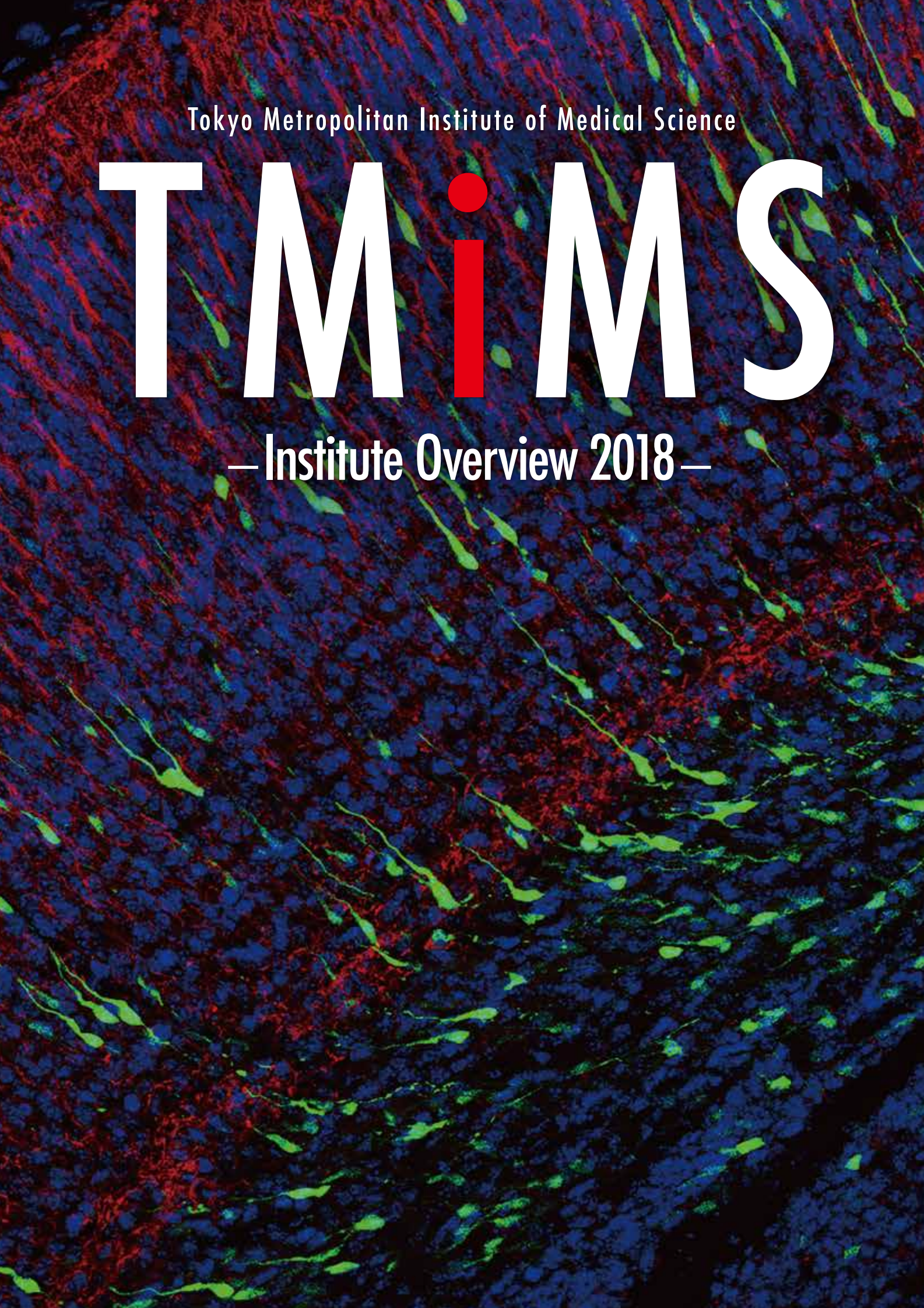
Tokyo Metropolitan Institute of Medical Science

TMiMS

–Institute Overview 2018–



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Message from Our Chairperson

Chairperson **Keiji Tanaka**

The metropolis of Tokyo is the nerve center of Japan. Developing Tokyo into a healthy welfare city will therefore go a long way toward building a prosperous future for Japan. The mission of the Tokyo Metropolitan Institute of Medical Science (TMIMS) is to promote research in the life and medical sciences to protect the lives and health of Tokyo citizens, with the goal of improving the health, medical care, and welfare of this metropolitan city. It is well known that Japan has the most rapidly ageing society in the world. Tokyo, which reflects Japan itself, is undergoing a steady increase in cancer and infectious diseases, which pose a threat to humanity, as well as lifestyle-related illnesses, neural and mental disorders, and various other health problems. Naturally, conquest of all of these diseases is a common goal of all humankind, and considerable efforts have been made at the national level. Even so, because Tokyo is one of the largest civilized cities in the world, it is also essential for the Tokyo Metropolitan Government to take the initiative in this endeavor. Besides, Tokyo has numerous problems unique to megacities. For instance, many people suffer from rare and intractable diseases that researchers often overlook. TMIMS has been actively working on these important problems, promptly and practically addressing health-related issues with the aim of protecting the health of numerous Tokyo citizens.

