diseases

Topics of our research

Selective inhibitor of Wnt/β-catenin/CBP signaling ameliorates hepatitis C virus-induced liver fibrosis in mouse model

Chronic hepatitis C virus (HCV) infection is one of the major causes of serious liver diseases, including liver cirrhosis. We investigated the effects of a β-catenin/CBP inhibitor on liver fibrosis. PRI-724, a selective inhibitor of β-catenin/CBP, reduced liver fibrosis in HCV-Tg mice while attenuating αSMA induction. PRI-724 led to increased levels of matrix metalloproteinase (MMP)-8 mRNA in the liver, along with elevated levels of intrahepatic neutrophils and macrophages/monocytes. These results suggest that inhibition of hepatic stellate cells activation and induction of fibrolytic cells expressing MMP-8 contribute to the anti-fibrotic effects of PRI-724.

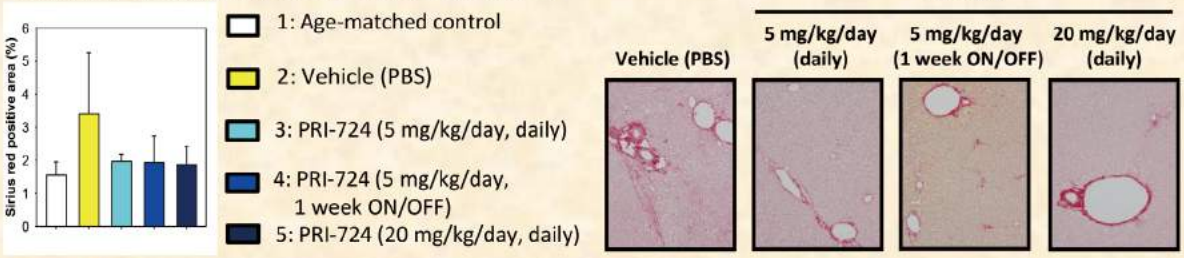
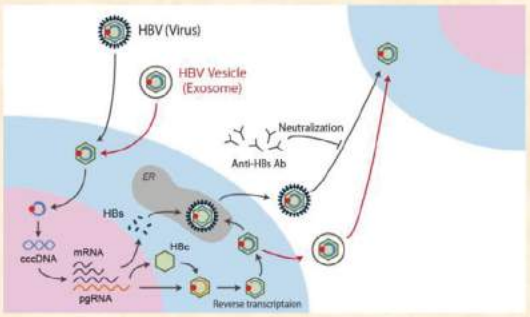
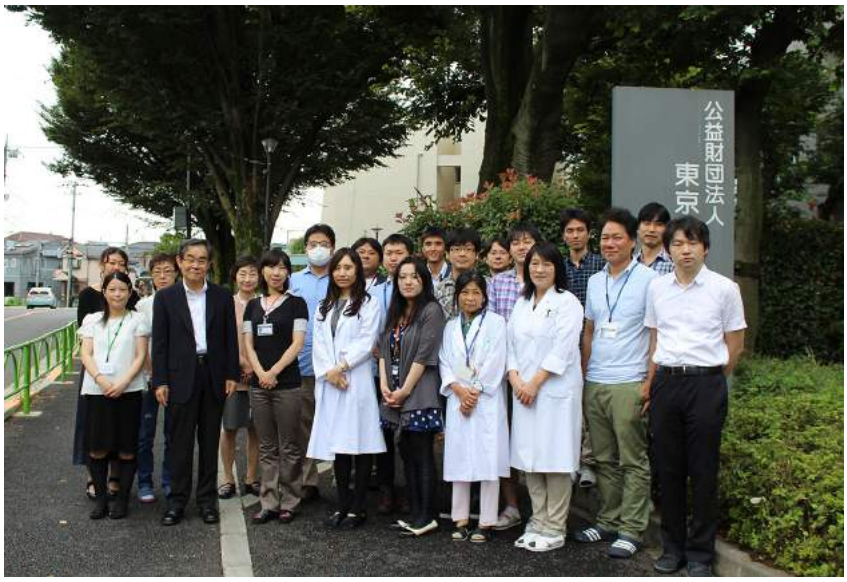


Figure. PRI-724ameliorates hepatitis C virus-induced liver fibrosis.

Transmission of HBV DNA Mediated by Ceramide-Triggered Extracellular Vesicles

Extracellular vesicle is a nanovesicle that shuttles proteins, nucleic acids, and lipids, thereby influencing cell behavior. We showed that ceramide-triggered extracellular vesicles work as DNA cargo for hepatitis B virus-DNA and are capable of trasmitting to naive hepatocytes. Further, we demonstrated that the transmission of hepatitis B virus-DNA via these extracellular vesicles is resistant to antibody neutralization.





Members

Michinori Kohara
Tsubasa Munakata
Yasuyuki Miyazaki
Daisuke Yamane
Takayuki Hishiki
Kenzaburo Yamaji
Naoki Yamamoto
Chun-Chieh Lin
Takahiro Ohtsuki
Keisuke Munekata
Yuko Tokunaga
Takahiro Sanada
Tomoko Honda

Viral Infectious Diseases

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

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EV71 antigens in the spinal cord of SCARB2 tg mice

Project Leader **Satoshi Koike** Neurovirology Project

Protecting the Central Nervous System from Infectious Diseases

"The development of vaccines and antiviral drugs, and the use of experimental models for the evaluation of these agents are important for controlling viral infections. We study the basic principles of neurotropic enterovirus infection to develop new technologies to control infectious diseases."

Enterovirus 71 (EV71) belongs to human enterovirus species A of the genus Enterovirus within the *Picornaviridae* family, and it is known to be one of the causative agents of hand-foot-and-mouth disease (HFMD). HFMD is considered to be a mild and self-limiting disease in general. However, in some infants and young children, HFMD caused predominantly by EV71 can be complicated by neurological manifestations. Thus, EV71 infection is a serious public health concern. Unfortunately, there is still very little information concerning EV71 pathogenesis, and vaccines or anti-EV71 drugs have yet to be developed.

Members

Ken Fujii

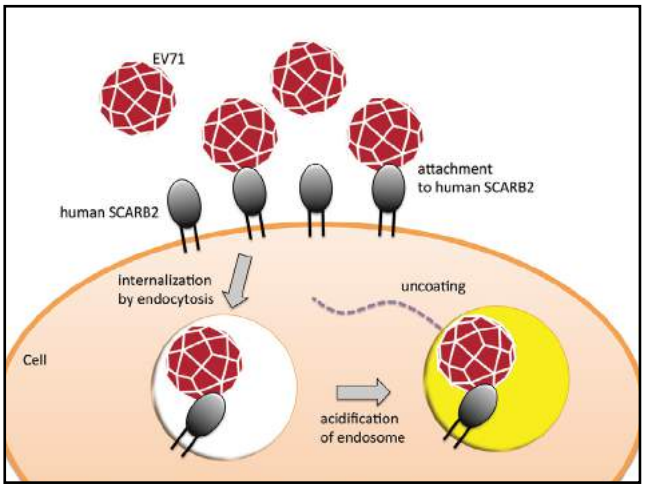
Kyosuke Kobayashi

Neurovirology

Research Topics

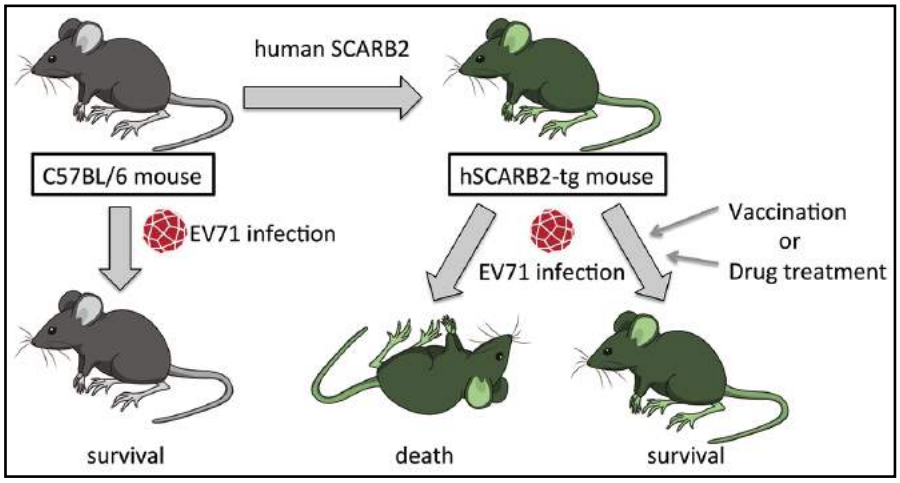
Mechanism of Enterovirus 71 infection

We recently found that Scavenger receptor B2 (SCARB2) is a receptor for EV71. SCARB2 plays a central role in early stages of EV71 infection. SCARB2 is able to mediate binding of the virus at the cell surface, internalization of the virus and initiation of uncoating.



Development of an animal model for Enterovirus 71 infection

The transgenic mouse expressing human SCARB2 is susceptible to EV71. It is a useful model for the study of EV71 pathogenesis and vaccine efficacy test.



Neurovirology

Nishimura, T., Kaminuma, O., Saeki, M., Kitamura, N., Matsuoka, K., Yonekawa, H., Mori, A., and Hiroi, T. (2016) "Essential contribution of CD4+ T cells to antigen-induced nasal hyperresponsiveness in experimental allergic rhinitis." ***PLOS ONE.*** 11, e0146686.

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Yokoyama, S., Takada, K., Hirasawa, M., Perera, LP., and Hiroi, T. (2011) "Transgenic mice that overexpress human IL-15 in enterocytes recapitulate both B and T cell-mediated pathologic manifestations of celiac disease." ***J Clin Immunol*** 31, 1038-1044.

Kaminuma, O., Kitamura, F., Miyatake, S., Yamaoka, K., Miyoshi, H., Inokuma, S., Tatsumi, H., Nemoto, S., Kitamura, N., Mori, A., and Hiroi, T. (2009) "T-box 21 transcription factor is responsible for distorted TH2 differentiation in human peripheral CD4+ T cells." ***J Allergy Clin Immunol*** 123, 813-823.

Yokoyama, S., Watanabe, N., Sato, N., Filkoski, L., Tanaka, T., Miyasaka, M., Waldmann, T.A., Hiroi, T., and Perera, PL. (2009) "Antibody-mediated blockade of IL-15 signaling reverses autoimmune intestinal damage in a mouse model of celiac disease." ***Proc. Natl Acad Sci USA.*** 106, 15849-15854.

Project Leader **Takachika Hiroi** Allergy and Immunology Project

Allergy and Mucosal Immunology:

Investigating molecular mechanisms of sublingual immunotherapy (SLIT) and developing therapeutic biomarkers for allergic diseases.

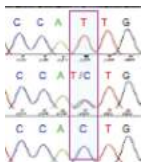
Japanese cedar pollen allergy is the major allergic disease in Japan, and the approximately 35% of Japanese people are affected. In recent years, sublingual immunotherapy has been recognized as an effective curative treatment for the allergic diseases.

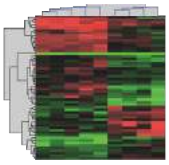
However, the molecular mechanisms of mucosal tolerance still remain unclear. In our laboratory, we focus on the following subjects.

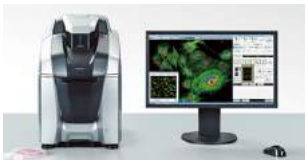
"We are developing new diagnostics and treatments for allergies."

1. Search for effective biomarkers of SLIT

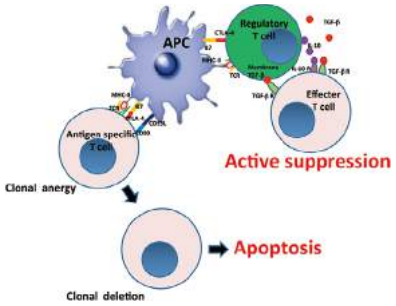
- CNVs
- SNPs
- Epigenome
- Proteome, etc.







2. Elucidation of molecular mechanisms to induce immunological tolerance by SLIT

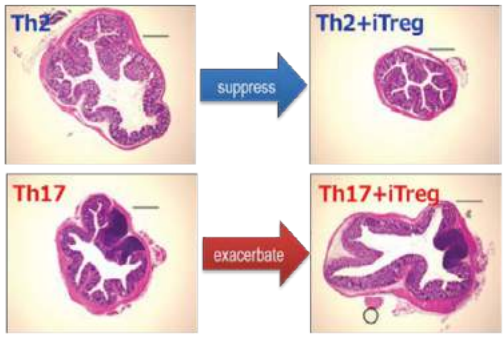


- iTregs
- Apoptosis
- CTLA-4
- TGF-β
- IL-10 etc.

Allergy and Immunology

Current Topics of Another Research

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



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

(Watanabe N, et al. (2016) *PLOS ONE*, 11: e0150244.)

2. The mechanisms of allergic inflammation investigated using "cloned mice" of antigen-specific CD4⁺ T cells

Allergens bind to a T-cell receptor (TCR) on CD4⁺ T cells and induce a series of immune reaction. TCR-transgenic mice are important tools to analyze antigen-response mechanisms, but their non-endogenous TCR might induce immune responses in a manner distinct from those induced by the endogenous TCR. Cloning by the nuclear transfer method enables us to produce animals that retain the donor genotypes in all tissues including germline and immune systems. We generated cloned mice carrying TCR genes of antigen-specific CD4⁺ T cells that have rearranged in an endogenous manner. These cloned mice express antigen-specific TCR under the intrinsic promoter, and present a unique animal model with which one can investigate CD4⁺ T cell-mediated pathogenesis and cellular commitment in immune diseases.

(Kaminuma O, et al. (2017) *EMBO Rep.* 18: 885-93.)

Allergy and Immunology

1. Endo F, et al.: Development of a simple and quick immun-chromato-graphy method for detection of anti-HPV-16/-18 antibodies. ***PLoS One.*** 2017;12(2):e0171314.

2. Sakurai A, et al.: Fluorescent immunochromatography for rapid and sensitive typing of seasonal influenza viruses. ***PLoS One.*** 2015;10(2):e0116715.

3. Nakano S, et al.: Immunochromato-graphic Detection of Serum Anti-a-Galactosidase A Antibodies in Fabry Patients after Enzyme Replacement Therapy. ***PLoS One.*** 2015;10(6):e0128351.

4. T. Hashimoto and F. Shibasaki. Hypoxia-inducible factor as an angiogenic master switch. ***Front Pediatr.*** 2015;3:33.

5. Sakurai A, et al.: Multi-colored immunochromatography using nanobeads for rapid and sensitive typing of seasonal influenza viruses. ***J Virol Methods.*** 2014;209:62-8.

6. Sakurai A, et al.: Broad-spectrum detection of H5 subtype influenza A viruses with a new fluorescent immunochromatography system. ***PLoS One.*** 2013;8(11):e76753.

7. Nakano S, et al.: Development of a highly sensitive immuno-PCR assay for the measurement of alpha-galactosidase A protein levels in serum and plasma. ***PLoS One.*** 2013;8(11):e78588.

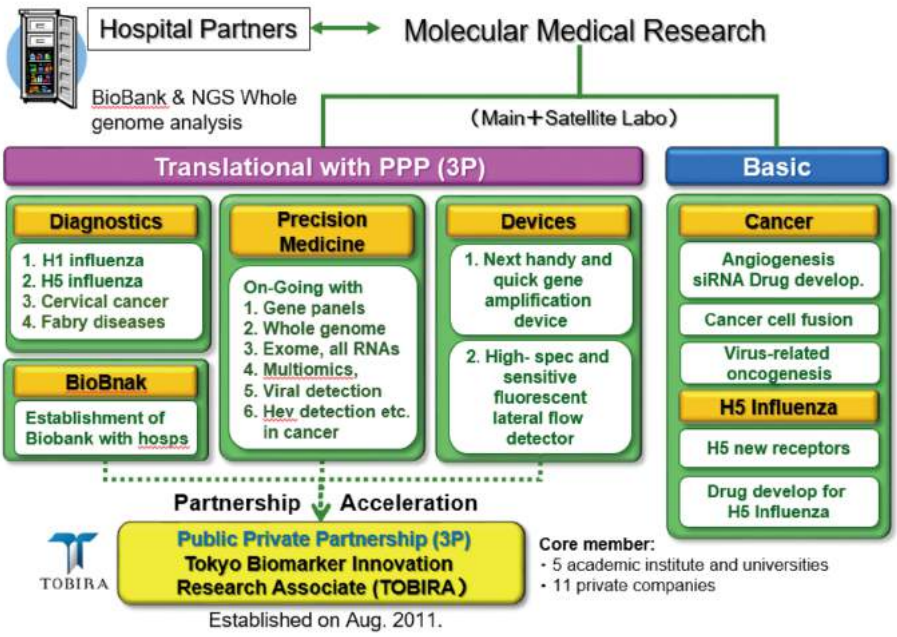
8. Li Chen, et al.: Mammalian Tumor Suppressor Int6 Specifically Targets HIF-2αTo Degradation by Hypoxia-And pVHL- Independent Regulation. ***J. Biol. Chem.*** 282. 12707-12716 (2007)

9. Chen L, et al.: Int6/eIF3e Silencing Promotes Functional Blood Vessel Outgrowth and Enhances Wound Healing by Upregulating HIF2-a Expression. ***Circulation*** 122: 910-919 (2010)

Project Leader **Futoshi Shibasaki** Molecular Medical Research Project

Translational Research for Cancer and Infectious Diseases: Basic to Applied Science

Recent discoveries of biomarkers and novel technologies have opened the new aspects of the mechanisms and drug developments especially in cancer and infectious diseases. In basic science, whole genome reads by next generation sequence (NGS) led to the paradigm shift from small fragment to whole genome analysis. The detection of frequent mutation in exon sequences in important kinases and other growth factor genes helps us to precise selection of new anti-cancer drugs (Precision Medicine) to ameliorate the prognosis even though the cancer is extremely malignant. Our specific aims are to perform the basic science and be to develop the new findings to the translational research.



In basic Research, we focusing on the mechanisms of cancer angiogenesis and the drug development using siRNA, and on malignant transformation and metastasis caused by cell fusion. The novel receptor candidate for H5 influenza virus entrance into cell surface would be a drug target.

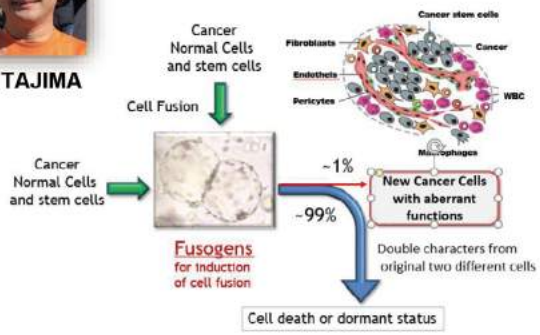
In clinical and translational research, we focus on the establishment of platform to perform “Precision Medicine” by Whole genome analysis with next generation sequence in collaboration with Metropolitan Hospitals. For Private Public Partnership (3P), we have already established the Bio-Consortium “Tokyo Biomarker Innovation Research Association” (TOBIRA).

Molecular Medical Research

Malignant progression in cancer to stem cell fusion

Y. TAJIMA

Cancer cells fused MSC promote metastasis than original cancer cells



Development of drugs against highly pathogenic avian influenza A viruses

N. KAJIWARA

H5N1 has multiple basic amino acids at HA cleavage site.

H1N1 Cleavage site
KYVRSTKLRMVTGLRNIPSIQYR----/GLF
H3N2
KYVKQNTLKLATGMRNVPEKQTR----/GLF
H5N1
HA KYVKSNRLVLATGLRNSPQRERRRKKR/GLF

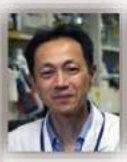
The goal of our research is to provide new insights into the molecular mechanism of H5N1 infection as well as the development of novel antiviral drugs.

Rapid gene amplification for infections and cancers

We aim to develop a rapid and handy device to amplify the target DNAs and RNAs for diagnosis of infectious diseases and cancers.

By N. N. and M. U.

Drug development of Int6-siRNA



A. IRIE

S. GOTO

Int6 is a key factor to negatively regulate HIF2a-induced angiogenesis and cell protection. The specific siRNA against *int6* would be a possible candidate to treat ischemic diseases and cancers.

D. S

Secretary Y. K

Secretary M. Y

Endo F, et al.: ***PLoS One***. 2017; 12: e0171314.

Osawa Y, et al.:Inhibition of Cyclic Adenosine Monophosphate (cAMP)-response Element-binding Protein (CREB)-binding Protein (CBP)/β-Catenin Reduces Liver Fibrosis in Mice. ***EBioMedicine***. 2015; 2: 1751-8

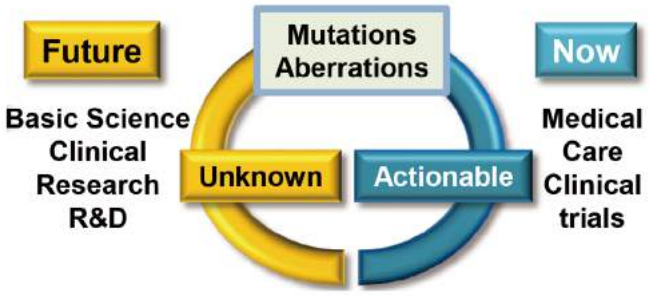
Senior Research Scientist **Keisuke Oboki**

Translational Research for Cancer

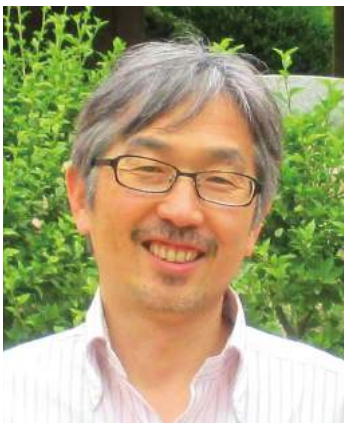
Genomics data brought by clinical specimens can now induce some medical actions that have never been before. We aim to build valuable research questions from clinical genomics data, and to progress basic science and clinical medicine.

Genomics as a *"lingua franca"* both for basic science and clinical medicine

With M. O,., T. H., and H. A.



Molecular Medical Research



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Shimozawa A, Ono M, Takahara D, Tarutani A, Imura S, Masuda-Suzukake M, Higuchi M, Yanai K, Hisanaga SI, Hasegawa M . (2017) "Propagation of pathological α-synuclein in marmoset brain. ***Acta Neuropathol Commun.*** 5,12.

Tarutani A, Suzuki G, Shimozawa A, Nonaka T, Akiyama H, Hisanaga S, Hasegawa M . (2016) "The Effect of Fragmented Pathogenic α-Synuclein Seeds on Prion-like Propagation." ***J Biol Chem*** 291, 18675-18688.

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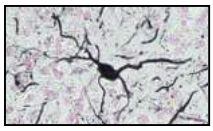
Taniguchi-Watanabe S, Arai T, Kametani F, Nonaka T, Masuda- Suzukake M, Tarutani A, Murayama S, Saito Y, Arima K, Yoshida M, Akiyama H, Robinson A, Mann D, Iwatsubo T, Hasegawa M. (2016) "Biochemical classification of tauopathies by immunoblot, protein sequence and mass spectrometric analyses of sarkosyl-insoluble and trypsin-resistant tau." ***Acta Neuropathol*** 131, 267-280 .

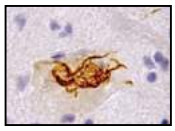
Project Leader **Masato Hasegawa** Dementia Research Project

Prion-like propagation of tau, α-synuclein and TDP-43 in neurodegenerative diseases

Neurodegenerative diseases are characterized by progressive degeneration of subsets of neurons and gliosis. Many of the diseases are accompanied with intracellular amyloid-like protein pathologies, such as tau in Alzheimer's disease (AD), α-synuclein in dementia with Lewy bodies (DLB) and TDP-43 in amyotrophic lateral sclerosis (ALS) and frontotemporal dementias (FTLD). Importantly, the distributions and spread of these proteins are closely correlated with clinical presentation and disease progression. However, little attention had been given to the questions of why these diseases are progressive, and why the pathologies spread to different brain regions during the course of the diseases.