By the way, I am of the opinion that “research represents culture”. Accordingly, TMIMS aims to be acclaimed both academically and culturally for the knowledge and wisdom of its excellent researchers, with the ultimate goal of becoming a symbol of the culture of Tokyo, the foremost megalopolis in the world. Academic research is often roughly divided into top-down, exit-oriented applied research (of immediate use) and bottom-up, future-oriented fundamental research (seemingly not of immediate use). Balancing these two research strategies, TMIMS endeavors to operate the organization in a flexible manner in order to achieve additive and synergic effects. In fact, these two research strategies are not incompatible, but can work in a cooperative and harmonious manner. Throughout the history of science, we can find numerous examples of seemingly useless research suddenly becoming useful, resulting in great service to society.

Our medical researchers are energetically pursuing their research day and night to develop preventive medicine and new therapeutic methods to protect citizens’ health in the future. While TMIMS naturally takes on the role of educating young researchers who will help develop human knowledge and wisdom, it also seeks to generate concrete research findings that contribute to social prosperity. Accordingly, all the staff members of TMIMS are working on life science research, ranging from fundamental to practical, making the most of cutting-edge technologies to achieve their specific goals. It is vitally important that TMIMS grow to be the world’s top-notch research institute, and advancing and enriching its research power will eventually create an institute capable of rendering wide-ranging services to society. To this end, the entire staff of TMIMS will strive as one to help pursue incomparable fundamental research and pass the benefit of its research findings on to society, while recruiting and educating talented people to build up momentum.

We look forward to your further guidance and encouragement, which are indispensable for the further development of TMIMS. Thank you in advance for your continued support.

Message from Our Director

Director **Hisao Masai**

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 the Tokyo Metropolitan Government and had been present at different locations in Tokyo. The scientists from three different disciplines came 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 of the Tokyo Metropolitan Government, and our aim is to advance medical research 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. 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 as well as infectious diseases caused by viruses such as hepatitis, influenza, and other outbreaks. 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, stem cells and development, genetic diseases, brain functions, neurobiology, neurodegeneration, stem cells and development, virus infection, allergy, schizophrenia, and depression. Using the state-of-art and newest technology and equipment, we are identifying molecules and mechanisms responsible for various biological phenomena as well as for disease progression. These knowledges and technologies will be used to predict and prevent diseases, and develop new drugs and therapies that can be tailored to individual patients.

We also emphasize importance of sociomedical approaches, including large scale cohort studies aimed at identifying social and environmental factors associated with mental health of youths. We develop effective care and nursing systems for elderly people suffering from dementia, and provide those suffering from progressive and currently incurable diseases such as ALS (amyotrophic lateral sclerosis) with innovative care systems to improve QOL of these patients.

We will pursue research that will contribute to prediction, prevention, diagnosis, and treatment of various diseases, will improve the care of patients, and will help realize longer healthy life. We will also keep the people of the Tokyo Metropolises as well as those from other areas informed of our latest progress by having various outreach activities including public lectures, science café , and lectures/ classes to students. Through these efforts, we hope to serve as a leader and model institute for the life/medical science in the coming decades.

History

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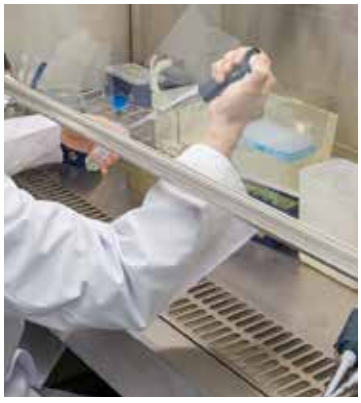
Our Mission