Tau in AD

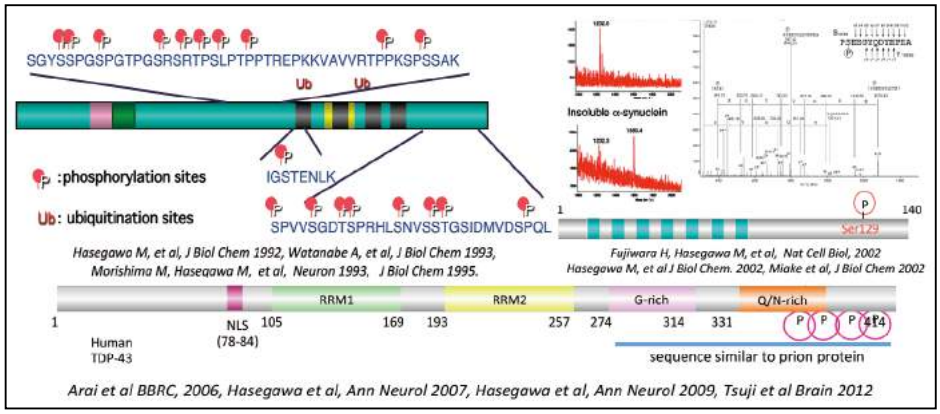


TDP-43 in ALS

α-synuclein in DLB

"Emerging evidence indicates that intracellular amyloid-like proteins have prion-like properties and propagate from cell to cell by converting normal proteins into abnormal forms. We are trying to elucidate the molecular mechanisms of 'prion-like propagation of these proteins."

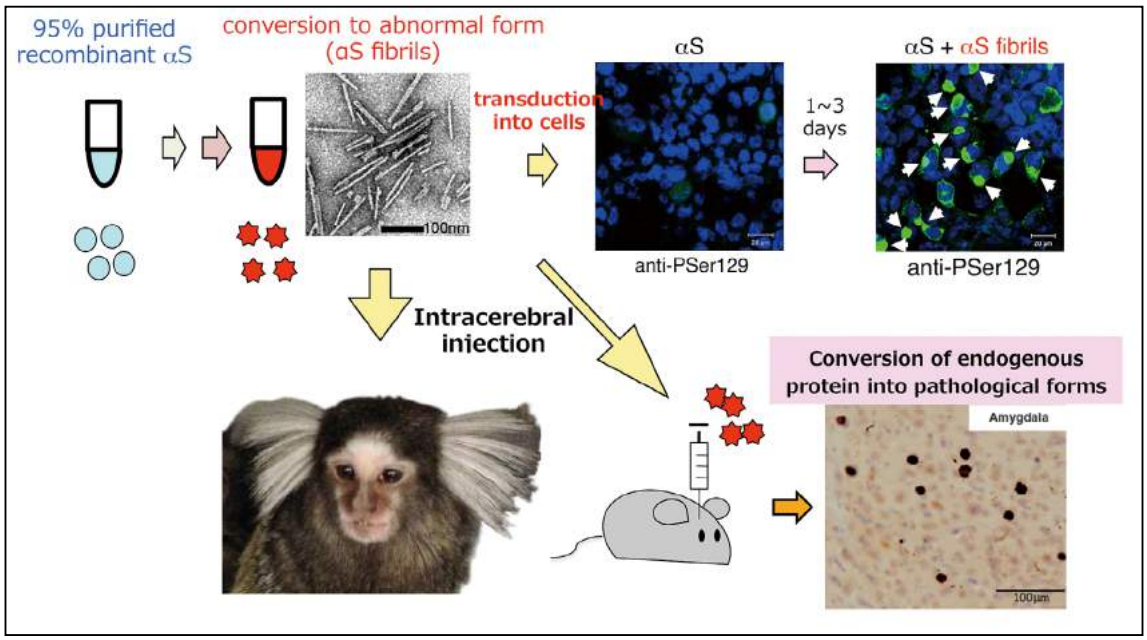
We have been investigating these intracellular abnormal proteins in brains of patients, proteinchemically using LC/MS/MS, immuno-histochemically with specific antibodies and ultrastructuraly. And we found that all of these proteins are accumulated in brains of patients as fibrous or filamentous forms in hyperphosphorylated and partially ubiquitinated states.



Schematic diagrams of human tau, α-synuclein and TDP-43.

Dementia Research

To investigate the molecular mechanisms of aggregation of these proteins, we established seed-induced aggregation model which recapitulate the pathological protein aggregation in vitro, cultured cells and in brains of animals (mouse and marmoset) and proposed a hypothesis “prion-like propagation of these intracellular pathological proteins in brain”. These models are highly useful not only for clarifying the molecular mechanisms involved in the pathogenesis and progression of neurodegenerative diseases but also for the development of disease modifying drugs and therapy.



Nonaka T et al. Phosphorylation of TAR DNA-binding Protein of 43 kDa (TDP-43) by Truncated Casein Kinase 1δ Triggers Mislocalization and Accumulation of TDP-43. ***J. Biol. Chem.*** 291: 5473-5483, 2016

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Nonaka T et al. Seeded aggregation and toxicity of alpha-synuclein and tau: cellular models of neurodegenerative diseases. ***J. Biol. Chem.*** 285: 34885-34898, 2010

Senior Research Scientist **Takashi Nonaka**

Molecular mechanisms of cell-to-cell propagation of aggregated proteins

I’m studying molecular mechanisms of cell-to-cell propagation of aggregated proteins (tau, α-synuclein and TDP-43) in neurodegenerative diseases. Also, I’m trying to make in vitro and in vivo models recapitulating abnormal features found in cells of brains of patients using cultured cells and mice. These models will contribute not only to a better understanding of the mechanisms involved in these diseases, but also to the development of novel therapeutic strategies.

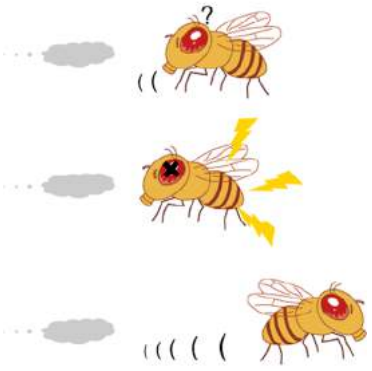
Dementia Research

Project Leader **Minoru Saitoe** Learning and Memory Project

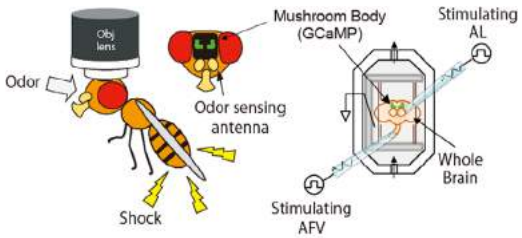
Investigating the Molecular Mechanisms that Generate Memory-encoding Neural Networks

Memories mold our personalities to make us who we are. Using powerful genetic tools, numbers of genes and neural substrates underlying memory-associated behaviors have been identified in Drosophila. Given these scientific backgrounds, we have investigated when, where and how identified memory-associated gene products function to produce memory-based behavior, and how the underlying mechanism is changed in response to changes in physical condition such as aging.
In addition to behavioral genetic approach, we employ in vivo and ex vivo imaging techniques to characterize physiological properties of memory-associated neural networks, and understand how memory-associated genes and neuromodulatory systems regulate function of these networks; how sensory information is associated and how memory information is stored in neural substrates and recalled upon receiving test stimuli.

"Combining of behavioral genetics and state-ofarts imaging techniques, we aim to understand how our brains store and retrieve memories."



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



Left, in vivo imaging of fixed fly under microscope is used to investigate activity of identified neurons and network during sensory association (odor and shock), reinforcement, storage and retrieval. Right, using ex vivo imaging we attempt to make artificial memory in cultured brain, thereby elucidate the whole picture of the memory-associated networks.

Ueno K, Suzuki E, Naganos S, Ofusa K, Horiuchi J, Saitoe M. (2017) "Coincident postsynaptic activity gates presynaptic dopamine release to induce plasticity in Drosophila mushroom bodies." ***eLife***, 6, e21076.

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Matsuno M, Horiuchi J, Yuasa Y, Ofusa K, Miyashita T, Masuda T, Saitoe M. (2015) "Long-term memory formation in Drosophila requires training-dependent glial transcription." ***J Neurosci*** 35, 5557-5565.

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Yamazaki D, Horiuchi J, Nakagami Y, Nagano S, Tamura T, Saitoe M. (2007) "The Drosophila DC0 mutation suppresses age-related memory impairment without affecting lifespan." ***Nat Neurosci*** 10, 478-484.

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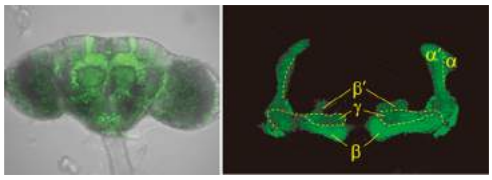
Learning and Memory

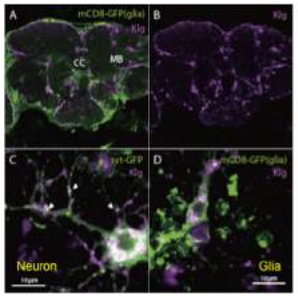
Current Research Topics

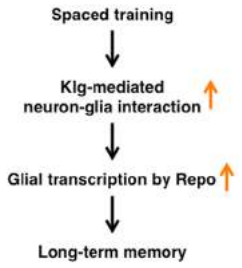
Encoding and decoding of memory: In Drosophila, the mushroom body (MB) is a neural center for olfactory memory. As described by Hermann Ebbinghaus (1885), repetitive olfactory conditioning with rest intervals, namely spaced training, stabilizes labile short-term memory (STM) into robust long-term memory (LTM), which requires transcriptional activity of CREB. Interestingly, STM and LTM are encoded in different subset of MB neurons. While aversive STM is encoded in gamma neurons, aversive LTM is encoded in alpha/beta neurons. We are interested in how such anatomical shifting is occurred during stabilization of STM to LTM, functional relationship between STM and LTM.



Structure of MBs and their lobe
Left: MBs in the fly brain expressing GFP.
Right: Subdivision of MB lobes derived from each type of MB neurons.

Neuron-glia interactions: Recent research demonstrates that neuron-glia communication is also important for memory formation. We have identified a cell adhesion molecule Klingon (Klg) that mediates neuron-glia communication required for LTM-based behavior. Currently, we are studying how Klg-mediated neuron-glia interaction regulates memory acquisition, stabilization and retrieval. Also, we are interested in how this mechanism is altered upon aging.



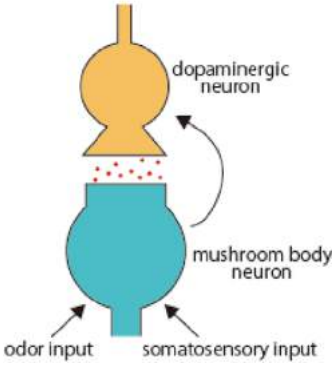


Klingon mediates neuron-glia interaction for LTM formation. A, B) Expression of Klingon (Klg) in the fly brain. C) Expression of Klg in neurons. D) Expression of Klg in glial cells.
Spaced training increases Klg-mediated neuron-glia interaction, thereby induces Repo-dependent glial transcription required for LTM.

Senior Research Scientist **Kohei Ueno**

Exploring Physiological Systems Underlying Learning and Memory

Neural plasticity is one of the important neurophysiological foundations of memory formation. To investigate the biological system, we have developed isolated brain method. In the isolated brain, if we simultaneously stimulate odor and somatosensory inputs, the neural activity in MB is enhanced for long-period. We believe that this physiological changes are basis of fly memory. Recently, we found that the plastic change depends dopamine
signaling, and the dopamine release for the plasticity requires MB activity. Thus, dopamine release is gated by postsynaptic neurons. We are trying to uncover the mechanism of this mode of transmission and test whether on-demand mode also works in other neuromodulatory systems and in other animals.



If mushroom body neurons are activated by two inputs, namely odor and somatosensory inputs, the activated mushroom body requires dopamine release from dopaminergic neurons.

Learning and Memory

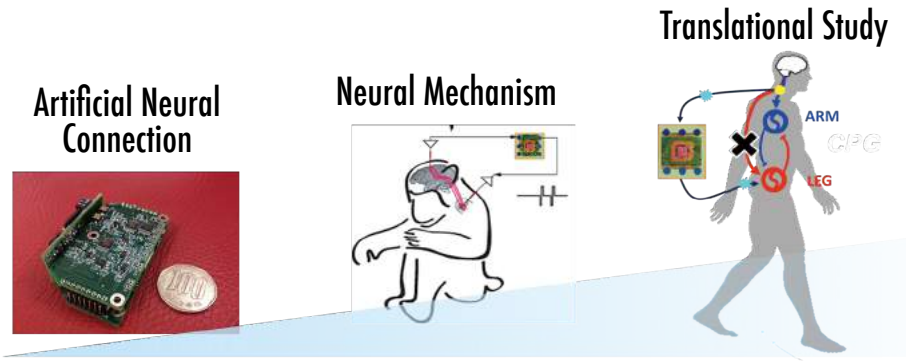
Project Leader **Yukio Nishimura** Neural Prosthesis Project

Restoring Lost Function After Neural Damage

Our research goal is to conceive innovative neruo-rehabilitation to restore lost functions after impairment of central nervous system, and to translate our findings into clinical applications capable of improving the quality of life for individual with neural damages.

"Bridging Damaged Neural Pathways using a Neural Interface."

Regaining the function of an impaired limb is highly desirable in individuals experiencing paralysis. Functional loss of limb control in individuals with spinal cord injury or stroke can be caused by transection of descending and ascending pathways.those connects cortical to spinal network, although neural circuits locate above and below the impaired site remains their function.



We are developing a neural interface which so-called "artificial neuronal connection (ANC)". The ANC bridges supra-spinal system and spinal network beyond the lesion site to restore lost function. We are conducting clinical trials to assess effectiveness of ANC in restoring motor function in paralyzed patients. We investigate neural changes that occur during recovery.

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Nishimura Y, Perlmutter SI, Fetz EE. (2013) "Restoration of upper limb movement via artificial corticospinal and musculospinal connections in a monkey with spinal cord injury." ***Front Neural Circuits.*** 7, 57.

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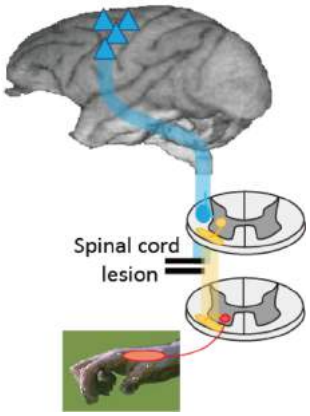
Neural Prosthesis

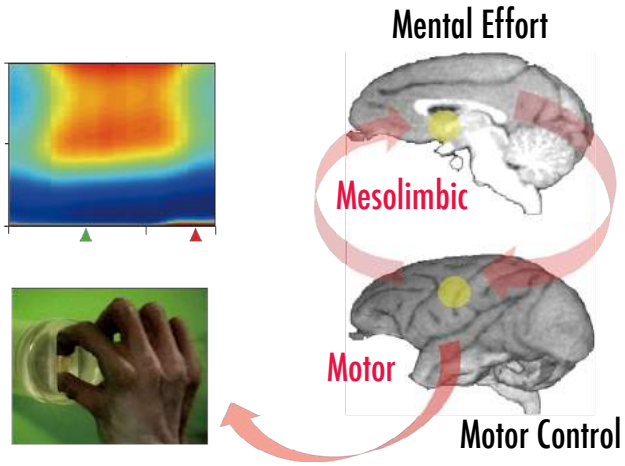
Neural Mechanisms of Functional Recovery

Using a large scale multichannel recording, pharmacological intervention, neuroanatomy, viral tools, computation and whole brain imaging, we seek to uncover the neural mechanisms underlying the voluntary limb movement in intact animals, as well as the processes that reestablish motor functions after neural damages such as spinal cord injury and stroke. We are also performing clinical studies to test the efficacy of the ANC in human patients.



Science. 2007, Brain 2009

Psychological Effect on Motor Control



PLoS ONE 2011, Science. 2015

Emotional states influence how we perform motor activities and how we perceive errors. Depression impedes and motivation enhances functional recovery after neuronal damage. However, the neuronal substrate underlying such psychological effects on functional recovery remains unclear. We investigate the neural substrate underlying such psychological effects on motor performance in human and animal model of neural damages.

Members

Yukio Nishimura
Toshiki Tazoe
Hiroaki Ishida
Nobuya Sano
Kei Obara
Yoshihisa Nakayama
Osamu Yokoyama
Michiaki Suzuki
Miki Kaneshige
Yu Shimada

Neural Prosthesis

Hashimoto M, Ho G, Sugama S, Takamatsu Y, Shimizu Y, Takenouchi T, Waragai M, Masliah E. Evolvability of Amyloidogenic Proteins in Human Brain. ***J Alzheimers Dis.*** 2018, 62:73-83.

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Takamatsu Y, Koike W, Takenouchi T, Sugama S, Wei J, Waragai M, Sekiyama K, Hashimoto M. Protection against neurodegenerative disease on Earth and in space. ***NPJ Microgravity*** 2016, 2: 16013.

Waragai M, Adame A, Trinh I, Sekiyama K, Takamatsu Y, Une K, Masliah E, Hashimoto M. Possible Involvement of Adiponectin, the Anti-Diabetes Molecule, in the Pathogenesis of Alzheimer's Disease. ***J Alzheimers Dis.*** 2016, 52:1453-1459.

Sekiyama K, Takamatsu Y, Koike W, Waragai M, Takenouchi T, Sugama S, Hashimoto M. Insight into the Dissociation of Behavior from Histology in Synucleinopathies and in Related Neurodegenerative Diseases. ***J Alzheimers Dis.*** 2016, 52:831-841.

Unit Leader **Makoto Hashimoto** Parkinson's disease Unit

Protection of neurodegenerative diseases

Research description

The number of patients with age-associated neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), is rapidly increasing worldwide. Consequently, huge costs for medical treatment and nursing care for these patients have become a serious socioeconomic dilemma. Nonetheless, extensive studies of amyloid immunotherapy in AD have been so far unsatisfactory. Thus, the development of an effective disease-modifying therapy is the highest priority in neurodegenerative disease research.

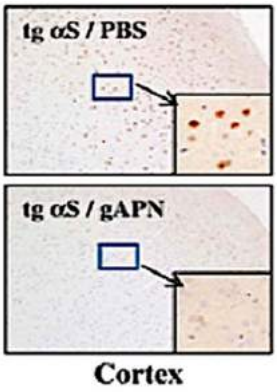


Fig. 1 APN ameliorates negeneration in mice.

In our laboratory, we seek to exploit a mechanism-based disease-modifying strategy for a-synucleinopathies, such as PD and de-mentia with Lewy bodies. In this context, we have a particular interest in the suppressive effect of adiponectin (APN) on neurodegeneration (Fig.1). We will also attempt to identify new molecules that could be useful for the prevention of neurodegenerative diseases. For such purposes, we cur-rently perform the Drosophila molecular genetics (Fig.2) in addition to cell biological and transgenic mice studies. Apparently, the results will be applicable to other diseases, including AD and Huntington's disease.

Members

Yoshiki Takamatsu
Masaaki Waragai
Hiromu Sugino
Yuka Shimizu

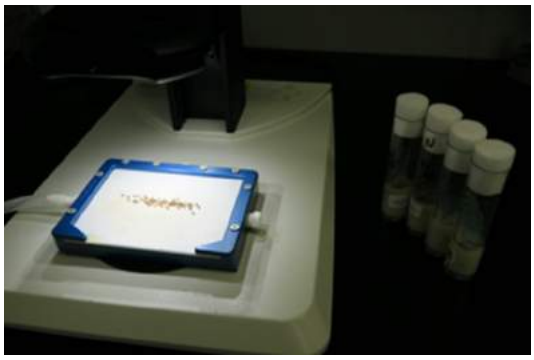


Fig. 2 Drosophila molecular genetics.

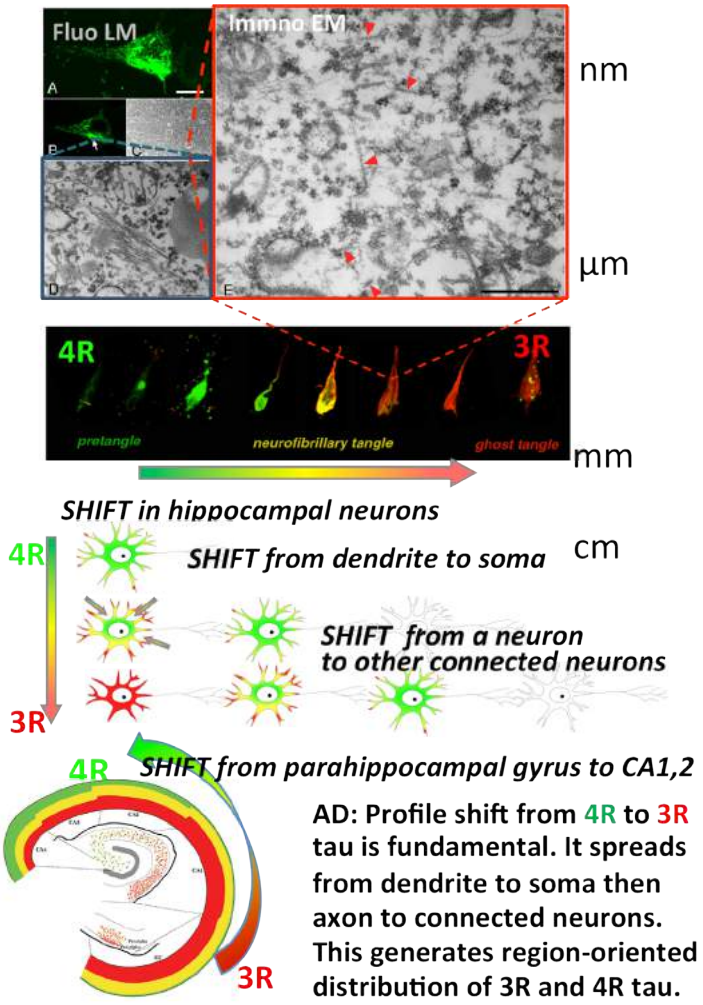
Parkinson's disease

Unit Leader **Toshiki Uchihara** Structural Neuropathology Unit

Correlating Clinical Diagnoses with Brain Lesion Progression in Alzheimer's and Parkinson's Diseases

Questions : AD, PD-selective vulnerability?
Challenge : Expand molecule-oriented view by tracing human brain lesions along connections.
Strategy : Seamless tracing from molecule to lesion distribution by integrating small parts into upper hierarchy.

"Identifying the earliest lesions and correlating them with clinical indices for early and specific diagnoses."



AD: Profile shift from 4R to 3R tau is fundamental. It spreads from dendrite to soma then axon to connected neurons. This generates region-oriented distribution of 3R and 4R tau.

PD: In contrast, αS deposition is initiated at axon terminal and spreads in retrograde direction to soma.

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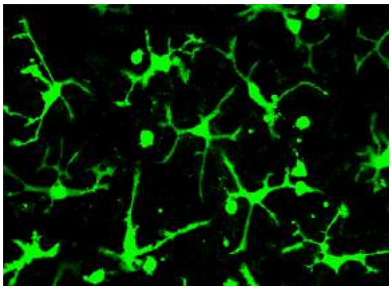
Project Leader **Hiroshi Sakuma** Developmental Neuroimmunology Project

Towards a Better Understanding of Neuro-immune Interactions in the Developing Brain

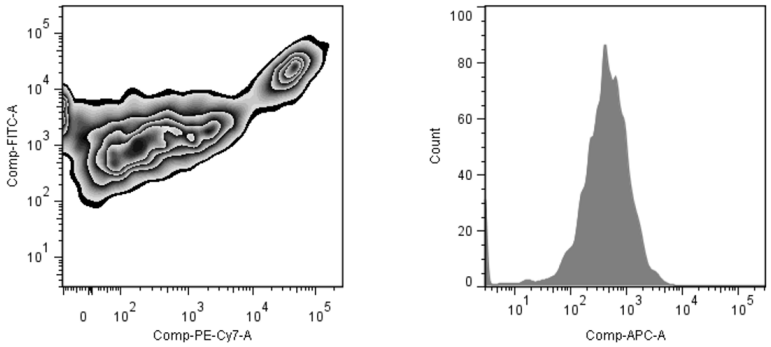


Our research focuses on the role of immune system in the developing brain. Immune and inflammatory responses not only combat pathogens but also play a variety of physiological roles in the central nervous system.
Microglia are brain-resident immune cells and play multiple roles in the protection from pathogens and the clearance of debris. In addition, recent studies have shed light on unexpected functions of microglia in the physiological condition. For example, microglia actively participate in the brain development by modulating synapses.

"We are investigating the mechanisms by which microglia maintain homeostasis in the developing brain."

Our main research areas include:

1) Development and differentiation of microglia
2) Neuron-microglia interaction
3) In-vitro differentiated myeloid cells for cell therapy
4) Autoantibodies associated with neurological diseases
5) New biomarkers for pediatric immune-mediated neurological diseases



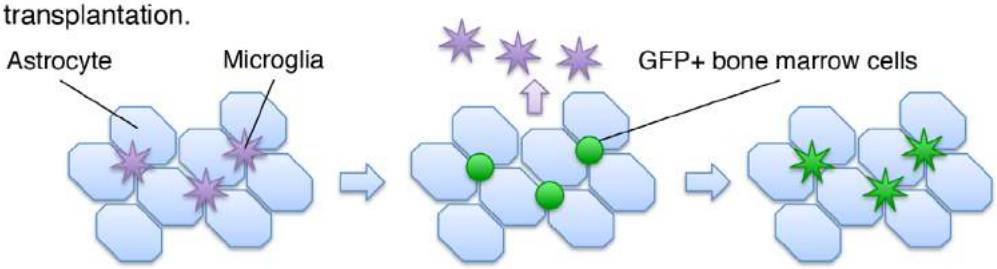
Flow cytometric analysis of microglia

Developmental Neuroimmunology

Research topic

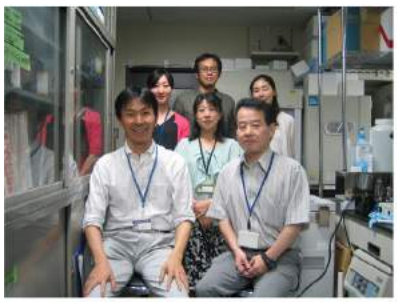
Astrocytes nurture microglia?

Microglial progenitors originate from yolk sac and develop into mature microglia in the fetal brain. This observation suggests that non-microglial brain cells support microglial development. We speculated that astrocyte-microglia interaction, both contact-dependent and -independent, is critical for phenotype acquisition of microglia. Based on this hypothesis, we have tried to induce microglia from hematopoietic stem-cells by co-culture with astrocyte. When bone-marrow lineage negative cells were co-cultured on astrocyte monolayer for one week, they develop into microglia-like cells characterized by process-bearing morphology and the expression of microglial markers including CX3CR1 and TREM-2. Differentiation of microglia-like cells was further facilitated by interleukin-34 and TGF-β. These findings provide theoretical basis for optimizing treatment of neurological diseases by hematopoietic cell transplantation.



Members

Hiroshi Sakuma	Tomonori Suzuki	Yasuo Hachiya
Takako Matsuoka	Taiki Shima	Hiroko Tada
Kuniko Kohyama	Hiroya Nishida	Masaharu Hayashi
Setsuko Hasegawa	Ayuko Igarashi	



Developmental Neuroimmunology

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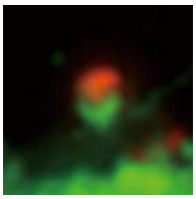
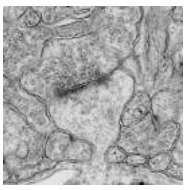
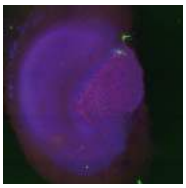
Project Leader **Kanato Yamagata** Synaptic Plasticity Project

Synaptic Plasticity and Brain Diseases: Elucidating the mechanism for developmental epilepsy, intellectual disability and autism

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

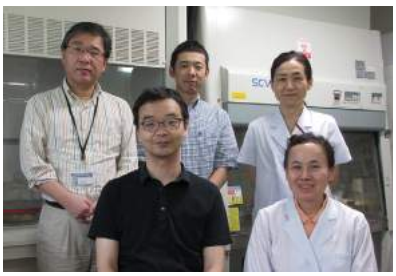






"We have clarified mechanisms of refractory epilepsy, intellectual disability and/or autism caused by impaired synaptic plasticity. Based on the novel mechanisms we found, we are trying to find new treatments for developmental brain disorders."

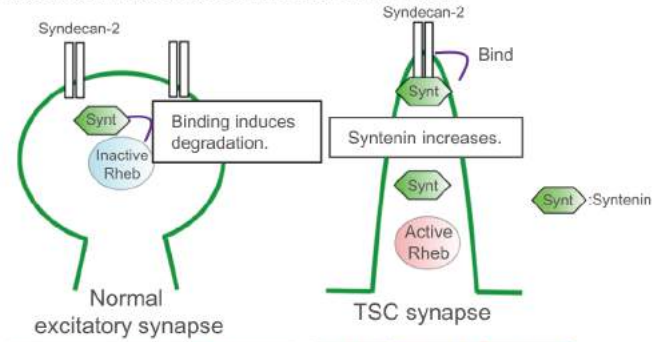
For example, COX-2 and mPGES-1 are prostaglandin synthases and exacerbate neuronal cell death after seizures, leading to intractable epilepsy. Arcadlin is a protocadherin and induces spine shrinkages after seizures, resulting in developmental delay or amnesia. Rheb regulates excitatory synapse formation via syntenin.
Its constitutive activation causes TSC (tuberous sclerosis complex), which is accompanied by epilepsy, mental retardation and autism. Finally, neuritin is a secreted or membrane-anchored protein and induces neurite branching. It may be involved in temporal lobe epilepsy. Thus, rapid de novo transcription provides novel insights into the cellular and neural network basis of behavioral plasticity.
We will also explore the possibility that these IEG products could be therapeutic targets for developmental disorders. We are making genetic mouse models of developmental disorders and are testing several drug inhibitors against IEGs for such diseases.

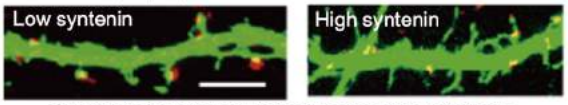


Synaptic Plasticity

Our Recent Topics

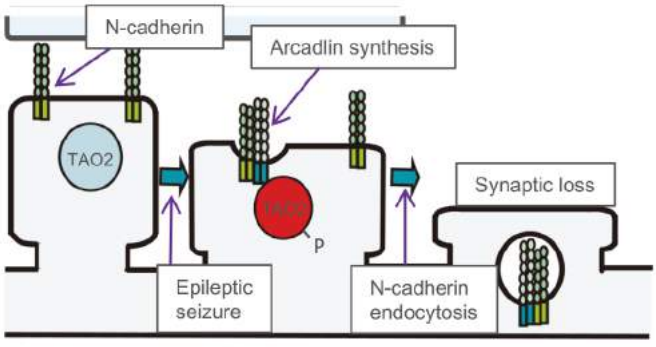
Mechanism of abnormal synapse formation in tuberous sclerosis model animals:

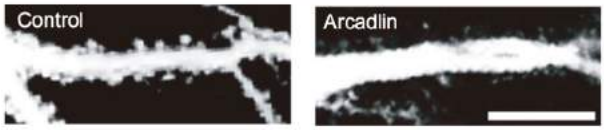




Syntenin levels regulate synapse morphology. *Nat. Commun.* 2015

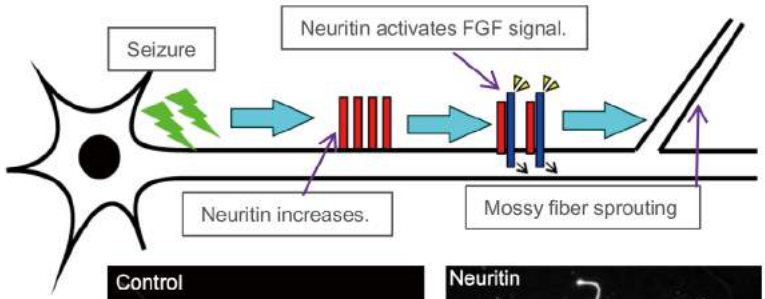
Mechanism of spine retraction after the epileptic seizure:

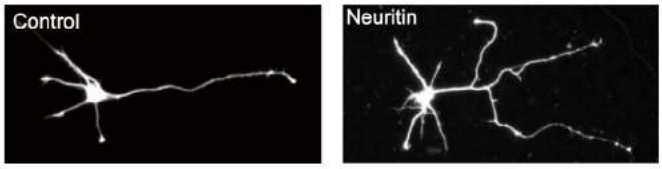




Overexpression of Arcadlin reduces spine number. *Neuron* 2007

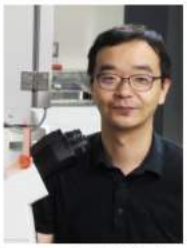
Mechanism of mossy fiber sprouting in epilepsy model animals:



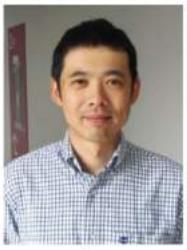


Overexpression of Neuritin promotes axonal branch formation. *J. Neurosci.* 2016

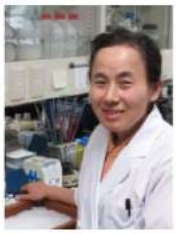
Members



Tadayuki Shimada



Teruaki Iyama

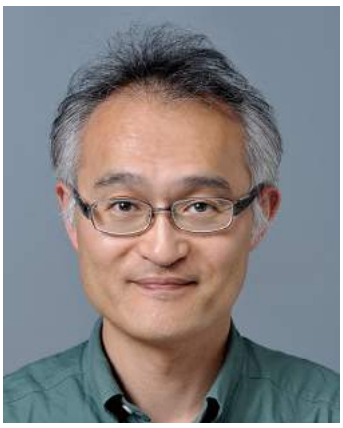


Hiroko Sugiura

Keiko Moriya

Shin Yasuda

Synaptic Plasticity

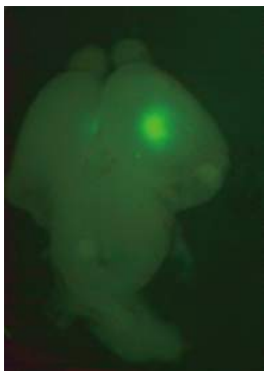


Project Leader **Haruo Okado** Neural Development Project

Brain Development and Maintenance:

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

Various gene-targeted mice



in utero electroporation

"We are studying the effects of various genetic and environmental factors on the molecular mechanisms of brain development and maintenance, with the ultimate goal of developing new treatments mental diseases."

Laboratory Members

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Hirai S., Miwa A., Ohtaka-Maruyama C., Kasai M., Okabe S., Hata Y., and Okado H. (2012) "RP58 controls neuron and astrocyte differentiation by downregulating the expression of Id1-4 genes in the developing cortex." ***EMBO J.*** 31, 1190-1202.

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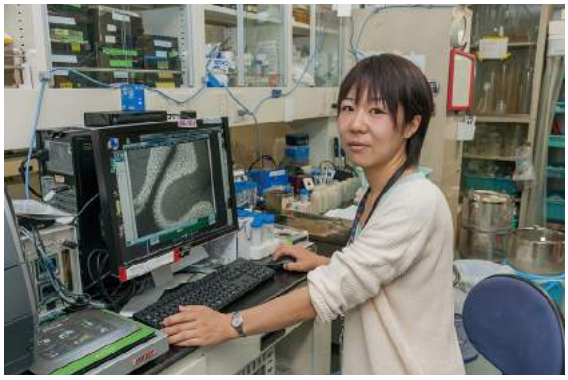
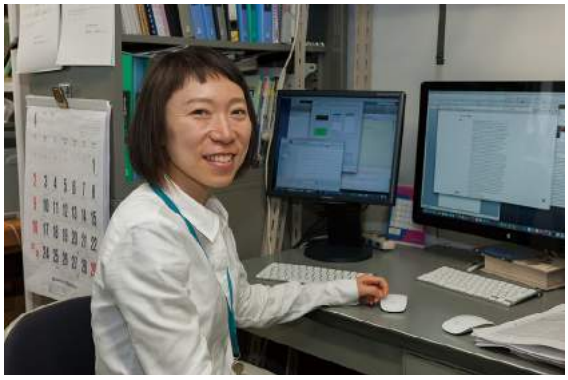
Neural Development



Shinobu Hirai



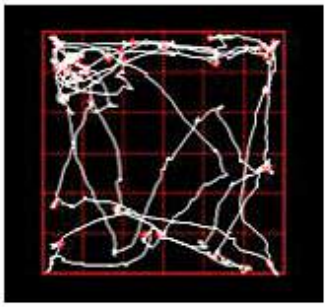
Tomoko Tanaka

Our major projects include

1) **Understanding the mechanisms of transcription repressor, RP58, for brain development and maintenance.**

2) **Exploitation of the nutritional environmental factors to manipulate brain development and functions.**

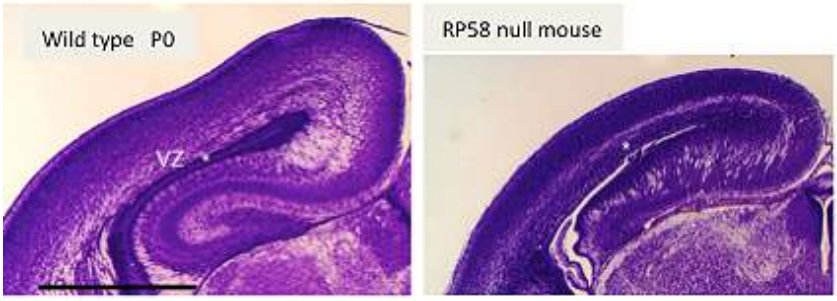
3) **Understanding the roles of environmental factors in development and ageing of brain functions.**



Locomotion, anxiety, memory, and sociality of mice are evaluated using the tracking system. Neuronal activity can be analyzed *in vivo* system.

Yoshie Matsumoto

Seiji Kanzaki



RP58 is required for development of cerebral cortex. The cell-cycle exit of progenitor cells, neuronal radial migration and maturation of cortical neurons are impaired in RP58-deficient mice.

Tomoko Fukuoka

Neural Development

Project Leader **Nobuaki Maeda** Neural Network Project

Mechanisms of Neural Network Formation: Neuronal migration and synapse formation

In the developing nervous system, diverse types of neurons are generated from neural progenitors, and migrate to specific destinations. Then, neurons extend axons toward specific target cells and form synapses on them. These developmental processes require complex cell-cell and cell-extracellular matrix interactions. The extracellular matrix is an intricate network of molecules composed of proteoglycans, hyaluronan, and fibrous glycoproteins, which fill up the extracellular space. In the meshwork of extracellular matrix, various signal molecules such as growth factors and chemokines are stored.

"We are interested in the roles of the extracellular matrix in neuronal network formation. In the developing nervous system, the extracellular matrix plays a dynamic role in regulating the behaviors of diverse types of neurons."

To explore the functions of extracellular matrix in the developing neural networks, we adopted two animal models: mouse cerebrum and Drosophila neuromuscular junction (NMJ). Using in utero eletroporation and live cell imaging techniques, we are investigating the migration of excitatory neurons in the mouse neocortex. Drosophila NMJ is a readily accessible model of excitatory synapses, which resemble the glutamatergic synapses of vertebrate central nervous system. By using the sophisticated genetic tools of Drosophila, it is possible to unravel the complicated roles of extracellular matrix in the synapse formation.

Ishii, M. and Maeda, N. (2008) "Oversulfated chondroitin sulfate plays critical roles in the neuronal migration in the cerebral cortex." ***J Biol Chem*** 283, 32610-32620.

Nishimura, K., Ishii, M., Kuraoka, M., Kamimura, K. and Maeda, N. (2010) "Opposing functions of chondroitin sulfate and heparan sulfate during early neuronal polarization." ***Neuroscience*** 169, 1535-1547.

Kamimura, K., Maeda, N. and Nakato, H. (2011) "In vivo manipulation of heparan sulfate structure and its effect on Drosophila development." ***Glycobiology*** 21, 607-618.

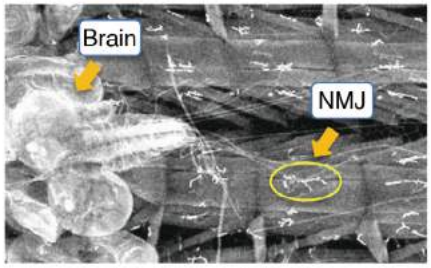
Kamimura, K., Ueno, K., Nakagawa, J., Hamada, R., Saitoe, M. and Maeda, N. (2013) "Perlecan regulates bidirectional Wnt signaling at the Drosophila neuromuscular junction." ***J Cell Biol*** 200, 219-233.

Maeda, N. (2015) "Proteoglycans and neuronal migration in the cerebral cortex during development and disease." ***Front Neurosci*** 9, 98.

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

Ohtaka-Maruyama, C. and Okado, H. (2015) "Molecular pathways underlying projection neuron production and migration during cerebral cortical development." ***Front Neurosci.*** 9, 447.

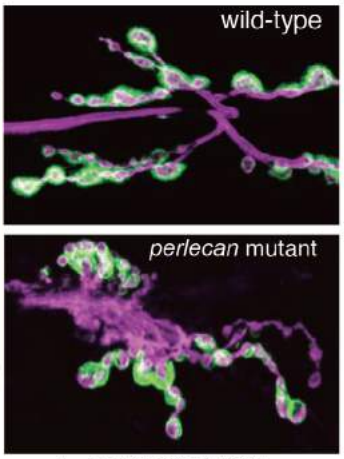
Neural Network



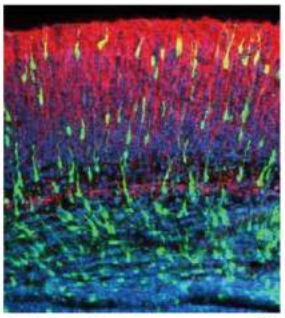
Brain and NMJ
of *Drosophila larva*

Perlecan is a secreted heparan sulfate proteoglycan, and its gene deletion leads to the diverse defects of *Drosophila* NMJ.

We demonstrated that Perlecan bidirectionally regulates pre- and post-synaptic Wnt signaling by precisely distributing Wnt at NMJ.

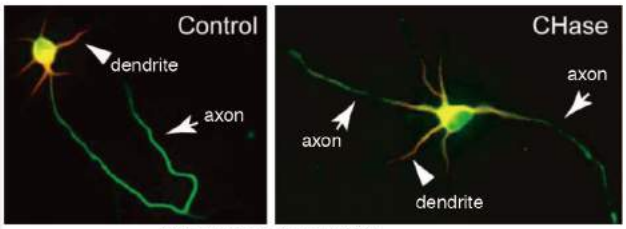


from ***J Cell Biol*** 200, 219 (2013)



Migrating neurons in
the mouse neocortex

In the developing cerebral cortex, newborn neurons first extend several short processes, one of which differentiates into an axon during their migration to the pial surface (neuronal polarization).



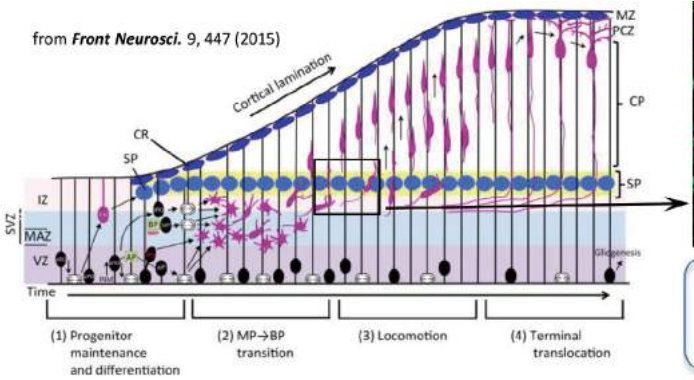
from ***Neurosci*** 169, 1535 (2010)

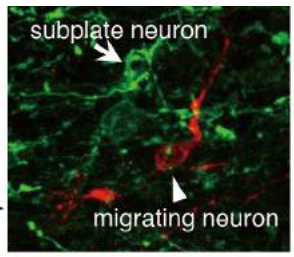
We revealed that chondroitin sulfate proteoglycans play critical roles in neuronal polarization.

Senior Research Scientist **Chiaki Ohtaka-Maruyama**

The Role of Subplate Neurons in the Development and Evolution of the Neocortex

How does mammalian neocortex acquire a unique six-layered structure that is a structural basis for the complex neural circuits, the remarkable product of evolution? To approach this question, we are focusing on the subplate (SP) neurons in the developing neocortex: one of the first born and matured cortical neurons that disappear postnatally. Recently, we found that SP neurons play critical roles in radial neuronal migration via direct interaction with migrating young neurons. Moreover, SP layer is rich in extracellular matrix, which may play important regulatory roles in the neuronal polarization. Functional elucidation of SP layer should lead to the better understanding of brain development and evolution.





Multipolar migrating neurons (red) interact with subplate neurons (green).

Schematic representation of the neuronal differentiation and radial migration in the neocortex.

Neural Network

Nakanishi M, Niimura J, Yamasaki S, Nishida A (2017) "Death of dementia inpatients in Japanese psychiatric hospitals accounts for one-fifth of discharge destination in national data from 1996 to 2014" ***J Alzheimers Dis.*** 56, 817-824.

Nakanishi M, Nakashima T, Shindo Y, Niimura J, Nishida A (2016) "Japanese care location and medical procedures for people with dementia in the last month of life." ***J Alzheimers Dis.*** 51, 747-755.

Ando S, Koike S, Shimodera S, Fujito R, Sawada K, Terao T, Furukawa TA, Sasaki T, Inoue S, Asukai N, Okazaki Y, *Nishida A. "Lithium levels in tap water and the mental health problems of adolescents: an individual level cross-sectional survey." ***J Clin Psychiatry.*** 78, e252-e256.

Yamasaki S, Ando S, Koike S, Usami S, Endo K, French P, Sasaki T, Furukawa TA, Hasegawa-Hiraiwa M, Kasai K, Nishida A (2016) "Dissociation mediates the relationship between peer victimization and hallucinatory experiences among early adolescents." ***Schizophr Res Cogn.*** 4, 18–23.

Project Leader **Atsushi Nishida** Mental Health Promotion Project

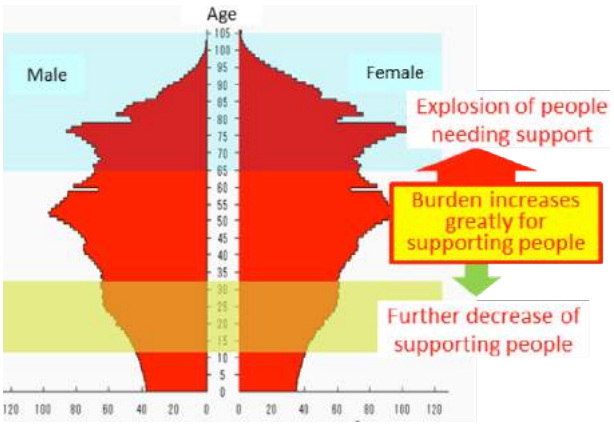
No health without Mental Health:

Mental Health promotion as the first priority in our society

While life in big cities, microcosms of today's stressful societies, is a full of risk factors for mental health, interpersonal bonds that support individuals are increasingly weakening. Hence, multifaceted research of mental health promotion via clinical medicine and sociomedical methodologies needs to be promoted.
Mental Health Promotion Project engages in promoting mental well-being in big cities through: empirical findings from large-scale birth cohort studies conducted in partnership with municipalities of Tokyo which is experiencing increasingly aging population and low birthrate; and developing programs in collaboration with clinical forefront of care.

"We are trying to elucidate preventive factors to mental health problems and enhancing factors to mental well-being, and to improve care for people living in the community and their families."

Our goals are as follows: 1) Elucidate preventive factors to mental health problems and enhancing factors to mental well-being in adolescence. 2) Improve care for people with dementia living in the community and their families. 3) Develop transition support program connecting acute-phase hospital treatment and post-discharge outpatient treatment.