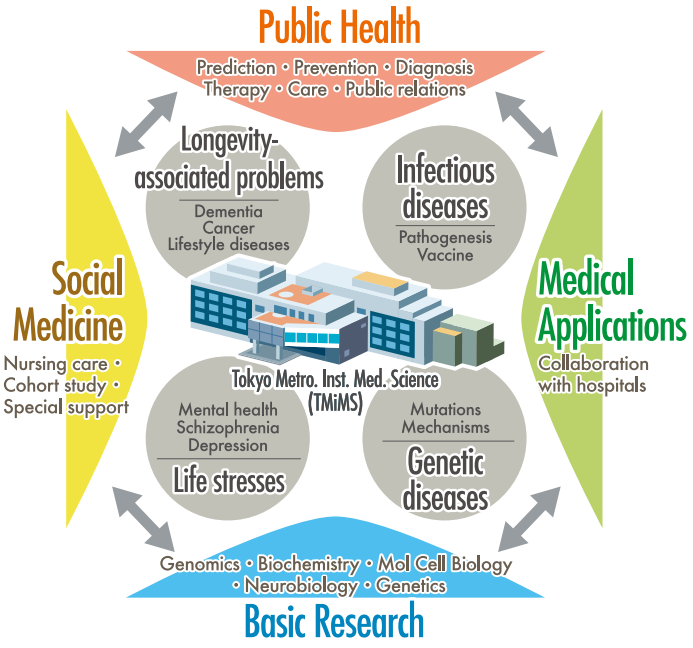


The mission of our institute is to pursue research that will lead to the development of solutions for health-related problems commonly observed in large urban areas and developed countries. Utilizing results from the forefront basic research on molecular and cellular mechanisms of biological pathways 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, schizophrenia, 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.



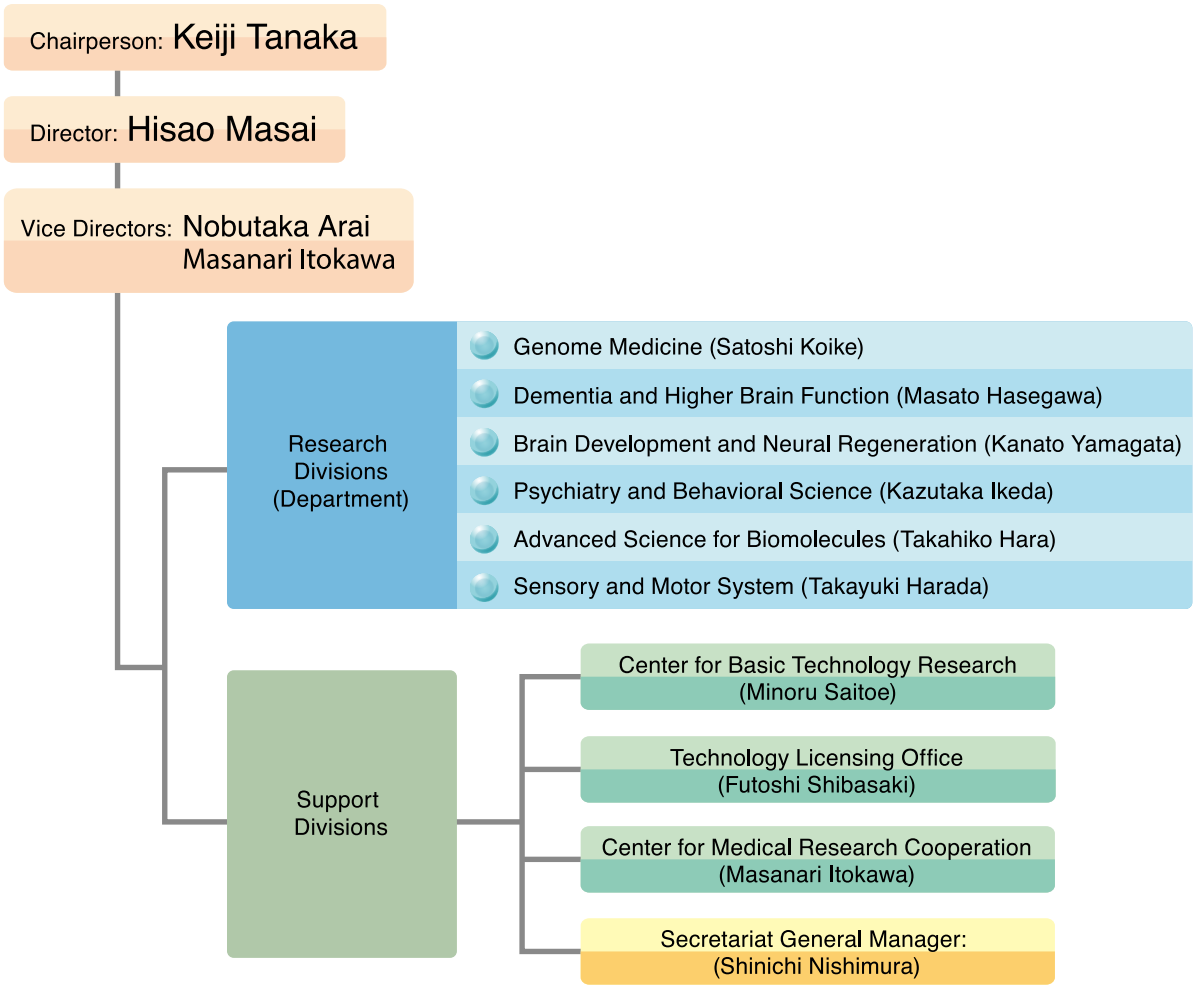
We are also combining sociomedical approaches with molecular and genomic approaches to discover unique and effective treatments for mental disorders. Our institute takes advantage of a multi-disciplinary structure to provide novel solutions to various health-related issues. Located in one of the biggest 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.

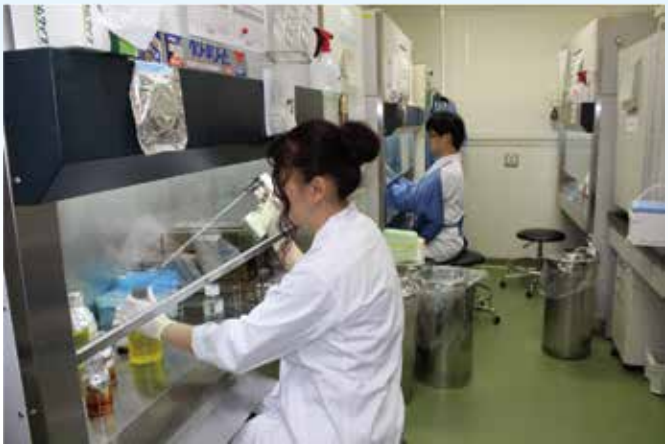
Organizational Chart

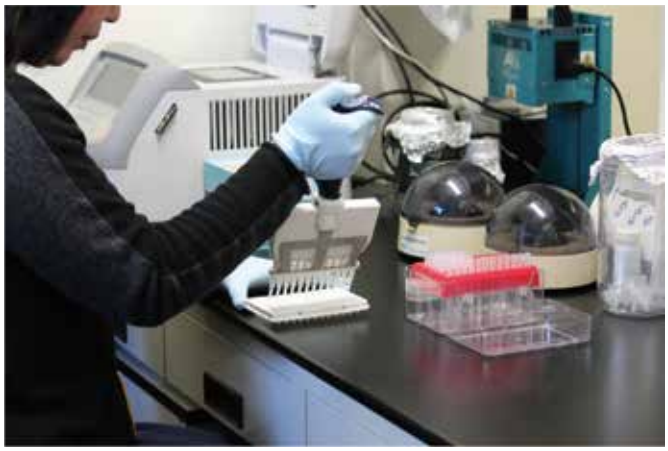


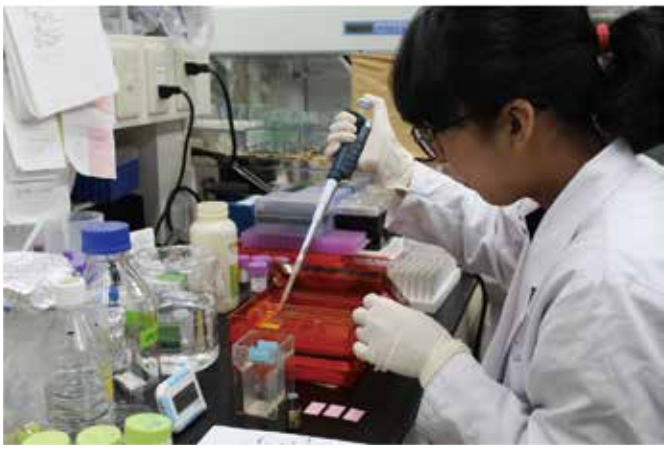
Our People at a Glance

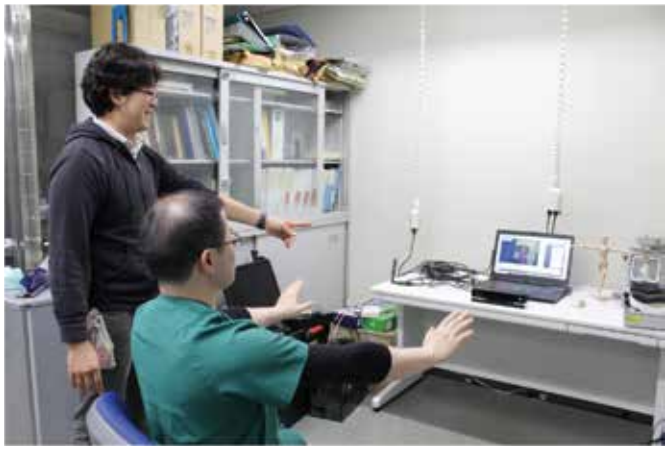
Position	Number
Researchers	157
Postdoctoral Fellows	57
Students	97
Visiting Scientists	145
Guest Scientists	130
Administrative Staffs	29
Total	615

As of October 1, 2018









Research Activities

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Moriyama K, Yoshizawa-Sugata, N, and Masai H. (2018) "Oligomer formation and G-quadruplex binding by purified murine Rif1 protein, a key organizer of higher-order chromatin architecture." ***J. Biol. Chem.*** 293:3607-3624.

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Yang C-C, Suzuki M, Yamakawa S, Uno S, Ishii A, Yamazaki S, Fukatsu R, Fujisawa R, Sakimura K, Tsurimoto T, and Masai H. (2016) "Claspin recruits Cdc7 kinase for initia-tion of DNA replication in human cells." ***Nature Commun.*** 7: 12135.

Kanoh Y, Matsumoto S, Fukatsu R, Kakusho N, Kono N, Renard-Guillet C, Masuda K, Iida K, Nagasawa K, Shirahige K, and Masai H. (2015) "Rif1 binds to G-quadruplexes and suppresses replication over long distances." ***Nature Struct. Mol. Biol.*** 22: 889-897.