- **Increase of dementia people:** Est. number in 2025 is 7 million (MHLW, 2014)
- The biggest cause of health damage among **young people** is **mental illnesses and suicide** (Patton, Lancet, 2009)

Mental Health Promotion

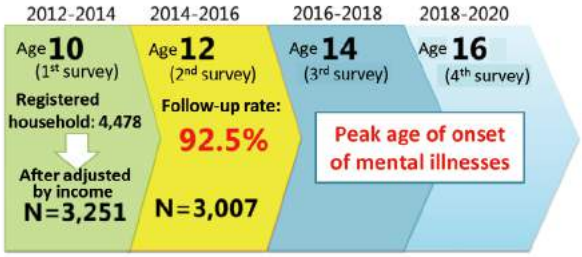
What we do

Elucidating contributing factors to adolescent mental health

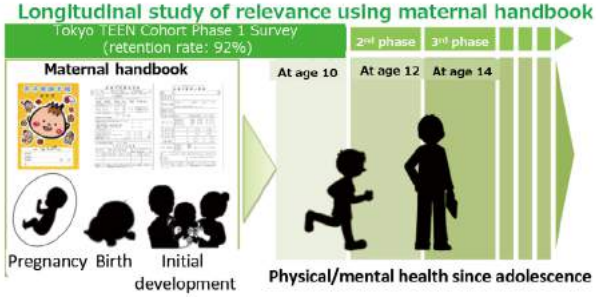
In adolescence, body and mind change significantly. Adolescents, therefore, are vulnerable to mental problems. Adolescent Health/Development Survey is a large-scale longitudinal birth cohort study included 10-year-old children and their carers living in Setagaya-ward, Chofu-city, and Mitaka-city. Currently, the study has completed the follow-up of children at their age 12; the follow-up rate is as high as 92.5%. The longitudinal relevance between the initial development at birth/childhood and the physical/mental health status since adolescence is also being studied based on information collected from maternal handbooks and various other health records.

[Adolescent Health/Development Survey]
TEEN COHORT

Progress of Health Development Survey (2017)

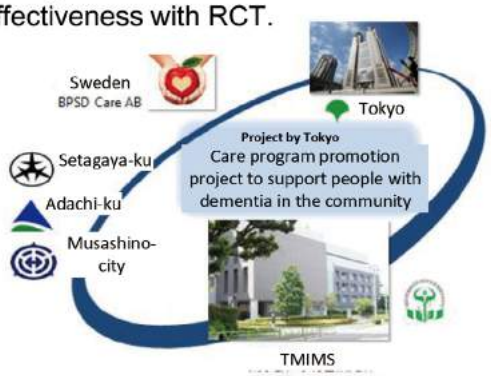


Longitudinal study of relevance using maternal handbook



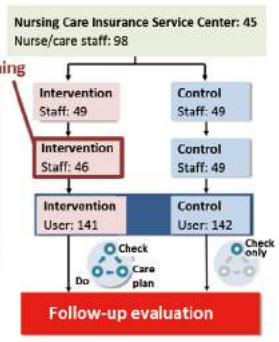
Care model development to support people with dementia at home

To support people with dementia living at home, it is indispensable to care Behavioral and Psychological Symptoms of Dementia (BPSD) as it is experienced by 90% of them. Being commissioned by Tokyo, we are working on to introduce highly-appreciated BPSD Care Program from Sweden. We aim to contribute to the dementia-related policies in Tokyo and improve the quality of dementia care through scientific verification of effectiveness with RCT.



Introduction of Sweden BPSD Care Program

World's first efficacy verification through RCT



Researchers

Atsushi Nishida
Syudo Yamasaki
Miharu Nakanishi
Junko Niimura
Kaori Endo
Kayo Hiro-oka
Yudai Iijima
Yu Yamamoto

Mental Health Promotion

Itokawa, M., Miyashita, M., Arai, M., Dan, T., Takahashi, K., Tokunaga, T., Ishimoto, K., Toriumi, K., Ichikawa, T., Horiuchi, Y., Kobori, A., Usami, S., Yoshikawa, T., Amano, N., Washizuka, S., Okazaki, Y., Miyata, T. (2017) "Pyridoxamine, A Novel Treatment For Schizophrenia With Enhanced Carbonyl Stress." ***Psychiatry Clin Neurosci.*** in press

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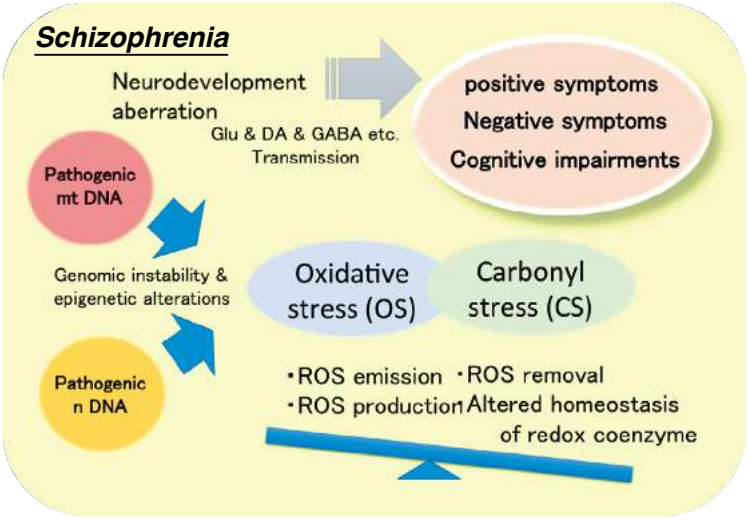
Project Leader **Makoto Arai** Schizophrenia Research Project

Identifying Biomarkers of Schizophrenia

The profiling of the peripheral metabolic system is a viable schizophrenia research strategy that can lead to earlier diagnostic methods, elucidation of its molecular mechanisms, and novel forms of treatment and prophylaxis.

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

"Identifying biomarkers will allow us to classify schizophrenia into different types, and aid in earlier diagnoses and better treatments, leading to improvements in patients' quality of life."



This biomarker-based approach is anticipated to become an innovative and creative strategy for elucidating the metabolic system of schizophrenia disease expression independently of conventional pathological hypotheses. Verification in cellular and animal models can shed light on the molecular mechanisms underlying the utility of naturally-derived substances, and is expected to lead to the future development of much safer treatments and prophylactic methods.

Topics of our research

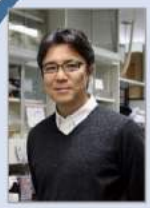
- Clinical study
- Genomics
- Metabolomics
- Neuropsychology
- iPS cell models
- Mouse models
- Post-mortem brain analysis
- Genetic counseling

Yasue Horiuchi

Research of schizophrenia cell models and genetic counseling

Induced pluripotent stem cells (iPSCs) are believed to provide a powerful strategy to obtain and characterize central nervous system-relevant cells in vitro. We have successfully generated iPSCs, neurons and glial cells derived from patients with schizophrenia and carbonyl stress. We are confident such cellular models will supply us with a unique tool to study major mental disorders. Our other focus is making genetic counseling pervasive in the research and psychiatric field in Japan. (Please see our web site for more detail).

Mitsuhiro Miyashita



Investigating the pathophysiology and clinical relevance of schizophrenia with carbonyl stress.

We have found that carbonyl stress-related schizophrenia (SZ) presents a treatment-resistant phenotype. In our research, we try to elucidate the mechanism underlying how carbonyl stress affects onset and increases both hospitalization time and symptom severity in SZ, by investigating the elements of the AGEs-RAGE-inflammation axis. Additionally, we will examine longitudinally how carbonyl stress alters the clinical prognosis and physical complications in patients with SZ.

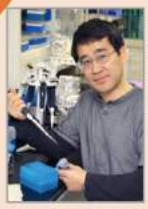
Our projects contribute to future innovation for preventive medical research in the areas of psychiatry, health, and welfare

Kazuya Toriumi

Development and analysis of mouse models based on schizophrenia pathophysiology

Based on clinical findings, we have developed genetic and/or environmental mouse models for schizophrenia, and analyzed them to uncover the molecular mechanisms underlying schizophrenia with carbonyl stress, oxidative stress and/or vitamin B6 deficiency. Moreover, using these mouse models, we have tried to explore new types of therapeutic drugs for schizophrenia that use different mechanisms of action than existing antipsychotics.

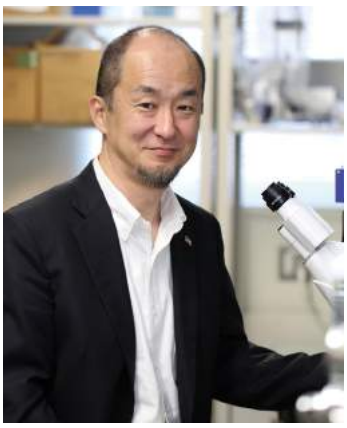
Masanari Itokawa



Clinical pharmacology of TM8001 in patients with carbonyl stress-related schizophrenia

TM8001 is a dihydrochloride of pyridoxamine, one of the vitamin B6 groups. TM8001 can act to capture reactive carbonyl compounds, and has inhibitory activity against the production of AGE by reactive carbonyl compounds. Thus, by reducing carbonyl stress, it is expected to be therapeutic in this type of schizophrenia. Removal of these substances is the key to a possible new treatment method based on the root cause of carbonyl stress-related schizophrenia.

Schizophrenia Research



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

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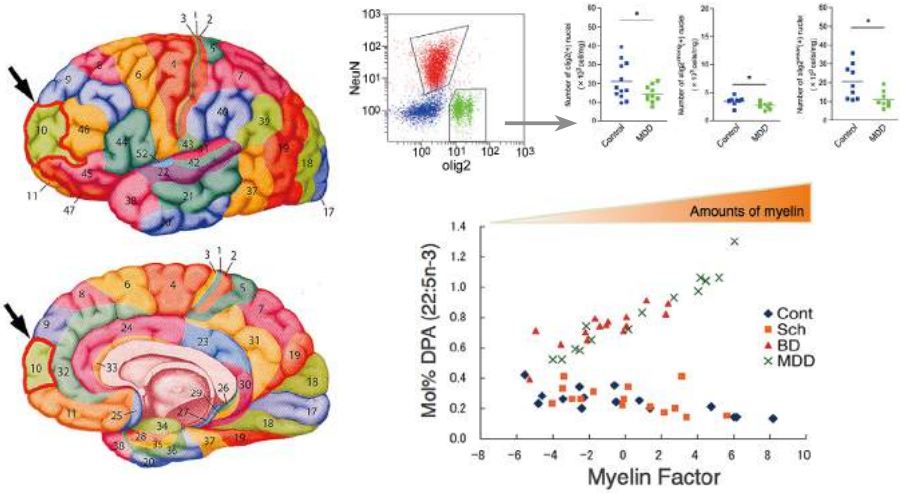
Hayashi Y, Nihonmatsu-Kikuchi N, Yu XJ, Ishimoto K, Hisanaga SI, Tatebayashi Y. (2011) "A novel, rapid, quantitative cell-counting method reveals oligodendroglial reduction in the frontopolar cortex in major depressive disorder." ***Mol Psychiatry*** 16, 1155-1158.

Project Leader **Yoshitaka Tatebayashi** Affective Disorders Research Project

Our Goal is to Decipher the Neurobiological Bases of Affective Disorders.

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

"Our human postmortem brain studies reveal oligodendroglial reductions and myelindependent fatty acid abnormalities in the frontopolar cortex in affective disorders."

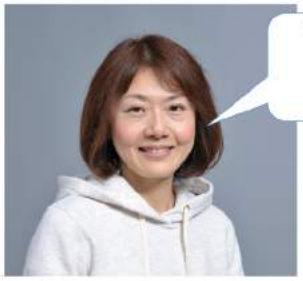


The exact functions of the human frontopolar cortex (BA10) remain enigmatic. Given that the BA10 is thought to be the most evolutionarily recent expansion of the primate prefrontal cortex, its function may uniquely reflect human adaptations in the context of selecting and updating models of reward contingency in dynamic environments. As adulthood cortical myelination is an essential process for the establishment of efficient neuronal signaling networks, any abnormalities in this process may have important roles in the pathophysiology of affective disorders.

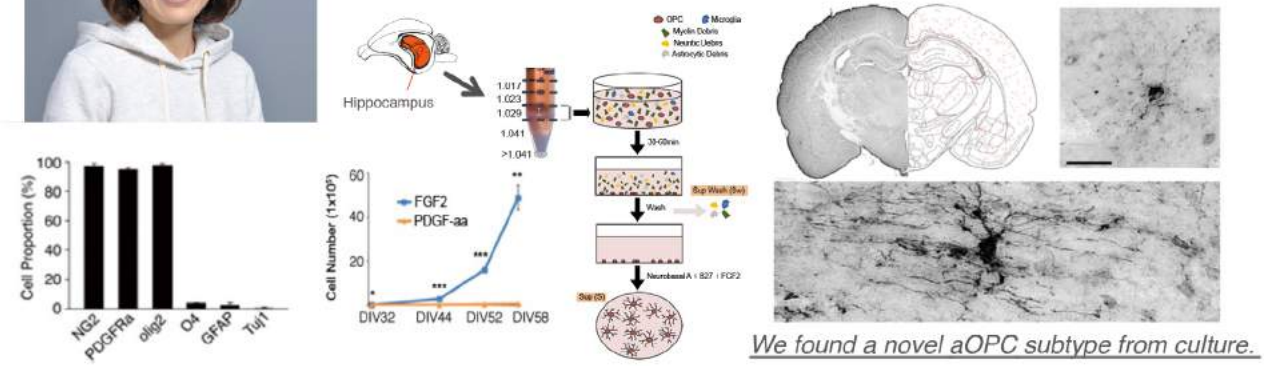
Affective Disorders Research

"Better understanding of these phenomena will provide important insights to facilitate the more effective diagnosis, treatment and prevention of affective disorders."

Naomi Nihonmatsu-Kikuchi

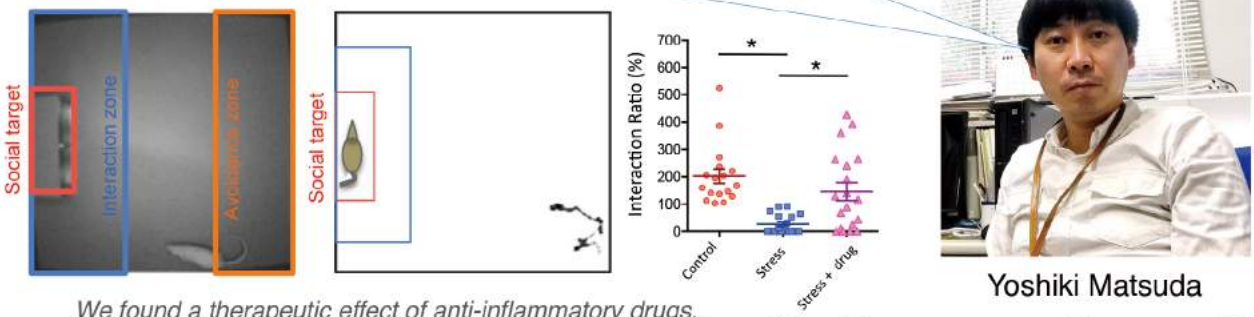


We purify and culture adult oligodendrocyte progenitor cells (aOPCs) from adult mammalian brains to understand their roles in the pathogenesis of affective disorders.



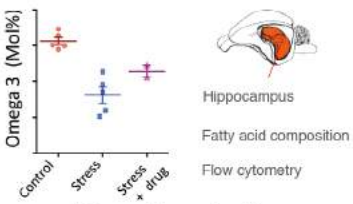
We found a novel aOPC subtype from culture.

Our animal model clearly indicates essential roles of inflammation in the pathophysiology of depression. Chronic stress induces changes not only in behavior but also in electrophysiology and cellular structure.



Yoshiki Matsuda

We found a therapeutic effect of anti-inflammatory drugs.



Fatty acid composition

Flow cytometry

Kazuhisa Aoki

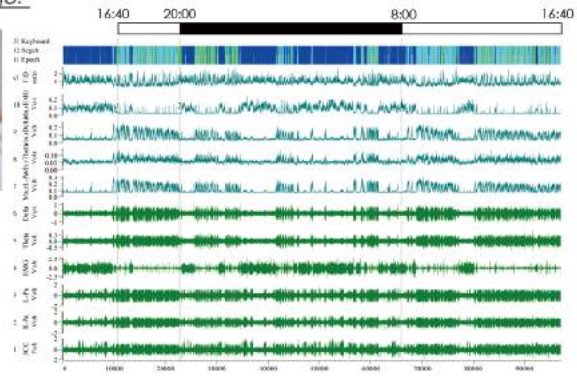
Blood

Luminex

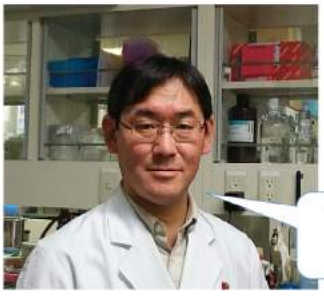
CE-TOFMS

iTRAQ

etc.



We found several candidate blood biomarkers for psychosocial stress.



We are conducting detailed omics analyses of our animal models to discover novel biomarkers for depression.

Affective Disorders Research

Project Leader **Makoto Honda** Sleep Disorders Project

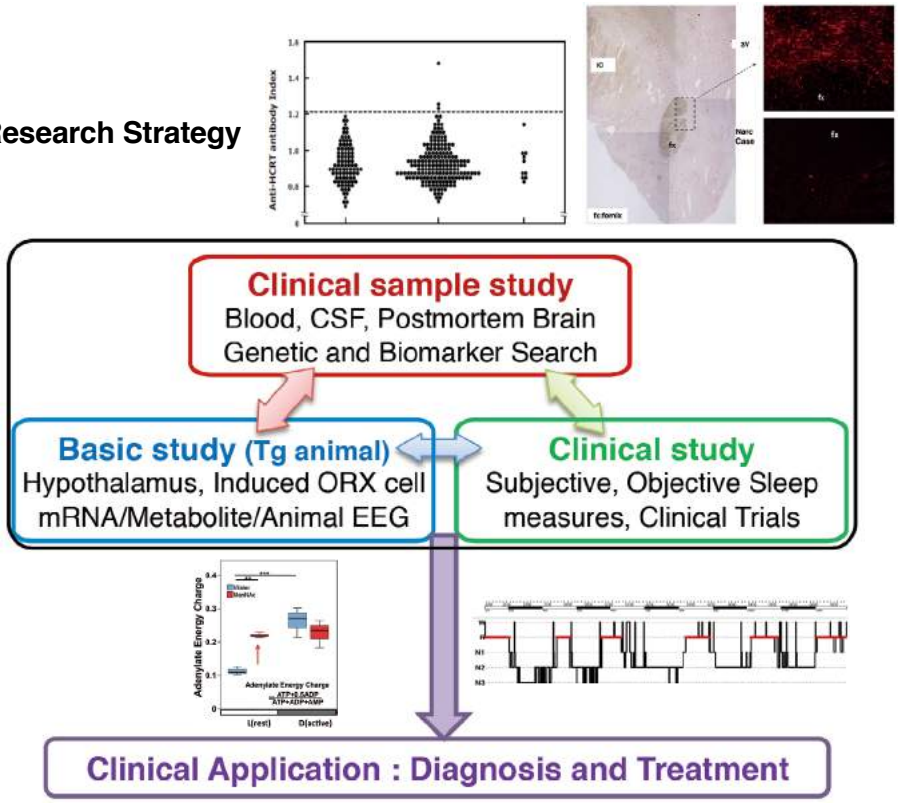
Narcolepsy and Hypersomnia:
Find the causes to develop better treatments

Narcolepsy is a sleep disorder with abnormal intrinsic sleep-wake regulation, resulting in unique symptoms including frequent lapses into sleep, nocturnal sleep instability and REM sleep related manifestations such as cataplexy (abrupt loss of muscle tone triggered by emotion), sleep paralysis and hypnagogic hallucination.
Narcolepsy is associated with a deficiency of wake-promoting orexin/hypocretin producing neurons localized in hypothalamus, and virtually all the patients carry human leukocyte antigen (HLA)-DQB1*06:02.

"We are trying to solve the mystery of narcolepsy: Listen to the patients, get the whole picture, and improve their lives."

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

Research Strategy



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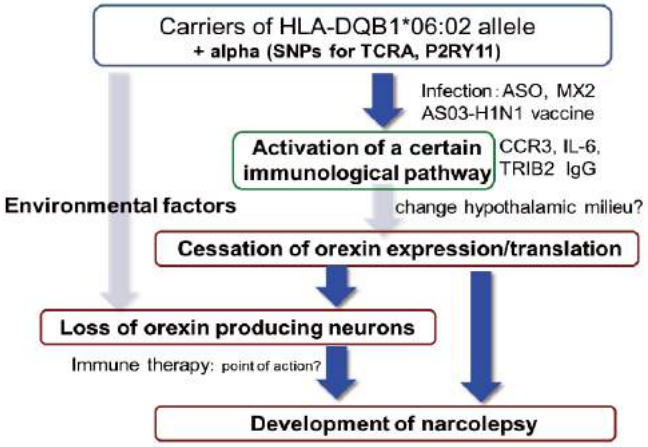
Sleep Disorders

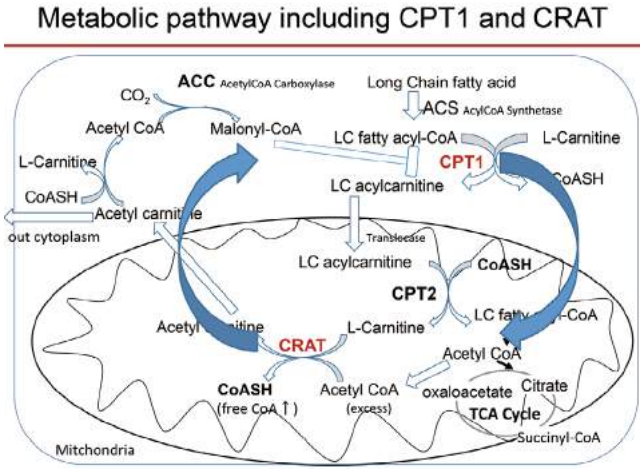
Research Interests

Hypothalamus works as a center for sleep-wake switch in coordination with the integrated information from the body. Among them, we have particular interests in immune and metabolic status, which can be the key to understand altered sleep-wake regulation in narcolepsy.

1. HLA association and immune abnormality

In addition to the tight association with HLA, narcolepsy is also associated with T cell receptor (TCR) alpha locus, indicating the HLA-TCR mediated immunological alterations. Both genetic and environmental factors are implicated in narcolepsy predisposition. We have reported the altered immune status in narcolepsy, but so far could not confirm the leading hypothesis that orexin neurons are destructed by direct autoimmune attacks. Immune mechanisms other than autoimmunity might lead to stop producing orexin neuropeptide.





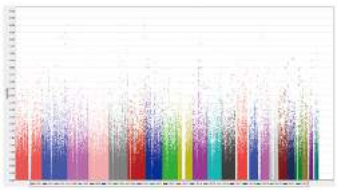
2. Metabolic aspect of narcolepsy and related hypersomnia

Through genome-wide association studies (GWAS), we have identified novel narcolepsy (and other hypersomnia) related genes. They are key enzymes located in the pathway of fatty acid metabolism. We confirmed their functional relevance, performed the clinical trials, and analyzing the potential efficacy of the novel therapy (promoting metabolism) in hypersomnia patients.

Members of Sleep Disorders Project (2017)

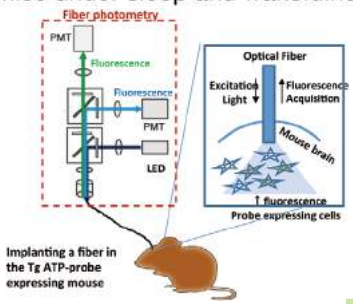
Taku Miyagawa

Understanding the genetic background and mechanism of sleep disorders.



Akiyo Natsubori

Understanding the brain metabolic dynamics of mice under sleep and wakefulness.