Yamazaki S, Ishii A, Kanoh Y, Oda M, Nishito Y, and Masai H. (2012) "Rif1 protein is a key regulator of the genome-wide DNA replication timing in human cells." ***EMBO J.*** 31: 3167-3177.

Hayano M, Kanoh Y, Matsumoto S, Shrahige K, and Masai H. (2012) "Rif1 is a global regulator of timing of replication origin firing in fission yeast." ***Genes and Development*** 26: 137-150.

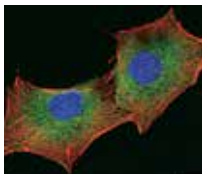
Matsumoto S, Hayano M, Kanoh Y, and Masai H. (2011) "Multiple path-ways can bypass the essential role of fission yeast Hsk1 kinase in DNA replication initiation." ***J. Cell Biol.*** 195: 387-401.

Masai H, Matsumoto S, You Z, Yoshizawa-Sugata N, and Oda M. (2010) "Eukaryotic DNA replication; where, when and how?" ***Annual Rev. Biochem.*** 79: 89-130.

Project Leader **Hisao Masai** Genome Dynamics Project

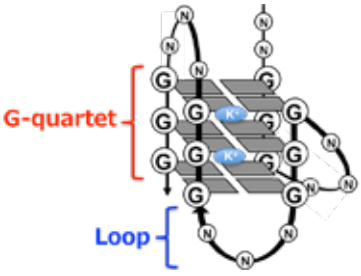
Genome Replication and Maintenance:
In search of unexplored messages in the genome

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.