Sleep Disorders

Sugaya N, Ogai Y, Aikawa Y, Yumoto Y, Takahama M, Tanaka M, Haraguchi A, Umeno M, and Ikeda K. (2018) "A randomized controlled study of the effect of ifenprodil on alcohol use in patients with alcohol dependence." ***Neuropsychopharmacology Rep.***

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Ide S, Takahashi T, Takamatsu Y, Uhl G, Niki H, Sora I, and Ikeda K (2017) "Distinct roles of opioid and dopamine systems in lateral hypothalamic intracranial self-stimulation." ***Int. J. Neuropsychopharmacol.*** 20, 403-409.

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Project Leader **Kazutaka Ikeda** Addictive Substance Project

Addictive Drugs are Double-edged Swords: They can become both harmful and beneficial depending on how they used

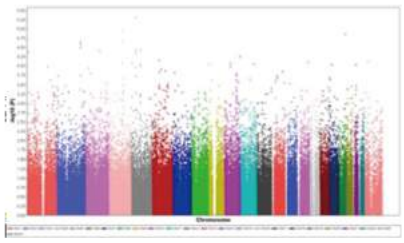
Addiction to substances (e.g. drugs, alcohol, tobacco) and behavior (e.g. internet, gambling) is a serious public health problem. Moreover, use of legal drugs has been increasing in Japan in recent years. It is important to prevent and solve problems of addictions.

On the other hand, some addictive drugs are also widely used as analgesics and treatment of developmental disorders. Thus, it is considered that some molecules involved in action of addictive drugs are commonly related to analgesics and developmental disorders.

The goals of our project are as follows: 1) Development of novel treatment and prevention of addiction. 2) Improvement of personalized pain treatment. 3) Development of novel treatment against developmental disorders.

"We are trying to improve treatment, prevention, and understanding of addiction, pain, and developmental disorders by revealing the mechanisms underlying addiction."

All goals can make significant contribution to the society. We aim to those goals through studying the action mechanisms of addictive drugs using molecular biological approach, behavioral pharmacological approach, human genome analysis, and clinical approach.



Addictive Substance

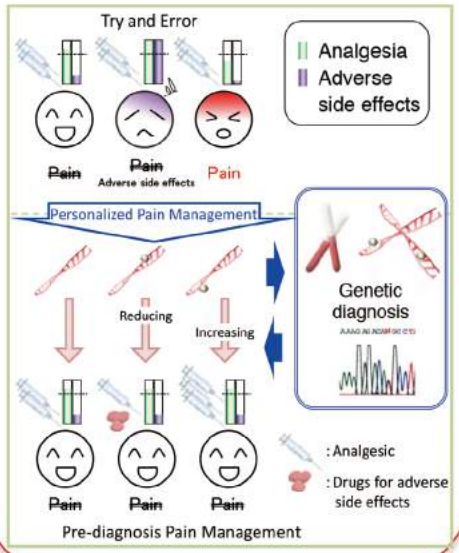
Topics of our research

Addiction research

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

Pain treatment research

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



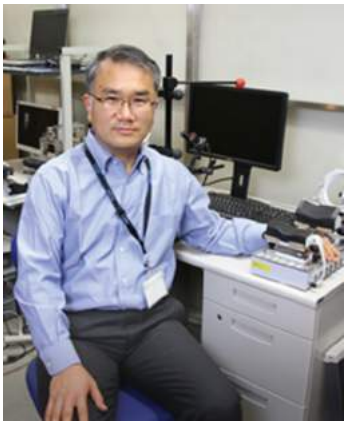
Developmental disorder research

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

Members

Kazutaka Ikeda
Shinya Kasai
Daisuke Nishizawa
Soichiro Ide
Seii Ohka
Masayo Fujita
Hiroko Kotajima

Addictive Substance



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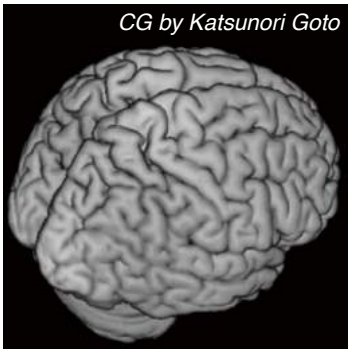
Project Leader **Shinji Kakei** Motor Disorders Project

From Neuron to Action and its Disorders

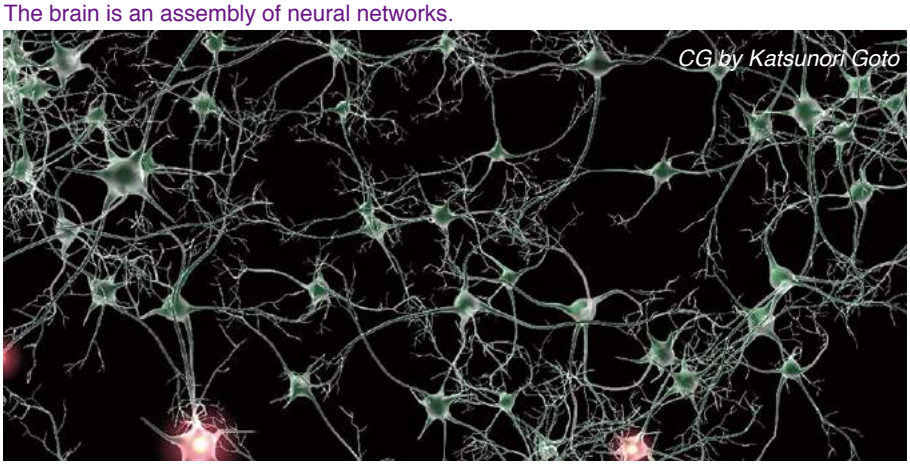
We try to understand how the brain controls our movements in the real world. We study the process of action generation at a single neuron level using animal models to understand how the movement is processed in the brain. We also study actions of healthy people, as well as those with neurological disorders,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

"Through our research, we are trying to understand the brain. The brain was first created to control movement and extended to control higher brain functions."


CG by Katsunori Goto

"The brain mechanism for motor control must provide a basic framework to understand higher brain functions."

The brain is an assembly of neural networks.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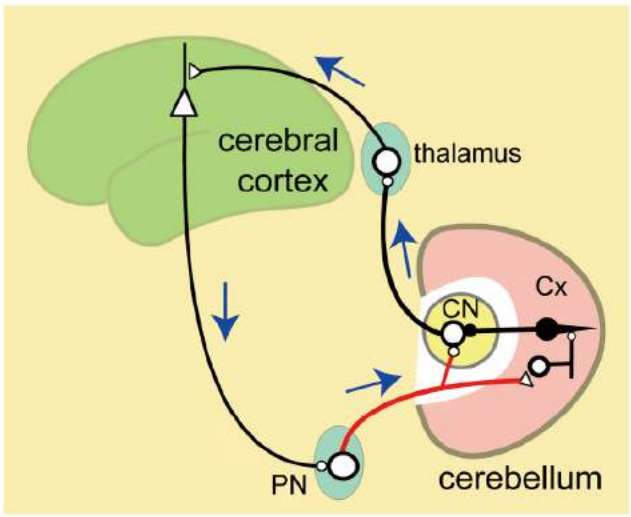
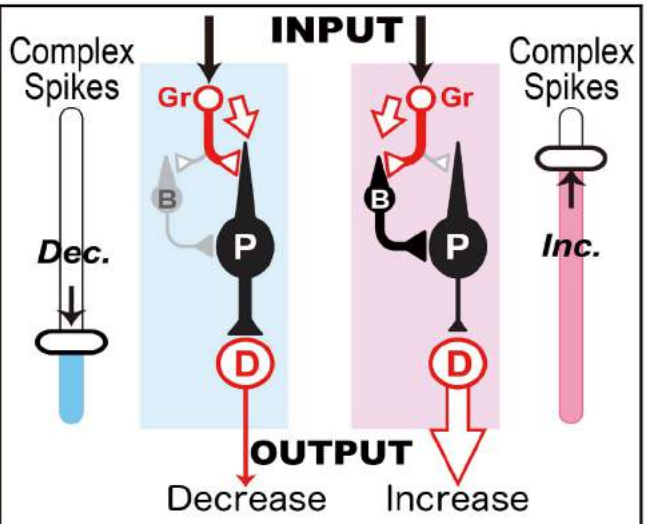
Motor Disorders

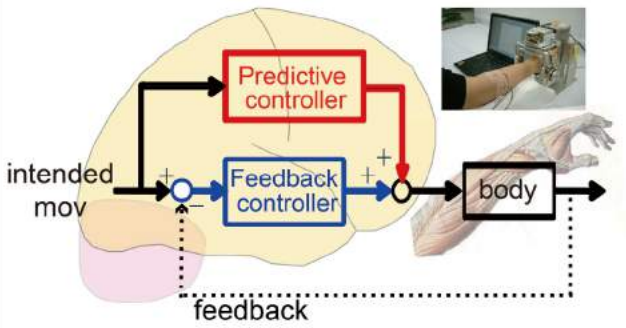
Hot Topics of Our Research



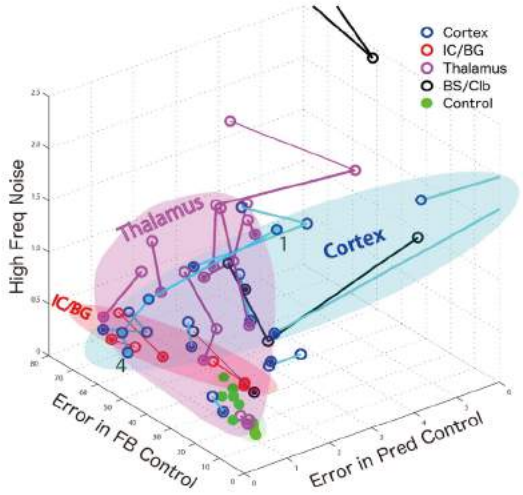
The cerebro-cerebellar communication loop plays essential roles to organize both motor control and higher brain functions such as thought and speech[1,2,4].



We found two modes of cerebellar input-output relationship that explain generation of precise motor commands[1,2,4].



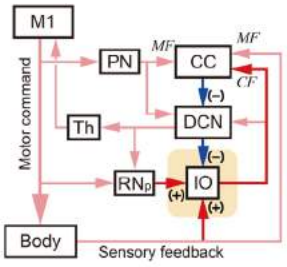
We were the first group in the world to build a system (*inset*) to dissociate predictive motor control and feedback motor control (below) in patients with neurological disorders. This system provides quantitative parameters that characterize the two controllers[3].



With new quantitative parameters, we were the first group to visualize different courses of recovery for stroke patients with different localization of brain lesions.

Members

Kyuengbo Min,
Jongho Lee,
Takahiro Ishikawa,
Takeru Honda



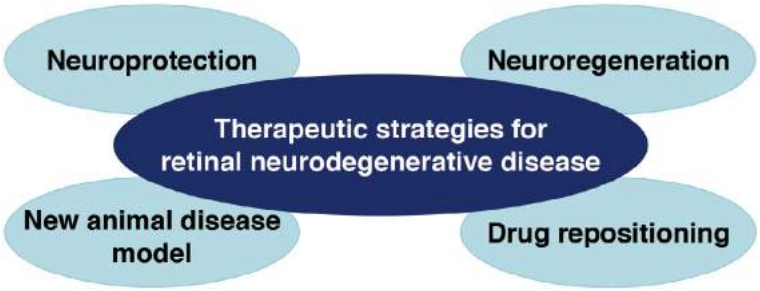
Motor Disorders

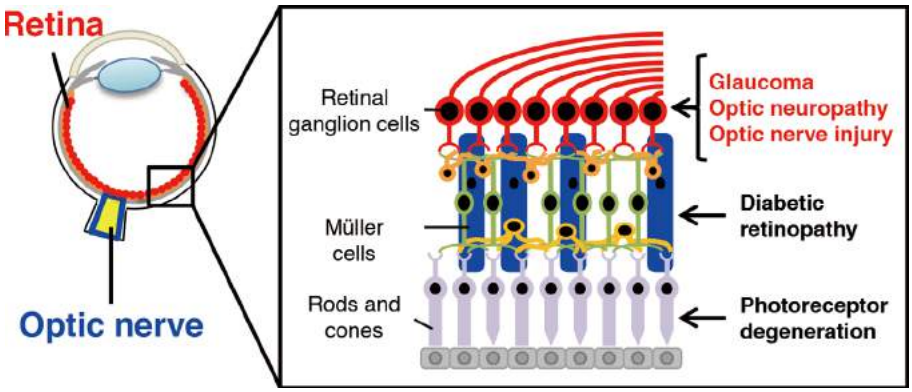
Project Leader **Takayuki Harada** Visual Research Project

Elucidation of Pathology and Development of Therapeutic Strategies for Retinal Neurodegenerative Diseases

More than 1.6 million people in Japan are visually impaired, representing economic social losses estimated at more than 8 trillion yen. In the particular context of the increased penetration of Western lifestyles and an aging society, the increase in the number of patients with conditions such as glaucoma and diabetic retinopathy, which could be called "adult eye diseases," has become a major social issue.
To achieve improved quality of life (QOL) for the visually impaired in an increasingly aging population, we seek to elucidate detailed pathogenic mechanisms and develop new therapies through the development of a model of intractable eye disease.

"We are focusing on elucidating the molecular mechanisms of neuroprotection and neuroregeneration, and our final goal is the prevention or treatment of blindness in retinal neurodegenerative disorders such as glaucoma and traumatic injury."





Kimura, A., Namekata, K., Guo, X., Noro, T., Harada, C., and Harada, T. (2015) "Valproic acid prevents NMDA-induced retinal ganglion cell death via stimulation of neuronal TrkB receptor signaling." ***Am. J. Pathol.*** 185, 756-764.

Noro, T., Namekata, K., Kimura, A., Guo, X., Azuchi, Y., Harada, C., Nakano, T., Tsuneoka, H., and Harada, T. (2015) "Spermidine promotes retinal ganglion cell survival and optic nerve regeneration in adult mice following optic nerve injury." ***Cell Death Dis.*** 6, e1720.

Harada, C., Guo, X., Namekata, K., Kimura, A., Nakamura, K., Tanaka, K., Parada, LF., and Harada, T. (2011) "Glia- and neuron-specific functions of TrkB signalling during retinal degeneration and regeneration." ***Nature Commun.*** 2, 189.

Guo, X., Harada, C., Namekata, K., Matsuzawa, A., Camps, M., Ji, H., Swinnen, D., Jorand-Lebrun, C., Muzerelle, M., Vitte, P., Ruckle, T., Kimura, A., Kohyama, K., Matsumoto, Y., Ichijo, H., and Harada, T. (2010) "Regulation of the severity of neuroinflammation and demyelination by TLR-ASK1-p38 pathway." ***EMBO Mol. Med.*** 2, 504-515.

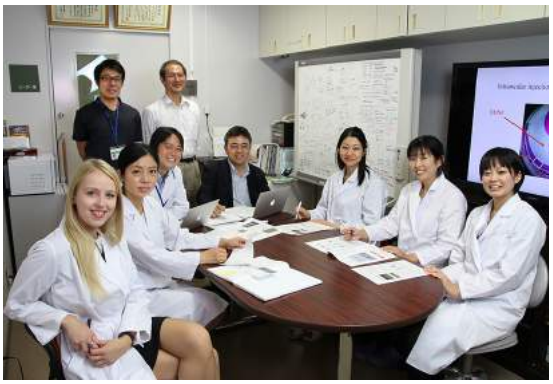
Harada, T., Harada, C., Nakamura, K., Quah, HA., Okumura, A., Namekata, K., Saeki, T., Aihara, M., Yoshida, H., Mitani, A., and Tanaka, K. (2007) "The potential role of glutamate transporters in the pathogenesis of normal tension glaucoma." ***J. Clin. Invest.*** 117, 1763-1770.

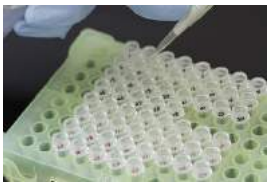
Visual Research

Our major aim

- **To develop a neuroprotective retinal therapy using animal disease models**
- **To elucidate the mechanisms involved in the onset of optic neuritis**
- **To establish a method to promote regeneration of the optic nerve**



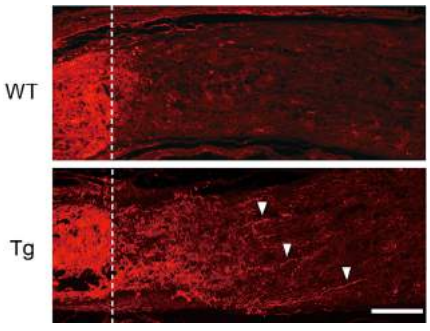




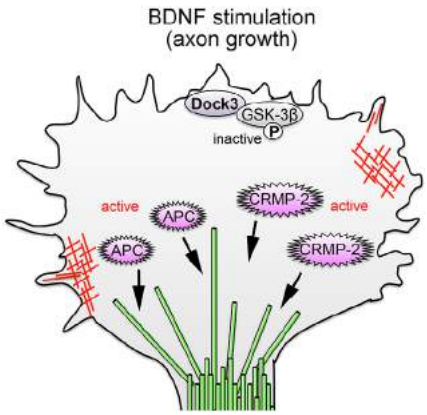
Senior Research Scientist **Kazuhiko Namekata**

Dock family proteins

The dedicator of cytokinesis (Dock) family is composed of atypical guanine exchange factors (GEFs) that induce actin polymerization. To date, 11 Dock family members have been identified. Dock3 is predominantly expressed in the central nervous system. In the growth cone, Dock3 induces actin polymerization by activating WASP family verprolin-homologous (WAVE) and modulates microtubule dynamics through inactivation of GSK-3β, leading to axon elongation. In addition, Dock3 plays a role in protecting retinal ganglion cells from neurotoxicity and oxidative stress. Dock3 may be a therapeutic target for optic neuropathy including glaucoma.



Axonal regeneration was enhanced in Dock3 overexpressing mouse (Tg) (Arrow heads indicate regenerating axons)



Namekata, K., Kimura, A., Kawamura, K., Harada, C., and Harada, T. (2014) "Dock GEFs and their therapeutic potential: Neuroprotection and axon regeneration." Prog. Retin. Eye Res. 43, 1-16.

Namekata, K., Harada, C., Guo, X., Kimura, A., Kittaka, D., Watanabe, H., and Harada, T. (2012) "Dock3 stimulates axonal outgrowth via GSK-3β-mediated microtubule assembly." J. Neurosci. 32,264-274.

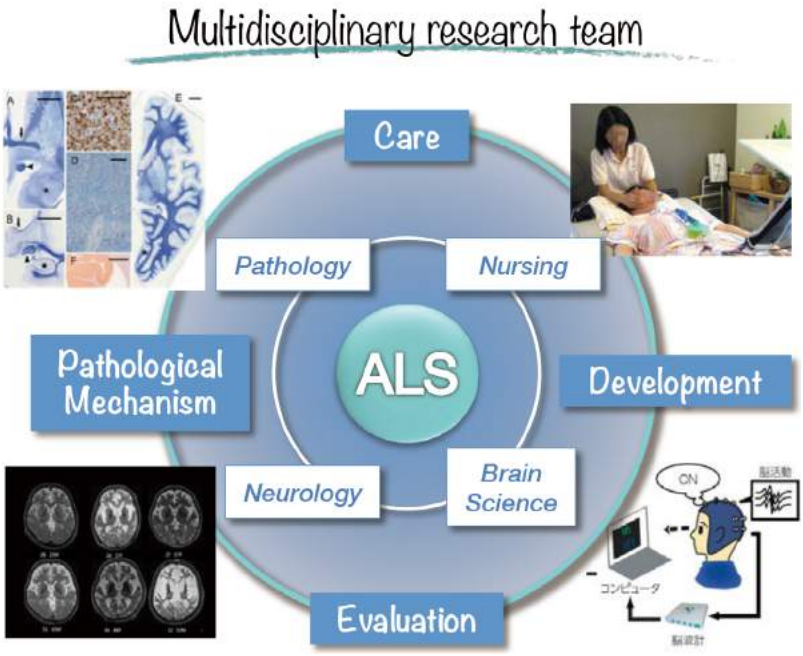
Namekata, K., Harada, C., Taya, C., Guo, X., Kimura, H., Parada, LF., and Harada, T.(2010) "Dock3 induces axonal outgrowth by stimulating membrane recruitment of the WAVE complex." Proc. Natl. Acad. Sci. USA. 107, 7586-7591.

Visual Research

Project Leader **Yuki Nakayama** ALS Nursing Care Project

Improving the Quality Of Life of Patients with Amyotrophic Lateral Sclerosis

"Our mission is to establish the best practices for respiratory and communication management for ALS patients in a community-based setting . We have established a multidisciplinary research team to develop a Brain Machine Interface for ALS patients."



Nakayama Y, Shimizu T,Matsuda C, Mochizuki Y, Hayashi K,Nagao M, Kawata A, Isozaki E.(2017) " Non-Motor Manifestations in ALS Patients with Tracheostomy and invasive ventilation." ***Muscle & Nerve.***

Shimizu T, Takata K, Sakata A, Nagaoka.U, Ichihara N,Ishida C, Nakayama Y, Komori T, Nishizawa M. (2016) "The measurement and estimation of total energy expenditure in Japanese patients with ALS: A doubly labelled water method study." ***Amyotroph Lateral Scler Frontotemporal Degener.*** 18, 37-45.

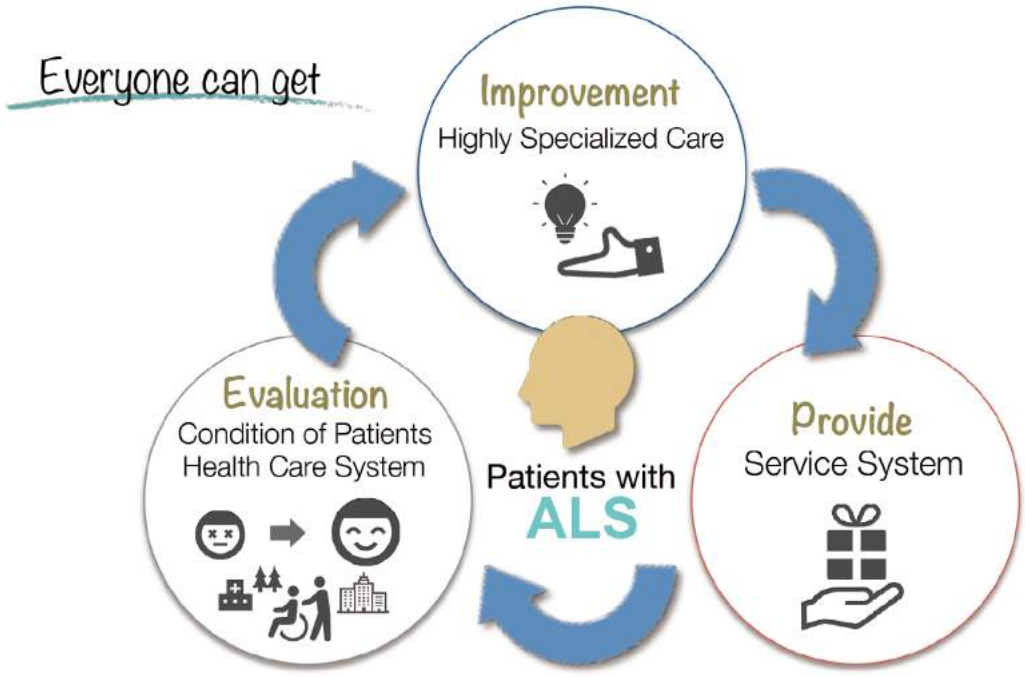
Mochizuki Y, Hayashi K, Nakayama Y, Shimizu T, Kamide M, Ogino M, Komori T, Hasegawa M, Isozaki E, Nakano I. (2016) "IALS patients with ability to communicate after long-term mechanical ventilation have confined degeneration to the motor neuron system." ***J Neucol Sci.*** 363, 245-248.

Matsuda C, Shimizu T, Nakayama Y, Haraguchi M, Hakuta C, Itagaki Y, Ogura A, Murata K, Taira M, Numayama T, Kinoshita M. (2016) "Macroglossia in advanced amyotrophic lateral sclerosis." ***Muscle & Nerve.*** 54, 386-390.

Nakayama Y, Shimizu T, Mochizuki Y, Hayashi K, Matsuda C, Nagao M, Watabe K, Kawata A, Oyanagi K, Isozaki E, Nakano I. (2016) "Predictors of impaired communication in amyotrophic lateral sclerosis patients with tracheostomy invasive ventilation." ***Amyotroph Lateral Scler Frontotemporal Degener.*** 17, 38-46.