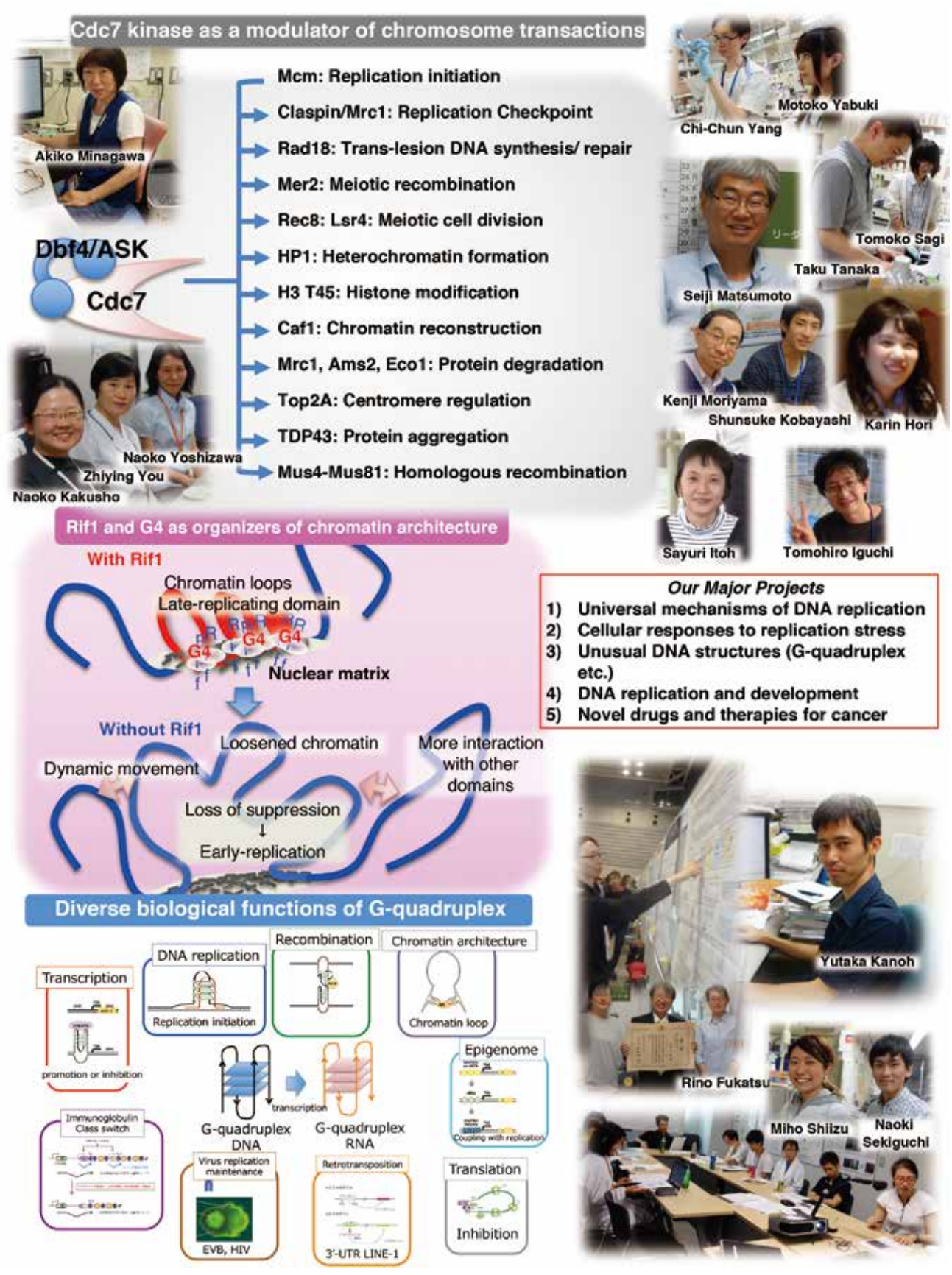



"We are trying to decipher 'unexplored messages' of the genome that are crucial for shaping the chromosomes, copying and reading out genetic information, and even for causing detrimental diseases."

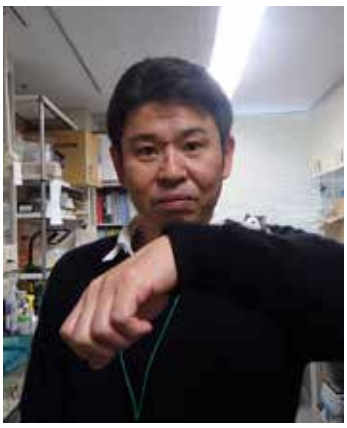
We recently discovered novel and crucial roles of non-standard DNA structures in regulation of DNA replication and transcription. Notably, we found that G-quadruplex structures, which are widely present on genomes (estimated to be present at more than 370,000 locations on the human genome), regulate 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 and neurodegenerative diseases are related to alteration and mal-formation of these non-B DNA structures, which are likely to be essential components of genomes but somehow have been disregarded in the past.



Genome Dynamics



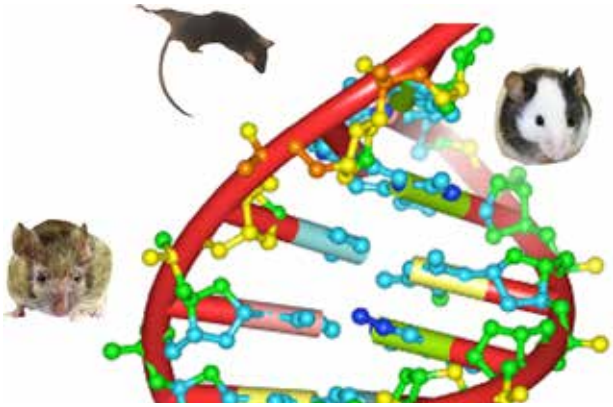
Genome Dynamics



Project Leader **Yoshiaki Kikkawa** Mammalian Genetics Project

Gene discovery: Phenotype- and gene-driven approaches to identify disease-associated genes in mice

Mouse disease models have contributed to the study of pathogenic mechanisms. The demand for mouse disease models will continue to increase because the genetic factors and molecular mechanisms behind many human genetic diseases are still unknown. Mouse disease models are important tools for identifying genes that are responsible for genetic diseases. They are also important for studying the processes that regulate the onset of genetic diseases and for evaluating the effectiveness of new drugs. We aim to develop novel mouse disease models via forward and reverse genetics for the phenotypic analysis of human genetic diseases and for the study of pathogenic mechanisms.



"We are trying to identify genes associated with human diseases using mutant mice and are aiming to develop new mouse models for human disease."

Yasuda SP, Miyasaka Y, and Kikkawa Y. (2018) "Effects of genetic background on susceptibility and the acceleration of hearing loss in mice." ***An Excursus into Hearing Loss*** 3–23.

Wada K, Saito J, Yamaguchi M, Seki Y, Furugoria M, Takahashi G, Nishito Y, Matsuda H, Shitara H, and Kikkawa Y. (2018) "*Pde6b*^{rd1} mutation modifies cataractogenesis in *Foxe3*^{rct} mice." ***Biochem. Biophys. Res. Commun.*** 496: 231-237.

Seki Y, Miyasaka Y, Suzuki S, Wada K, Yasuda SP, Matsuoka K, Ohshiba Y, Endo K, Ishii R, Shitara H, Kitajiri SI, Nakagata N, Takebayashi H, and Kikkawa Y. (2017) "A novel splice site mutation of myosin VI in mice leads to stereociliary fusion caused by disruption of actin networks in the apical region of inner ear hair cells." ***PLoS One*** 12, e0183477.

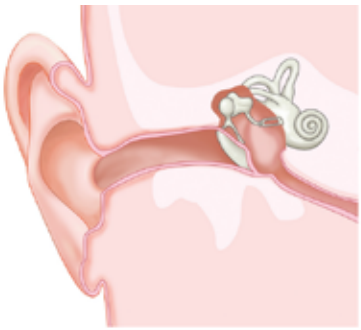
Miyasaka Y, Shitara H, Suzuki S, Yoshimoto S, Seki Y, Ohshiba Y, Okumura K, Taya C, Tokano H, Kitamura K, Takada T, Hibino H, Shiroishi T, Kominami K, Yonekawa H, and Kikkawa Y. (2016) "Heterozygous mutation of *Ush1g/Sans* in mice causes early-onset progressive hearing loss, which is recovered by reconstituting the strain-specific mutation in *Cdh23*." ***Hum. Mol. Genet.*** 25: 2045-2059.

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

Suzuki S, Ishikawa M, Ueda T, Ohshiba Y, Miyasaka Y, Okumura K, Yokohama M, Taya C, Matsuoka K, and Kikkawa Y. (2015) "Quantitative trait loci on chromosome 5 for susceptibility to frequency-specific effects on hearing in DBA/2J mice." ***Exp. Anim.*** 64: 241-251.