ALS Nursing Care

ALS Nursing Care Project Ground design

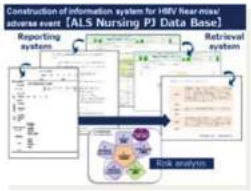


Administration of Community-Based Nursing

How many visiting nurse stations are there in this community?

" Do Patients live well? "

Akiko Ogura, Ph.D.



Quality Assurance of Home Care

Collaboration between visiting Nurse and care workers.
Risk management on Home Mechanical Ventilation, and Construction of information system for Medical Near-miss/adverse event.
Needs of Nursing Support in Outpatient Department on Patients with ALS.

Michiko Haraguchi, Ph.D.

Establishing specialized Oral Nursing care system for advanced amyotrophic lateral sclerosis patient

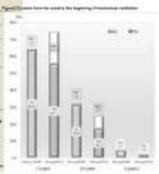
Chiharu Matsuda, Ph.D.

Multivariate analysis for the occurrence of macroglossia by logistic regression

Variables	Odds ratio	95% CI	*P*-value
Age at beginning of TIV use, years	0.937	0.845–1.041	0.225
Duration of TIV use, months	1.022	1.000–1.044	0.050
ALSFRS-R score	0.822	0.314–2.146	0.314
Body mass index, kg/m²	1.853	1.150–2.376	0.007
Energy intake, kcal/d	1.001	0.995–1.006	0.784
Stages of communication impairments (I, II–IV, V)	3.771	1.150–12.370	0.029

Table 1. Characteristics of patients, and comparisons between 2006 and 2012

Characteristic	Year 2006	2012	*p*-value
Sporadic ALS with MV (n)	212	325	
Men / Woman (n)	114 / 98	174 / 149	0.952
Age (years)	66.0 ± 11.1	66.7 ± 11.4	0.541
Age at onset (years)	59.5 ± 12.8	59.2 ± 13.5	0.858
Duration from onset to diagnosis (years)	2.2 ± 4.6	0.7 ± 1.1	0.004*
Duration from onset to the beginning of MV (years)	3.7 ± 4.5	2.6 ± 2.3	0.003*
NIV (n)	5	55	<0.001*
TIV (n)	207	270	0.432
Changes from NIV to TIV (n)	15	25	
Duration of TIV use (months)	(n= 189) 42.7 ± 45.0	(n=243) 63.7 ± 49.9	<0.001*
Duration of NIV use (months)	(n= 3) 10.3 ± 7.0	(n=27) 29.0 ± 30.5	0.307



Patients with Intractable Diseases Analyze their physical and psycho-social Data

Yumi Itagaki, M.S.

ALS Nursing Care

Sango, K., Mizukami, H,. Horie, H., and Yagihashi, S. (2017) "Impaired axonal regeneration in diabetes. Perspective on the under-lying mechanism from in vivo and in vitro experimental studies." ***Front. Endocrinol.*** 8, 12.

Niimi, N., Yako, H., Tsukamoto, M., Takaku, S., Yamauchi, J., Kawakami, E., Yanagisawa, H., Watabe, K., Utsunomiya, K., and Sango, K. (2016) Involvement of oxidative stress and impaired lysosomal degradation in amiodarone-induced schwannopathy. ***Eur. J. Neurosci.*** 44, 1723-1733.

Suzuki, M., Fujikake, N., Takeuchi, T., Kohyama-Koganeya, A., Nakajima, K., Hirabayashi, Y., Wada, K., and Nagai, Y. (2015) Glucocerebrosidase deficiency accelerates the accumulation of proteinase K-resistant α-synuclein and aggravates neurodegeneration in a Drosophila model of Parkinson's disease. ***Human Mol. Genet.*** 24, 6675-6686.

Tsukamoto, M., Niimi. N., Sango, K., Takaku, S., Kanazawa, Y., and Utsunomiya, K. (2015) Neurotrophic and neuroprotective properties of exendin-4 in adult rat dor-sal root ganglion neurons: involvement of insulin and PI3 kinase/RhoA signaling. ***Histochem. Cell Biol.*** 144, 249-259.

Sango, K., and Yamauchi, J. (2014) ***Schwann Cell Development and Pathology.*** Springer Japan K.K.

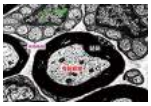
Takaku, S., Yanagisawa, H., Watabe, K., Horie, H., Kadoya, T., Sakumi. K., Nakabeppu, Y., Poirier, F., and Sango, K. (2013) GDNF promotes neurite outgrowth and up-regulates galectin-1 through the RET/PI3K signaling in cultured adult rat dorsal root ganglion neurons. ***Neurochem. Int.*** 62, 330-339.

Project Leader **Kazunori Sango** Diabetic Neuropathy Project

Pathogenesis-based Therapeutic Approaches to Diabetic Neuropathy

Peripheral neuropathy is one of the most common complications of Diabetes Mellitus, and its irritating symptoms such as pain and numbness can be the cause of insomnia and depression, and when allowed to progress to more advanced disease stages can result in serious consequences such as lower limb amputation and lethal arrhythmia. In addition, recent studies have indicated that diabetes is a major risk factor for cognitive disorders such as Alzheimer's disease.

"We are trying to improve QOL for diabetics and help them to live longer lives by elucidating the pathogenesis of neurological disorders and establishing effective treatments."



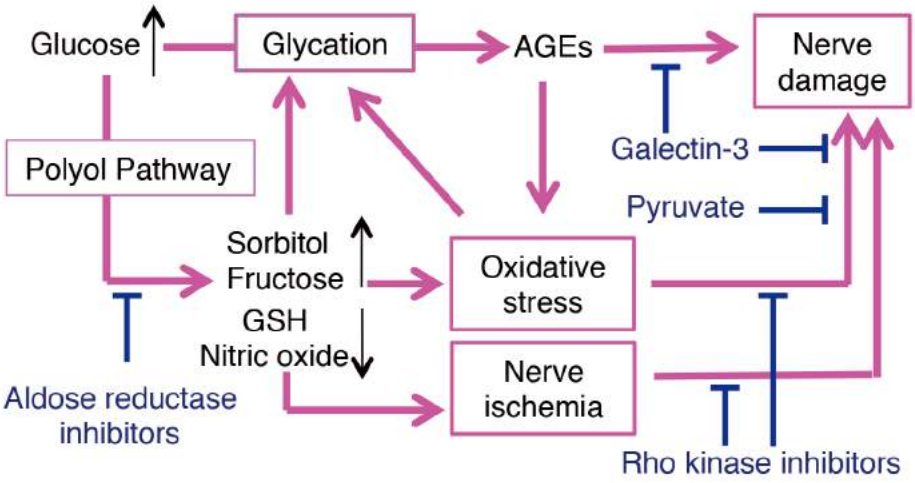
The goals of our project are as follows: 1) Establishing effective pathogenesis-based treatments for diabetic peripheral neuropathy. 2) Elucidating mechanistic link between metabolic dysfunction and neurodegenerative diseases.

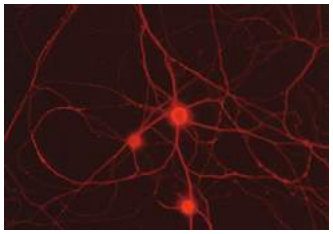
Diabetic Neuropathy

Project 1: Therapeutic Approaches to Diabetic *Peripheral Neuropathy*

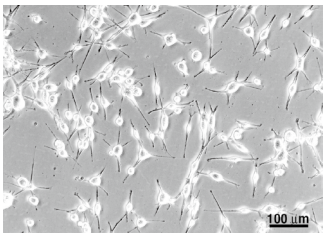
[Sango, Yako, Niimi, Takaku, Akamine]

Metabolic disorders and vascular abnormalities caused by hyperglycemia appear to be closely related to the development and progression of diabetic peripheral neuropathy. Using diabetic model animals and culture systems of adult rodent **dorsal root ganglion (DRG) neurons** and **immortalized Schwann cells**, we seek to establish effective pathogenesis-based treatments for peripheral neuropathy.





Adult rat DRG neurons



Immortalized mouse Schwann cells IMS32

Project 2: Mechanistic link between *Metabolic dysfunction* and *Neurodegenerative Diseases* [Suzuki, Oba]

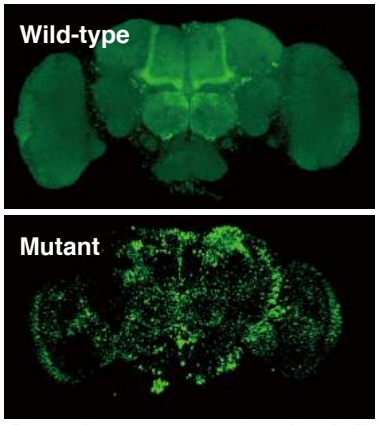
Neurodegenerative diseases are considered to share a common molecular pathogenesis involving protein misfolding and aggregation. Recently, increasing evidence suggests a relationship between metabolic syndrome and Alzheimer's disease. By using ***Drosophila* model**, we aim to understand the molecular mechanism by which metabolic condition influences misfolding protein-induced neurodegeneration.

High-nutrient diet

Nutrient-restricted diet

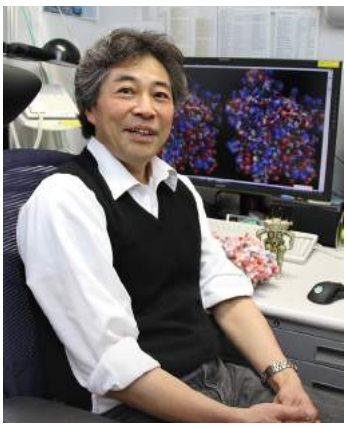
Drosophila models of neurodegenerative diseases

- Alzheimer's
- Parkinson's
- Polyglutamine
- ALS *etc*…



Protein aggregation (brain)

Diabetic Neuropathy



Hata, S., Kitamura, F., Yamaguchi, M., Shitara, H., Murakami, M., Sorimachi, H. (2016) "A Gastrointestinal Calpain Complex, G-calpain, Is a Heterodimer of CAPN8 and CAPN9 Calpain Isoforms, Which Play Catalytic and Regulatory Roles, Respectively." ***J. Biol. Chem.***, 291, 27313-27322.

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Shinkai-Ouchi, F., Koyama, S., Ono, Y., Hata, S., Ojima, K., Shindo, M., duVerle, D., Ueno, M., Kitamura, F., Doi, N., Takigawa, I., Mamitsuka, H., Sorimachi, H. (2016) "Predictions of cleavability of calpain proteolysis by quantitative structure-activity relationship analysis using newly determined cleavage sites and catalytic efficiencies of an oligopeptide array." ***Mol. Cell. Proteomics***, 15, 1262-1280.

Ojima, K., Ono, Y., Hata, S., Noguchi, S., Nishino, I., Sorimachi, H. (2014) "Muscle-specific calpain-3 is phosphorylated in its unique insertion region for enrichment in a myofibril fraction." ***Genes Cells***, 19, 830-841.

Tonami, K., Hata, S., Ojima, K., Ono, Y., Kurihara, Y., Amano, T., Sato, T., Kawamura, Y., Kurihara, H., Sorimachi, H. (2013) "Calpain-6 deficiency promotes skeletal muscle development and regeneration." ***PLoS Genet.***, 9, e1003668.

Hata, S., Abe, M., Suzuki, H., Kitamura, F., Toyama-Sorimachi, N., Abe, K., Sakimura, K., Sorimachi, H. (2010) "Calpain 8/nCL-2 and calpain 9/nCL-4 constitute an active protease complex, G-calpain, involved in gastric mucosal defense." ***PLoS Genet.***, 6, e1001040.

Ojima, K., Kawabata, Y., Nakao, H., Nakao, K., Doi, N., Kitamura, F., Ono, Y., Hata, S., Suzuki, H., Kawahara, H., Bogomolovas, J., Witt, C., Ottenheijm, C., Labeit, S., Granzier, H., Toyama-Sorimachi, N., Sorimachi, M., Suzuki, K., Maeda, T., Abe, K., Aiba, A., Sorimachi, H. (2010) "Dynamic distribution of muscle-specific calpain in mice has a key role in physical-stress adaptation and is impaired in muscular dystrophy." ***J. Clin. Invest.***, 120, 2672-2683.

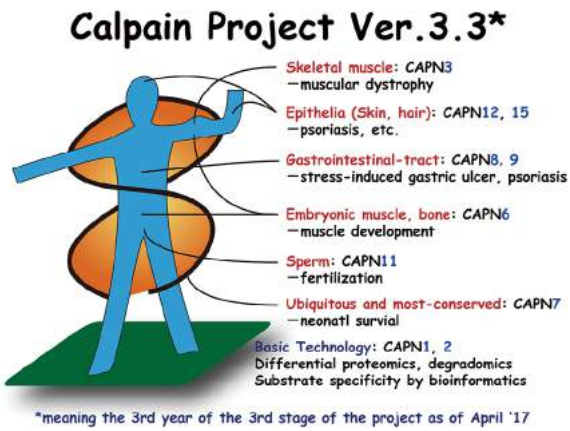
Calpain

Project Leader # Hiroyuki Sorimachi* **Calpain Project**

* passed away on Jan. 6, 2018 and taken over by Yasuko Ono

Calpain: Structure-Function Relationships

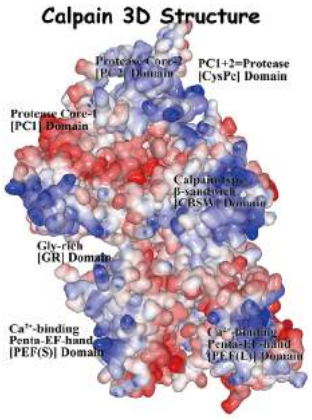
Exploring calpain-mediated biological modulation

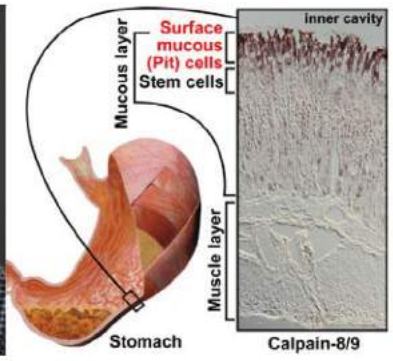


Proteins are chains of amino acids, and their functions change by partial cuts. Calpains are enzymes that perform such "cuts" or "limited proteolytic processing" in cooperation with calcium. Humans have 15 calpain species. Defects of either calpain cause various deficiencies, such as muscular dystrophy, stomach ulcer, and embryonic lethality. Calpains from infectious organisms also play essential roles in their pathogenicity; thus, calpains are promising targets in combat with infectious diseases like malaria, schistosomiasis, and periodontitis. Furthermore, calpains provide attractive subjects in protein science; was an original calpain structure anciently generated by fusion of protease and calciumbinding domains?

In this project, we aim to understand biology of calpains with wide scope of interest, and translate the knowledge to the development of our health as well as science.

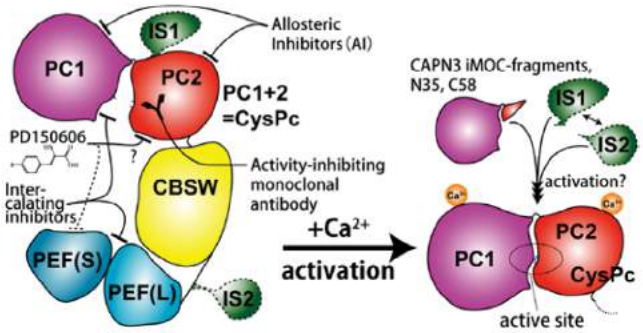
"Translational research involving calpains is still at the developmental stage. We need to learn more about the calpains themselves, as well as their impact on various physiological systems and molecular pathways." (*Nat. Rev. Drug Discov.* 2016)



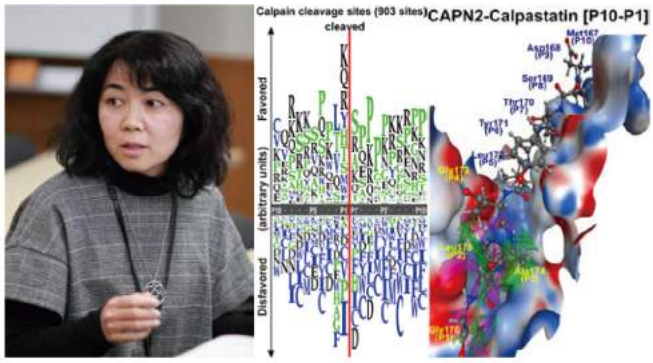


Shoji Hata, Ph.D.

Calpains in epithelial function and cell-adhesion

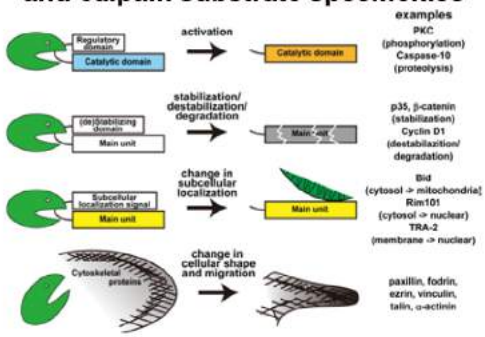


Strategy for activity regulation of calpains



Fumiko Shinkai-Ouchi, Ph.D.

Proteomic analysis of muscular dystrophy and calpain substrate specificities



Multiplicity of calpain actions

Ono, Y., Ojima, K., Shinkai-Ouchi, F., Hata, S., Sorimachi, H. (2016) "An eccentric calpain, CAPN3/p94/calpain-3." ***Biochimie***, 122, 169-187.

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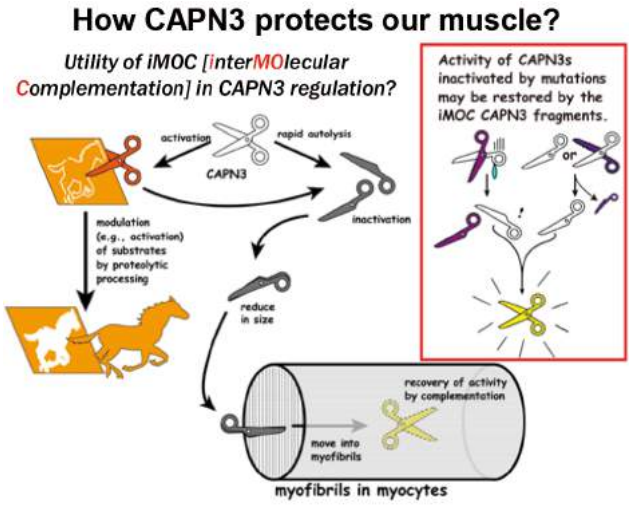
Ono, Y., Ojima, K., Torii, F., Takaya, E., Doi, N., Nakagawa, K., Hata, S., Abe, K., Sorimachi, H. (2010) "Skeletal muscle-specific calpain is an intracellular Na+-dependent protease." ***J. Biol. Chem.***, 285, 22986-22998.

Senior Research Scientist Yasuko Ono

Calpains in health and disease:

Exploring calpain-mediated biological modulation

Some calpains predominantly expressed in specific tissue(s) are responsible for genetic diseases; e.g., defects in CAPN3 cause muscular dystrophy. Other calpains with rather ubiquitous expression pattern lead to lethality if deficient.



To explore how calpains are usually protecting our health, analyses of mice lacking one of calpain genes, using biochemistry including proteomics, genetics, and bioinformatics, are being performed.

Calpain

Project Leader **Noriyuki Matsuda** Ubiquitin Project

Ubiquitin-Mediated Mitochondrial Quality Control: A shield against parkinson's disease

Ubiquitin is well-known as a signal for proteasome-dependent degradation; however, it also functions in autophagic degradation. Increasing evidence indicates that selective autophagy functions in intracellular quality control by using ubiquitin tags to delineate aggregated proteins and damaged organelles for degradation.

In 2000, Dr. Mizuno and Dr. Hattori (Juntendo Univ.) collaboration with Dr. Suzuki and Dr. Tanaka (TMiMS) reported for the first time that Parkin, which is a causative gene product of familial Parkinson's disease (PD), is an ubiquitin-protein ligase (Nat Genet 2000). In addition, the identification of another gene PINK1 that linked to the familial forms of hereditary recessive early-onset PD (Science 2004) has revealed that phosphorylation, ubiquitylation, and mitochondrial integrity are key factors in disease pathogenesis. Nevertheless, the exact mechanism underlying the functional interplay between Parkin and PINK1 remained an enigma. We thus have investigated how PINK1 and Parkin cooperate to keep mitochondrial integrity against mitochondrial stresses.

"We found that low-quality mitochondria are marked with ubiquitin for selective degradation, and the key factors in this process are PINK1 (a mitochondrial kinase) and Parkin (a ubiquitin ligase), two proteins implicated in Parkinson's disease."

PINK1 is a mitochondrial Ser/Thr kinase whereas Parkin is a ubiquitin-protein ligase that catalyzes ubiquitylation of diverse mitochondrial outer membranous proteins (J Cell Biol 2010). We revealed that PINK1 is rapidly and constitutively degraded under steady-state conditions in a mitochondrial membrane potential-dependent manner but that a loss in mitochondrial membrane potential stabilizes PINK1 mitochondrial accumulation (J Cell Biol 2010). Previously our and other groups found that PINK1 acts as an upstream factor for Parkin, but how PINK1 activates latent Parkin and recruits cytoplasmic Parkin to damaged mitochondria were still obscure.

Matsuda, N., Sato, S., Shiba, K., Okatsu, K., Saisho, K., Gautier, C., Sou, Y-S., Saiki, S., Kawajiri, S., Sato, F., Kimura, M., Komatsu, M., Hattori, N. and Tanaka, K. (2010) PINK1 stabilized by mitochondrial depolarization recruits Parkin to damaged mitochondria and activates latent Parkin for mitophagy. ***J. Cell Biology***, 189, 211-221.

Okatsu, K., Oka, T., Iguchi, M., Imamura, K., Kosako, H., Tani, N., Kimura, M., Go, E., Koyano, F., Funayama, M., Shiba-Fukushima, K., Sato, S., Shimizu, H., Fukunaga, Y., Taniguchi, H., Komatsu, M., Hattori, N., Mihara, K., Tanaka, K., and Matsuda, N. (2012) PINK1 autophosphorylation upon membrane potential dissipation is essential for Parkin recruitment to damaged mitochondria. ***Nature Commun.*** 3 : e1016 (10 pages).

Koyano, F., Okatsu, K., Kosako, H., Tamura, Y., Go, E., Kimura, M., Kimura, Y., Tsuchiya, H., Yoshihara, H., Hirokawa, T., Endo, T., Fon, E-A., Trempe, J-F., Saeki, Y., Tanaka, K., and Matsuda, N. (2014) Ubiquitin is phosphorylated by PINK1 to activate Parkin. ***Nature***, 510, 162-166.

Matsuda, N. and Tanaka, K. (2015) Tagged tags engage disposal. ***Nature***, 524, 294-295.

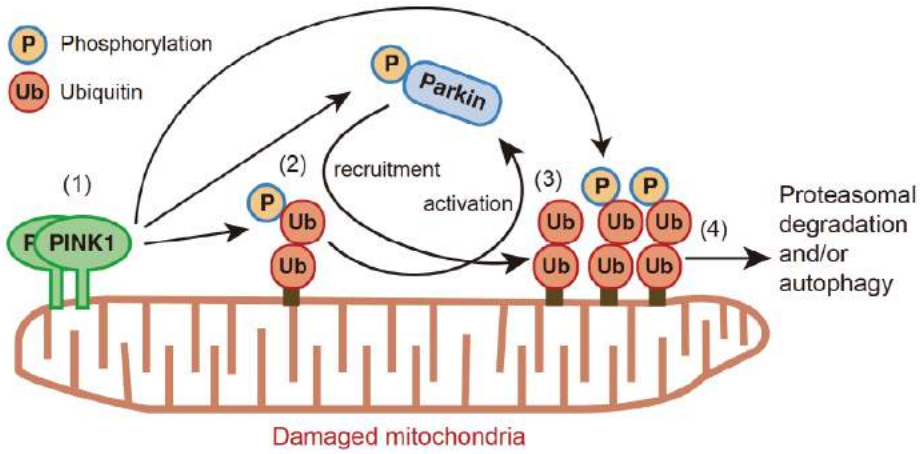
Okatsu, K., Koyano, F., Kimura, M., Kosako, H., Saeki, Y., Tanaka, K., and Matsuda, N. (2015) Phosphorylated ubiquitin chain is the genuine Parkin receptor. ***J. Cell Biology***, 209, 111-128.

Ubiquitin

We found that PINK1 phosphorylates both Parkin and ubiquitin at Ser65 that are sufficient for full activation of latent Parkin E3 activity, and that the S65 phosphorylated ubiquitin is a Parkin activator (Nature 2014). Subsequently we unveiled that the phosphorylated ubiquitin chain functions as the genuine Parkin receptor for its recruitment to depolarized mitochondria (J Cell Biol 2015). Ubiquitin phosphorylation enables us to understand comprehensively how PINK1 regulates Parkin to prevent predisposition to Parkinson's disease.

Our study has revealed that PINK1 and Parkin cooperate in the recognition, labeling, and clearance of damaged (i.e., depolarized) mitochondria by selective mitochondrial autophagy (mitophagy). To date, ubiquitylation has been a well-known post-translational modification; however, it is becoming increasingly clear that modified ubiquitin itself plays a critical cellular function as S65-phosphorylated ubiquitin functions in mitochondrial quality control.

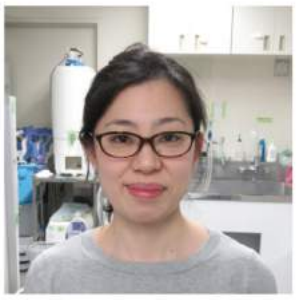
"We believe that big mystery in mitochondrial quality control has been unraveled, and our work can establish new principles of how a simple ubiquitin tag plays more varied roles than expected."



Our model for PINK1- and Parkin-catalyzed ubiquitylation for mitochondrial quality control.
We have revealed that accumulated PINK1 on damaged mitochondria (1) phosphorylates Parkin and ubiquitin, which (2) induces Parkin activation and its recruitment to the phosphorylated ubiquitin chain. Activated Parkin produces more ubiquitin chain (3), and the resultant ubiquitin is phosphorylated by PINK1 in a feed forward cycle. Parkin thus functions as an amplifier of the ubiquitin chain on depolarized mitochondria (4) for degradation.

Members

Yukiko Yoshida
Organellophagy via glycoprotein-specific ubiquitin ligase



Fumika Koyano
Molecular mechanism underlying Parkin-catalyzed ubiquitylation

Koji Yamano
Membrane dynamics upon mitochondrial quality control

Ubiquitin

K. Kitajima, K. Minehata, K. Sakimura, T. Nakano, and T. Hara. (2011) In vitro generation of HSC-like cells from murine ESCs/iPSCs by enforced expression of LIM-homeobox transcription factor Lhx2. ***Blood***, 117, 3748-3758.

K. Tanaka, K. Kondo, K. Kitajima, M. Muraoka, A. Nozawa, and T. Hara. (2013) Tumor-suppressive function of protein-tyrosine phosphatase non-receptor type 23 in testicular germ cell tumors is lost upon overexpression of miR142-3p microRNA. ***J. Biol. Chem.***, 288, 23990-23999.

K. Kitajima, M. Kawaguchi, M. Iacovino, M. Kyba, and T. Hara. (2013) Molecular functions of the LIM-homeobox transcription factor Lhx2 in hematopoietic progenitor cells derived from mouse embryonic stem cells. ***Stem Cells***, 31, 2680-2689.

Y. Kodaka, K. Tanaka, K. Kitajima, K. Tanegashima, R. Matsuda, and T. Hara.(2015) LIM homeobox transcription factor Lhx2 inhibits skeletal muscle differentiation in part via transcriptional activation of Msx1 and Msx2. ***Exp. Cell Res.***, 331, 309-319.

T. Suzuki, Y. Kazuki, M. Oshimura, and T. Hara. (2016) 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***, 11, e0157187.

K. Tanegashima, Y. Sato-Miyata, M. Funakoshi, Y. Nishito, T. Aigaki, and T. Hara. (2017) Epigenetic regulation of the glucose transporter gene Slc2a1 by b-hydroxybutyrate underlies preferential glucose supply to the brain of fasted mice. ***Genes Cells***, 22, 71-83.

Stem Cell

Project Leader **Takahiko Hara** Stem Cell Project

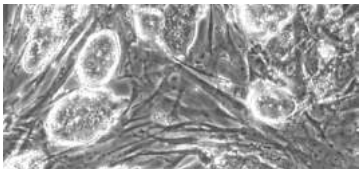
Blood regeneration from ESC/iPSC and development of novel anti-cancer drugs

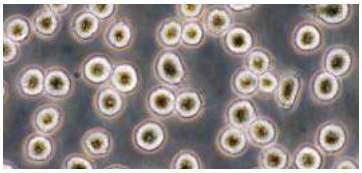
Dr. Yamanaka's inducible pluripotent stem cell (iPSC) technology has opened a new avenue to overcome incurable diseases by transplantation of missing cells. In 2011, we discovered that overexpression of Lhx2 in hemogenic mesodermal cells resulted in ex vivo expansion of transplantable hematopoietic stem cells (HSCs) from mouse embryonic stem cells (ESCs) and iPSCs. Since then, we are making great efforts to improve the system and apply this method to human iPSCs. We believe that comparison of the in vitro differentiation capacity of hematopoietic cells between mouse and human iPSCs would uncover novel and fundamental aspects of human HSC development.

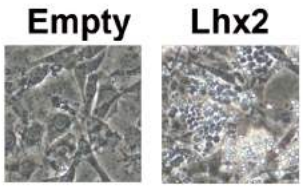
"We are making efforts to derive HSCs from human iPSCs in vitro. We are also challenging to develop novel anti-leukemia drugs and chemokine-based anti-cancer drugs."

The presence of cancer stem cells has been proposed in various types of human cancer. As with tissue stem cells, cancer stem cells reside in a niche and stay dormant, thereby surviving chemotherapy and radiotherapy. Presumably, both tissue and cancer stem cells commonly express critical transcriptional regulators and signal transducers. We have already identified DDX1 and PTPN23 as essential molecules for the onset of testicular tumors.

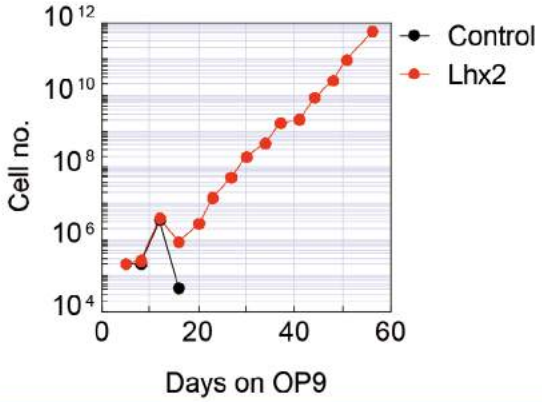
In 2007, we discovered that CXCL14, a CXC-type chemokine, is one of the causative factors for obesity-associated diabetes. In contrast, CXCL14 is known to possess tumor-suppressive activity against lung and oral carcinomas. Recently, we discovered that CXCL14 binds to CXCR4 with high affinity, thereby inhibiting the CXCL12-mediated cell migration. This could be one of the underlying mechanisms of the CXCL14's anti-tumor function. We are vigorously investigating physiological roles of CXCL14 and its action mechanisms. CXCL14 is a promising tool for developing novel anti-cancer and anti-diabetes drugs.





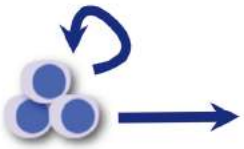


<Topic 1>
Enforced expression of *Lhx2* leads to robust *ex vivo* production of HSC-like cells from mouse ESCs/iPSCs.



HSC-like cells

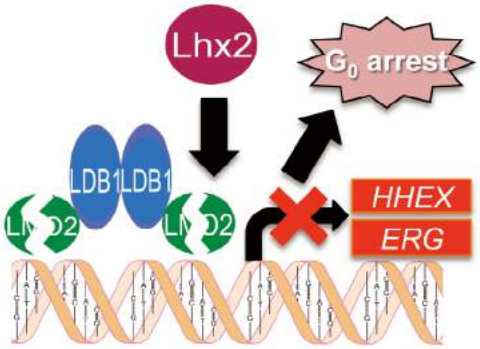
In vivo



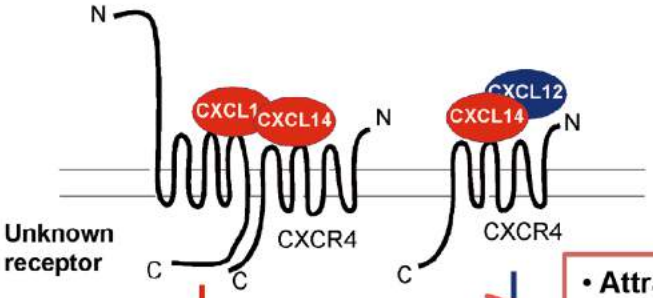
Lhx2 transduction

Myeloid cells
Erythrocytes
Platelets
B cells
T cells

<Topic 2>
Lhx2 induces degradation of Lmo2 protein, thereby inhibiting proliferation of human T-cell acute lymphoblastic leukemia (T-ALL) cells.



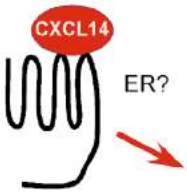
<Topic 3>
CXCL14 is one of the tuning molecules for CXCL12/CXCR4 signaling axis.



- Attraction of HSCs to bone marrow niche
- Neurogenesis in dentate gyrus
- Growth and metastasis of tumor cells

CXCL12-mediated signals

Attenuation of CXCL12 signals

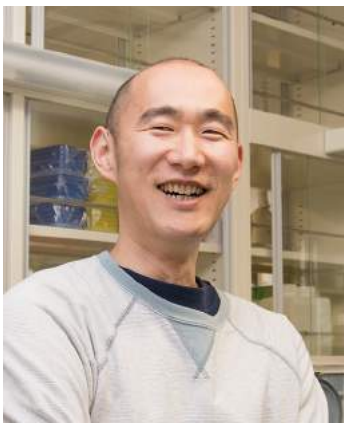


CXCL14-mediated signals

Physiological roles of CXCL14

Metabolic regulation

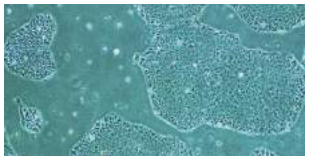
Stem Cell

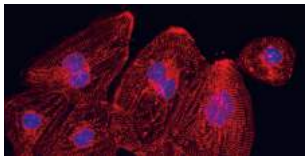


Project Leader **Yuichiro Miyaoka** Regenerative Medicine Project

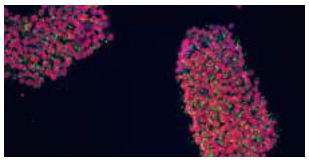
Genome Editing in Human iPS Cells: To study and cure genetic disorders

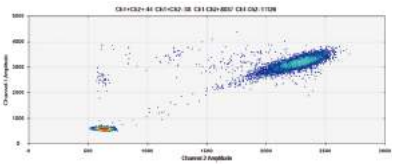
Genome editing technology allows us to rewrite the genetic information in virtually any species and any cell type including human cells. To study the pathogenesis of human diseases at the molecular level, and to develop new therapies using genome editing, we need appropriate human cellular models. Our focus is on human iPS (induced pluripotent stem) cells, a type of pluripotent stem cell that can be generated from patients' cells by introduction of specific transcription factors, and differentiated into other cell types. Our goal is to use genome editing of iPS cells to both model human diseases, and develop new therapies.



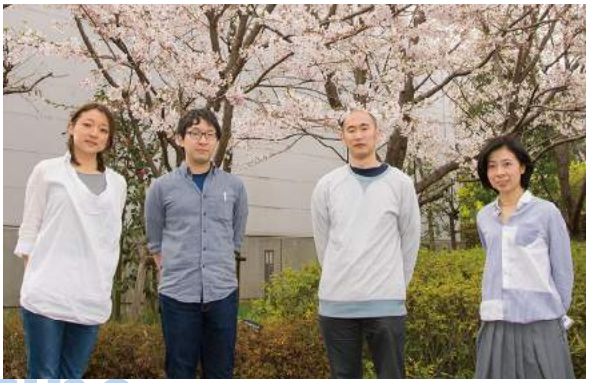


"Our goal is to develop methods to precisely and efficiently edit the genome in human iPS cells to allow us to develop disease models using human cells, and develop new therapies for these diseases."





We developed an efficient method to isolate iPS cell lines containing a single nucleotide substitution. The nucleotide substitution is created by genome editing based on digital PCR, and isolation is accomplished by repeated limited dilutions in the absence of selection markers (Miyaoka, Nat. Methods 2014). Using this method, we are analyzing the pathogenesis of cardiomyopathy caused by point mutations of RBM20 (RNA-binding motif protein 20) in isogenic cardiomyocytes derived from genome-edited iPS cells. We are also improving the precision and efficiency of genome editing technology, and developing new therapies based on correcting mutations in iPS cells from patients. In addition, we are developing a strategy to directly edit the genome in cells in the human body.



Miyaoka Y, Chan AH, Judge LM, Yoo J, Huang M, Nguyen TD, Lizarraga PP, So PL, Conklin BR. (2014) "Isolation of single-base genome-edited human iPS cells without antibiotic selection." ***Nat. Methods*** 11, 291-293.

Mandegar MA, Huebsch N, Frolov EB, Shin E, Truong A, Olvera MP, Chan AH, Miyaoka Y, Holmes K, Spencer CI, Judge LM, Gordon DE, Eskildsen TV, Villalta JE, Horlbeck MA, Gilbert LA, Krogan NJ, Sheikh SP, Weissman JS, Qi LS, So PL, Conklin BR. (2016) "CRISPR Interference Efficiently Induces Specific and Reversible Gene Silencing in Human iPSCs." ***Cell Stem Cell*** 18, 541-553.

Miyaoka Y, Berman JR, Cooper SB, Mayerl SJ, Chan AH, Zhang B, Karlin-Neumann GA, Conklin BR. (2016) "Systematic quantification of HDR and NHEJ reveals effects of locus, nuclease, and cell type on genome-editing." ***Sci. Rep.*** 6, 23549.

Miyaoka Y, Chan AH, Conklin BR. (2016) "Using Digital Polymerase Chain Reaction to Detect Single-Nucleotide Substitutions Induced by Genome Editing." ***Cold Spring Harb. Protoc.***

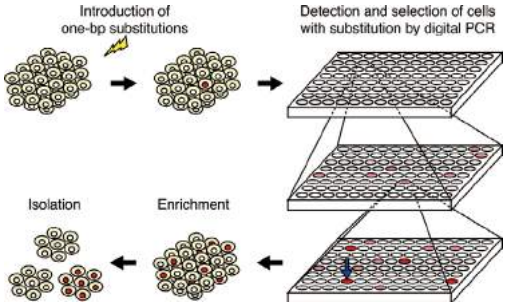
Nguyen DP, Miyaoka Y, Gilbert LA, Mayerl SJ, Lee BH, Weissman JS, Conklin BR, Wells JA. (2016) "Ligand-binding domains of nuclear receptors facilitate tight control of split CRISPR activity." ***Nat. Commun.*** 7, 12009.

Workman MJ, Mahe MM, Trisno S, Poling HM, Watson CL, Sundaram N, Chang CF, Schiesser J, Aubert P, Stanley EG, Elefanty AG, Miyaoka Y, Mandegar MA, Conklin BR, Neunlist M, Brugmann SA, Helmrath MA, Wells JM. (2017) "Engineered human pluripotent-stem-cell-derived intestinal tissues with a functional enteric nervous system." ***Nat. Med.*** 23, 49-59.

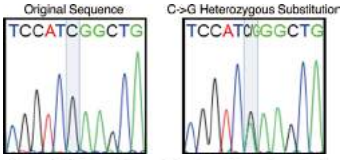
Regenerative Medicine

Changing a Single DNA Base-pair out of Three Billion

Single point mutations are often responsible for genetic disorders. Thus, the development of techniques to generate single point mutations is important for both modeling and curing diseases. However, thus far, it had been difficult to make specific single base-pair (bp) substitutions in the 3 billion-bp human genome. We have developed a method for isolating iPS cells with single-bp substitutions by combining genome editing, and serial limited dilutions using digital PCR .



Isolation of iPS cells with single nucleotide substitution

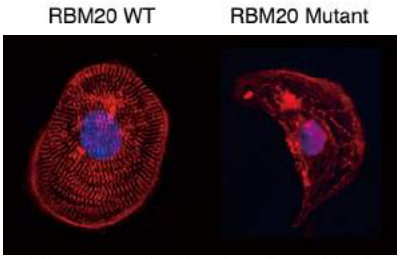


Isolated iPS cells with C→G substitution

Using this method, we can efficiently introduce single-bp substitutions at any location in the genome, allowing us to develop iPS cell-based disease models and transplantation therapies.

Heart Failure in a Dish

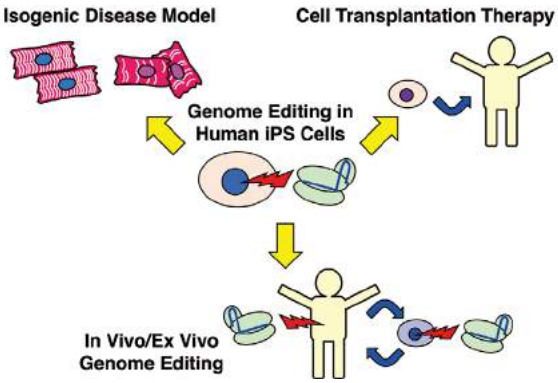
By editing the genome of iPS cells, we can study pathogenic mechanisms of genetic disorders in any cell type in a dish. For example, a point mutation in RBM20 (a cardiomyopathy mutation) introduced into iPS cells caused abnormal sarcomere structures (a functional unit of muscle contraction visualized as red stripes), when these cells were differentiated into cardiomyocytes. These cells can serve as a platform for drug screening.



Sarcomere (red) and nucleus (blue) in iPS cell-derived cardiomyocytes

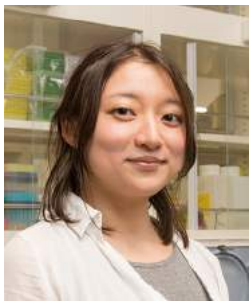
Development of Precise Ways to Edit the Genome

Current genome editing tools including CRISPR/Cas9 (Clustered regularly interspaced short palindromic repeats/CRISPR associated protein 9) have revolutionized our ability to modify the genetic information in cells. However, these tools still need to be improved for accuracy and efficiency when used in therapies. Therefore, we are developing a more precise and efficient way to edit the genome by modifying the Cas9 nuclease, and the guide RNA that directs Cas9 to the target regions. These improvements are necessary for further development of genome editing-based therapies.

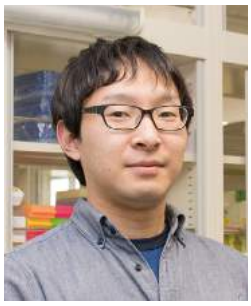


Genome editing in iPS cells to study and cure disease

Members



Tomoko Kato



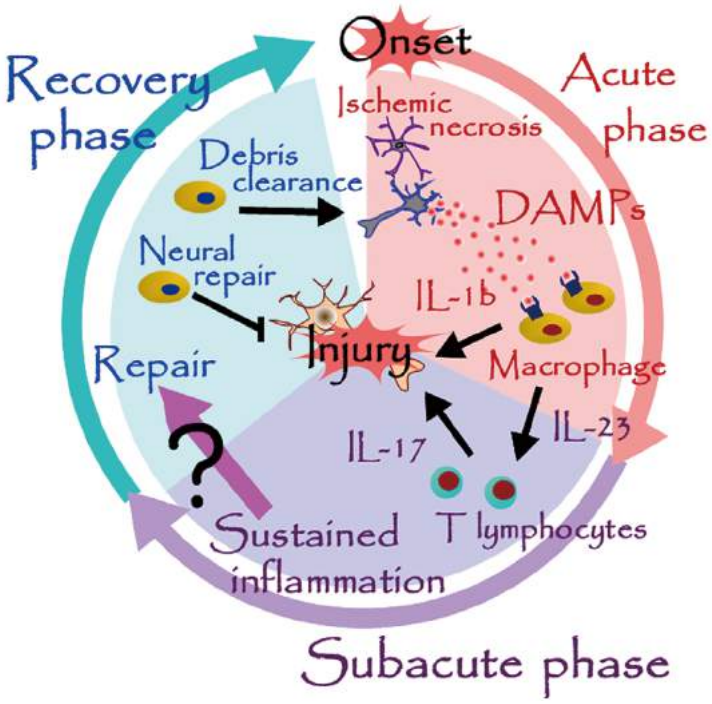
Gou Takahashi

Szuyin Hsu

Regenerative Medicine

Project Leader **Takashi Shichita** Stroke Renaissance Project

Sterile Inflammation After Ischemic Stroke



"What triggers neural repair after stroke?"

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

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

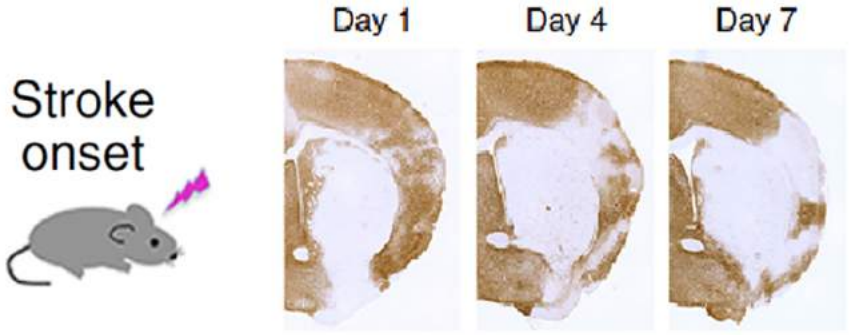
Shichita T, et al. (2012) Peroxiredoxin family proteins are key initiators of post-isch-emic inflammation in the brain. ***Nat Med.*** 18, 911-917.

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

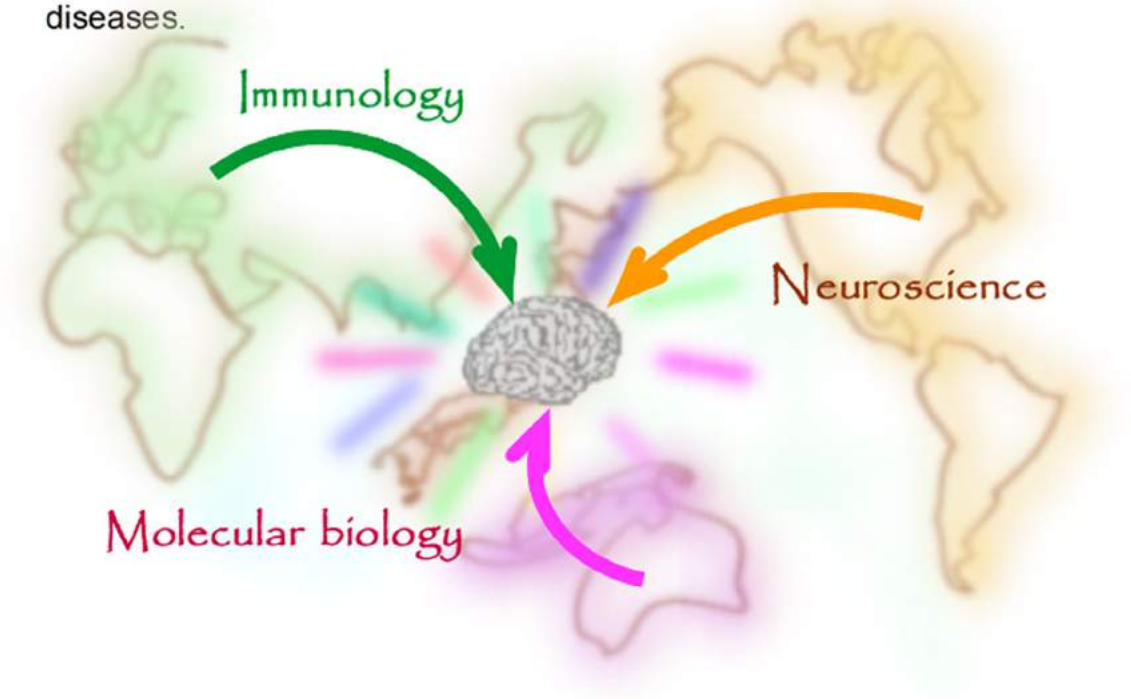
Stroke Renaissance

Stroke Renaissance Project

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



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



Stroke Renaissance

Kasahara, K., Kaneda, M., Miki, T., Iida, K., Sekino-Suzuki, N., Kawashima, I., Suzuki, H., Shimonaka, M., Arai, M., Ohno-Iwashita, Y., Kojima, S., Abe, M., Kobayashi, T., Okazaki, T., Souri, M., Ichinose, A., Yamamoto, N. (2013) "Clot retraction is mediated by factor XIII-dependent fibrin-aIIbb3-myosin axis in platelet sphingomyelin-rich membrane rafts." ***Blood*** 122, 3340-3348.

Sekino-Suzuki , N., Yuyama, K., Miki, T., Kaneda, M., Suzuki, H., Yamamoto, N., Yamamoto, T., Oneyama, C., Okada,M., Kasahara, K. (2013) "Involvement of gangliosides in the process of Cbp/PAG phosphoryla-tion by Lyn in developing cerebellar growth cones." ***J.Neurochem.*** 124, 514-522.

Kasahara, K., Souri, M., Kaneda, M., Miki, T., Yamamoto, N., Ichinose, A (2010) "Impaired clot retraction in factor XIII A subunit-deficient mice." ***Blood*** 115, 1277-1279.

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

Kasahara, K., Watanabe, K., Takeuchi, K., Kaneko, H., Oohira, A.,Yamamoto, T., and Sanai, Y. (2000) "Involvement of gangliosides in GPI-anchored neuronal cell adhesion molecule TAG-1 signaling in lipid rafts." ***J.Biol.Chem.*** 275, 34701-34709.

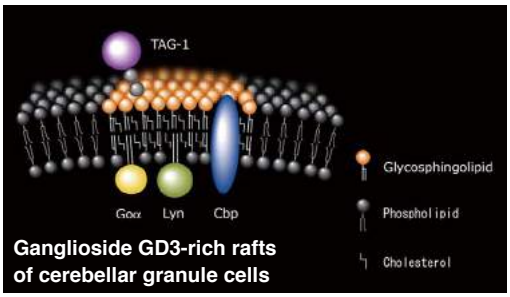
Kasahara, K., Watanabe, Y., Yamamoto, T., and Sanai, Y. (1997) "Association of src family tyrosine kinase Lyn with ganglioside GD3 in rat brain. Possible regulation of Lyn by glycosphingolipid in caveolae-like domains." ***J.Biol. Chem.*** 272, 29947-29953.

Biomembrane

Unit Leader **Kohji Kasahara** Biomembrane Unit

Physiological Functions of Lipid Rafts / Glycosphingolipid Microdomains in Transmembrane Signaling

Lipid rafts are dynamic assemblies of glycosphingolipids, sphingomyelin, cholesterol, and proteins that can be stabilized into microdomains involved in the regulation of a number of cellular processes.
We have been investigating the association of glycosphingolipids with specific proteins in the nervous system and blood platelets.
We demonstrated that anti-ganglioside GD3 antibody co-precipitates GPI-anchored neural cell adhesion molecule TAG-1, src-family kinase Lyn, its substrate Cbp, trimeric G protein Goα of cerebellar granule cells.

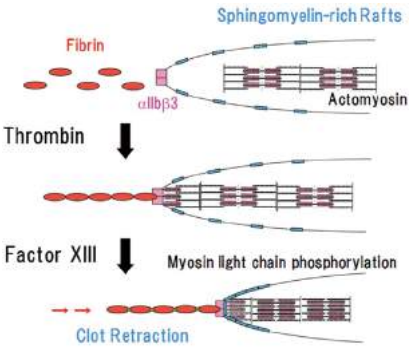


Ganglioside GD3-rich rafts of cerebellar granule cells

TAG-1 plays roles in axonal guidance, and cellular migration. GPI anchors have no direct contact with the cytoplasm. We demonstrated that TAG-1 transduces signal via Lyn/Cbp in ganglioside GD3-rich rafts of cerebellar granule cells. Chemokine SDF-1α triggers the chemoattraction of cerebellar granule cells during cerebellar development.
We demonstrated that SDF-1α stimulates GTPγS binding to Goα, and causes Goα translocation to lipid rafts, leading to growth cone collapse of cerebellar granule cells.

"We found that glycosphingolipids function as platforms in transmembrane signaling for the attachment of various signaling molecules of neurons and platelets."

Fibrin associates with lipid rafts on the platelets and raft integrity is required for clot retraction. We propose that clot retraction is mediated by factor XIII-dependent fibrin-integrin αIIbβ3-myosin axis in sphingomyelin-rich membrane rafts.

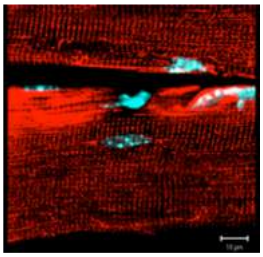


Sphingomyelin-rich rafts of platelets

Members: Ikuo Kawashima, Kiyoshi Ogura, Tomohiro Iguchi, Keisuke Komatsuya

Center for Basic Technology Research

Head of Center
Minoru Saitoe



The Basic Technology Research Center provides multiple resources to assist the researchers of the institute conduct researches with the maximum efficiency. The services provided include state-of-the art technologies required for biomedical and life science researches at their highest level, and maintenance of various facilities which are routinely used by the researchers. Details of the services provided and specific activities of related facilities are given below.

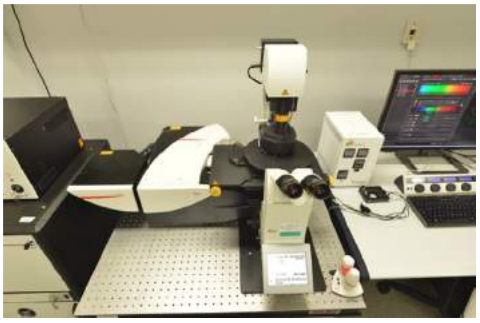
1. The Animal Research Division maintains the animal facility that is used by all the researchers who use animals for their research. It assists researchers generate knock-out or transgenic animals as well as maintain sperms and eggs of various lines of mutant animals. It also provides maximal care for the welfare of the animals used in the research.

2. The Advanced Technical Support Department consists of Protein Analyses, FACS, Microarray, Confocal Microscopy, Electron Microscopy, and Histology Laboratories etc. and offers state-of-the-art technology to the researchers.

3. The Information Support Department consists of Library, Information Technology Section, Media Technology Laboratory and Public Relation Office. It assists researchers search for references, provides supports for daily use of computer systems, and deals with the media.

4. The Authorized and General Core Facility Department consists of Radioisotope Laboratory, Hazardous Chemical Control Room and General Common Facility, and provides the researchers with various special and common facility as well as safety regulations for accident-free daily operation of the institute.

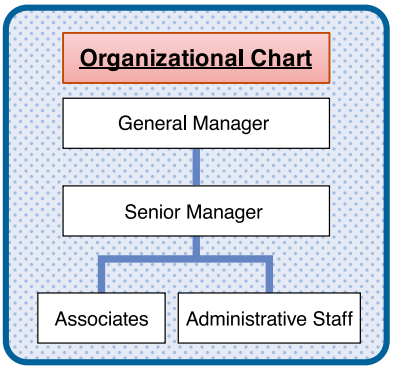
- Center for Basic Technology Research
  - Animal Research Division
    - Animal Research Control Laboratory
    - Laboratory for Transgenic Technology
  - Technology Research Division
    - Advanced Technical Support Department
      - Protein Analyses, FACS, Microarray, Confocal Microscopy, Electron Microscopy, and Histology Laboratories.
    - Scientific Advisory Office
    - Information Support Department
      - Library, Information Technology Section, Media Technology Laboratory, Graphic Design Unit.
    - Authorized and General Core Facility Department
      - Radioisotope Laboratory, Hazardous Chemical Control Room, General Common Facility.



Technology Licencing Office (TLO)

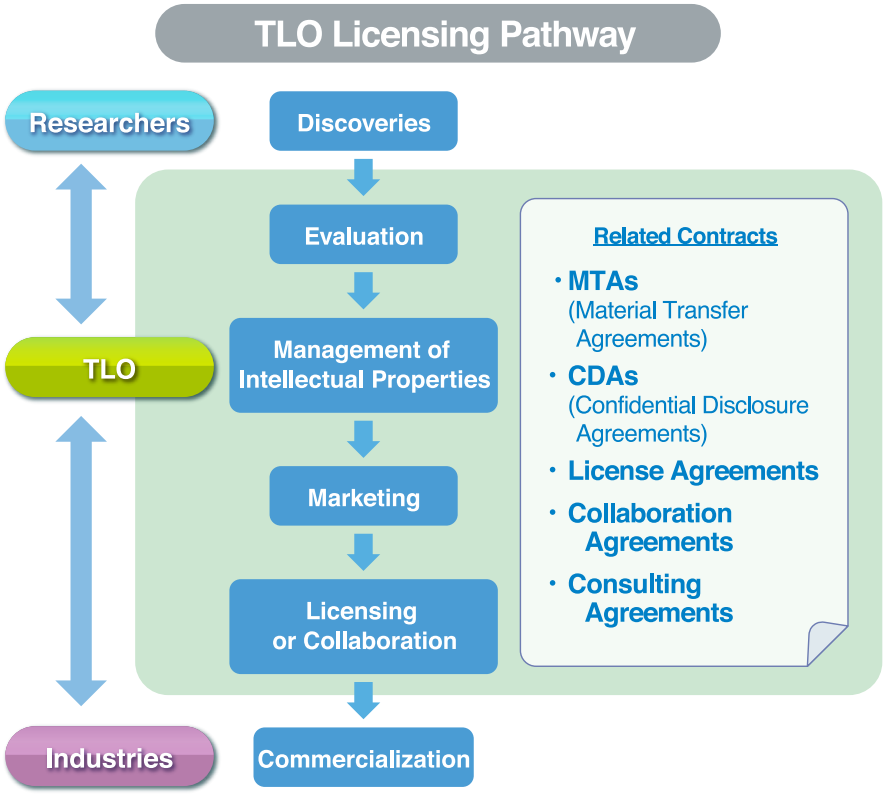
General Manager
Futoshi Shibasaki, MD, PhD

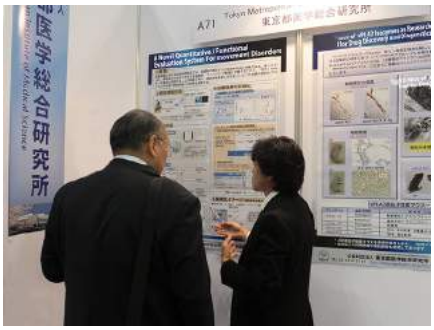
Senior Manager
Kazumasa Aoki, PhD



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 and BioJapan, to develop Public Private Partnership (PPP) opportunities between our institute and industries.
  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.

Center for Medical Research Cooperation

Head of Center
Masanari Itokawa

Making the Dream of Young Scientists Come True

– from bench to bed and back again –

We provide---
-Consultation on statistical analyses
-Ethical issues related to human specimens
-A bridge between basic scientists and medical doctors

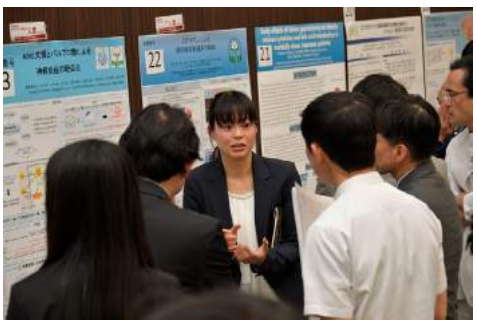
7,000 beds of Tokyo Metropolitan Hospitals

Tokyo Metropolitan Institute of Medical Science

Conference with researchers and medical doctors

We provide tools for developing medical technology from simple findings at the bench; the process similar to making a brilliantly sparkling jewelry by cutting a piece of crude stone. We provide consultation on statistical analyses of raw data. We manage ethical issues related to human specimens. We facilitate the communication between the basic scientists and medical doctors.

Most of discovery of scientific research is unexpectedly made by scientists who still have very “flexible” scientific mind, the privilege of young people.

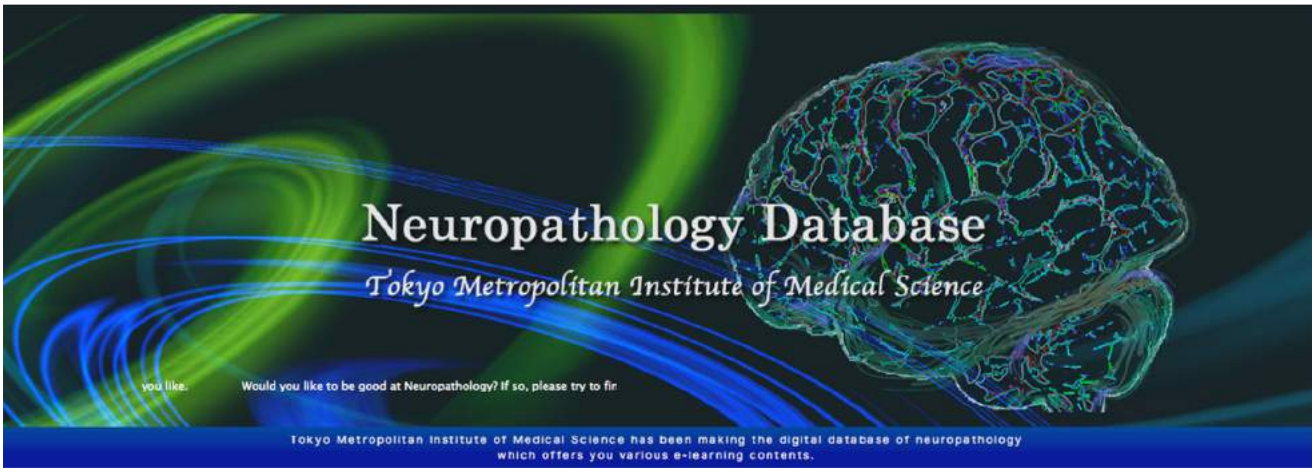


A young scientist discussing with medical doctors in a conference

Neuropathology Laboratory

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

Laboratory Head
Nobutaka Arai



Neuropathology Database Search **click**

Laboratory of Neuropathology (LONP) has more than 5,000 sets of human autopsied brain slides with a wide variety of human neurological diseases. In recent years, we have been scanning these slides with virtual slide instruments. Using those digital data and their derivatives, LONP is supposed to construct digital neuropathology database which could contribute to society through e-learning of basic knowledge, remote pathology and collaboration with neuroradiology. In addition, LONP has whole slide images of the marmoset brain which is open to researchers.

Neuropathology

Profession

Technical Researcher

Erika Seki
Brain Tissue Library
Stain Technology
Translational Research
Educational Lecture

Rika Kojima
Digital Pathology Archive
Stain Technology
Educational contents
e-Learning tool

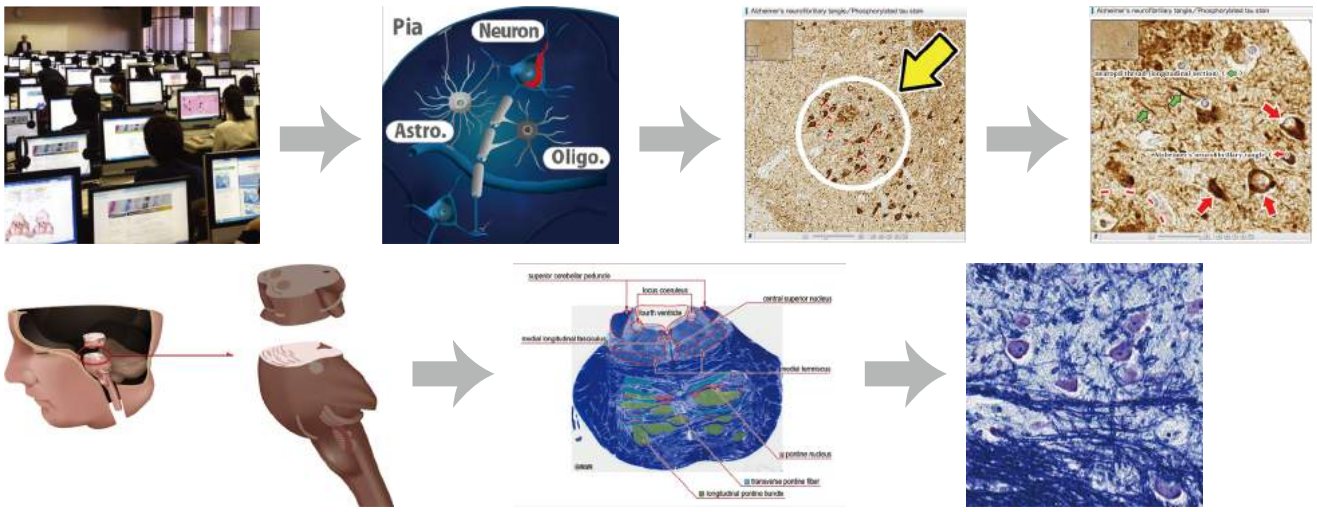
Digital Pathology Coordinator

Nobuko Ueki Web coding, server management
Tomoko Yagi Whole slide image, Web design

Neuroscience Illustrator

Tsunemi Yamanishi
Brain image illustrating, E-learning image

If you have an interest in our e-Learning, “Essential Brain Anatomy & Neuropathology”,
Please e-mail to: pathology-db@igakuken.or.jp



To request your own user ID and password to access the full contents of the digital atlas,
Please e-mail to: ns-marmoset@igakuken.or.jp

TMiMS Programs

Seminars/ lectures and related activities

Scientific seminars:
We have scientific seminars by renowned scientists from Japan and overseas almost every week in various subjects.

International Symposium:
We have three to four annual international symposium by inviting top-flight scientists from all over the world in various fields.

Science forum with industry:
We have annual forum hosted by our TLO office where scientists at our institute introduce our discovery and discuss potential applications with scientists from industry.

In-house and delivery lectures to high school students:
We give lectures to visiting high-school students or visit high schools to present lectures as a part of our effort to educate youngsters and introduce them into the field of medical science.

Joint graduate school programme:
Many scientists at our institute have joint appointment as a lecture or as a visiting professor at various universities. Many undergraduate and graduate students are conducting their master/ Ph.D. researches at our institute under the guidance of out scientists.

Open laboratory to graduate students:
Once a year we invite students to our institute, conduct presentation and give them opportunities to experience the laboratory.

Summer training courses:
We have annual summer training courses to provide in-house training on various experimental techniques.

Lectures to public:
We conduct public lectures (8 times a year) to let public know the scientific progress made at our institute and our various activities .

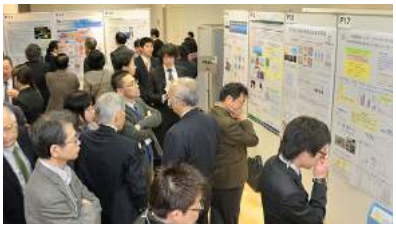
Science Café:
We have Café-style meetings (3-4 times a year) where we give public the opportunities to learn, discuss and experience science and let them know the joy of science in a very casual setting.

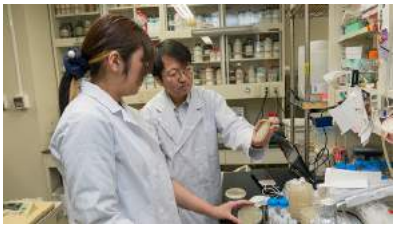
Supports for young scientists

Research Associate Fellowship:
We provide graduate students who conduct their master/ Ph.D. thesis research at our institute with research associate fellowship to give them financial support.

Travel support for young scientists attending an international meeting:
We provide students and young scientists of our institute with travel fellowships with which they can attend international meetings where they will present their latest findings.

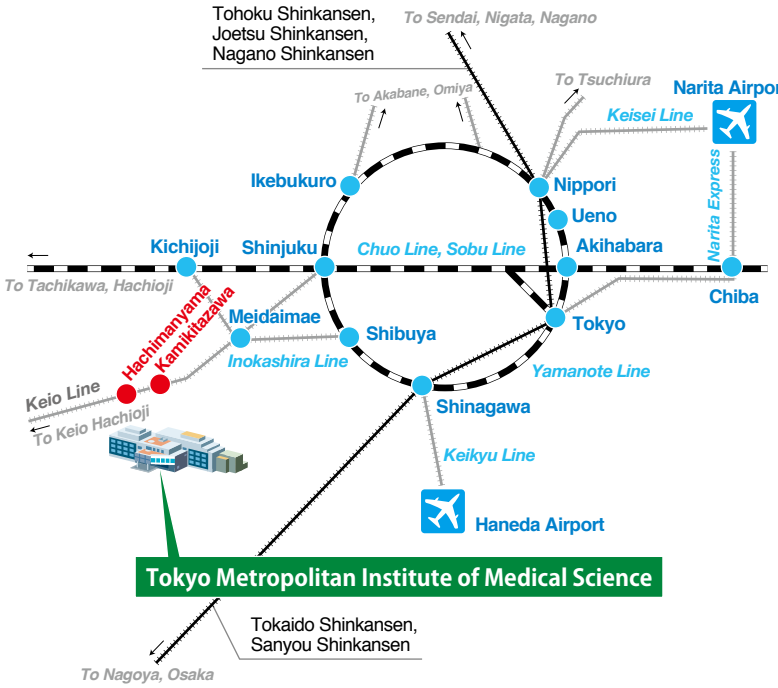







Access Map

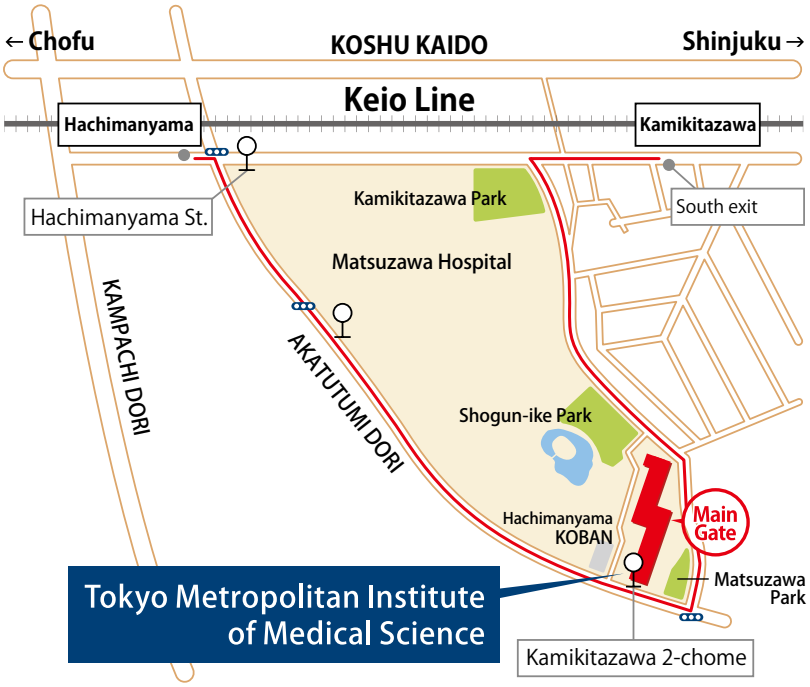
Tokyo Metropolitan Institute of Medical Science	
Address	2-1-6 Kamikitazawa, Setagaya-ku, Tokyo, 156-8506, Japan
Tel and Fax	+81-3-5316-3100 & +81-3-5316-3150
URL	http://www.igakuken.or.jp (Japanese) & http://www.igakuken.or.jp/english/ (English)



AIRPORT to INSTITUTE

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



- **From Kamikitazawa Station to Institute**
  Walk (approx. 10 min from the South exit of the station).
- **From Hachimanyama Station to Institute**
  Bus (5 min from Hachimanyama stop to Kamikitazawa 2-chome stop [in front of the institute])

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

As of February, 28, 2018