Mammalian Genetics

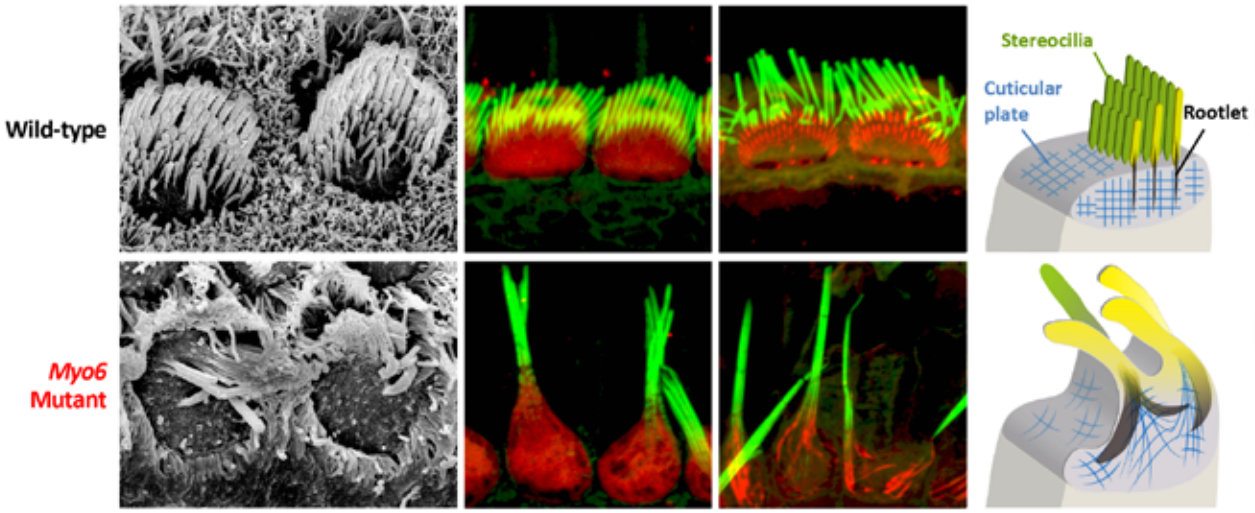
Main project: Genetics of deafness



Hearing loss is the most common sensory disease in humans, which severely affects one's quality of life. We continue to make significant advances in understanding the development, transduction, and homeostasis of the auditory system by studying corresponding mouse mutants. We exploit the similarities between the mouse and human genomes, physiology, and auditory system anatomy to identify and characterize genes related to deafness.

Current focus

Stereociliary fusion in Myo6 mutant mice caused by a disruption of actin networks in the apical region of inner ear hair cells



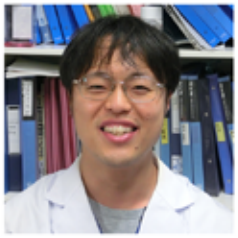
Stereocilia morphology of inner hair cells | Expression of the marker protein of the cuticular plate | Expression of the marker protein of the rootlet | Model for architecture of stereocila base

An unconventional myosin encoded by *MYO6*, a myosin VI gene, contributes to hearing loss in humans. Homozygous *Myo6* mutant mice exhibit congenital hearing defects caused by the fusion of stereocilia. We recently identified morphological changes at the base of the stereocilia in *Myo6* mouse mutants by scanning electron microscopy and analysis of the marker proteins of the cuticular plate and rootlet. In wild-type mice, stereocilia have dense rootlets that extend through the taper region of stereocilia to anchor them into the actin mesh of the cuticular plate. These structures are maintained when MYO6 is normally expressed in the stereociliary taper region, cuticular plate, and cytoplasm of the hair cells, but a reduction of MYO6 leads to stereociliary fusion accompanied by deformations of the cuticular plates and the extension of rootlets.

By Yuta Seki

Members

Kunie Matsuoka



Shumpei Yasuda

Xuehan Hou

Yuki Miyasaka

Kenta Wada

Mammalian Genetics

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, and Kohara M. (2017) "Selective inhibitor of Wnt/βcatenin/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, and 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, and 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, and 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, and Kohara M. (2015) "M2 Macrophages Play Critical Roles in Progression of Inflammatory Liver Disease in Hepatitis C Virus Transgenic Mice." ***J. Virol.*** 90: 300-307.

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

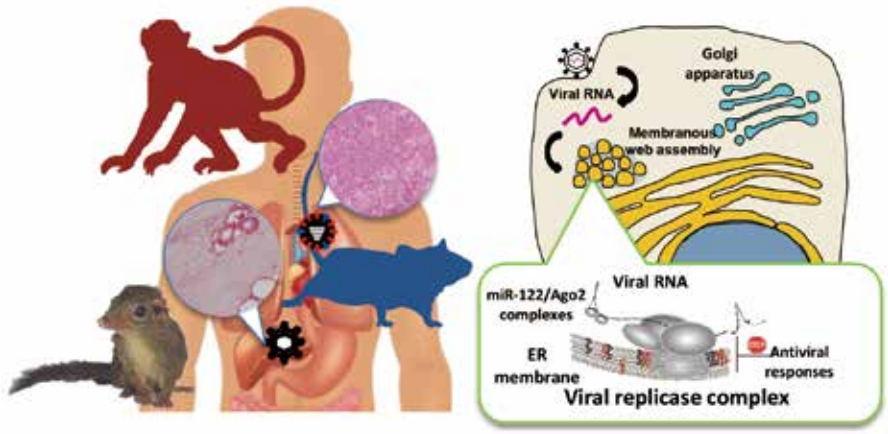
- Identification of host factors regulating virus growth.
- Elucidation of the mechanisms underlying pathogenesis caused by hepatitis virus infection.
- Development of therapeutic vaccine and drug for chronic HBV/HCV infection and other liver diseases.

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.



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.

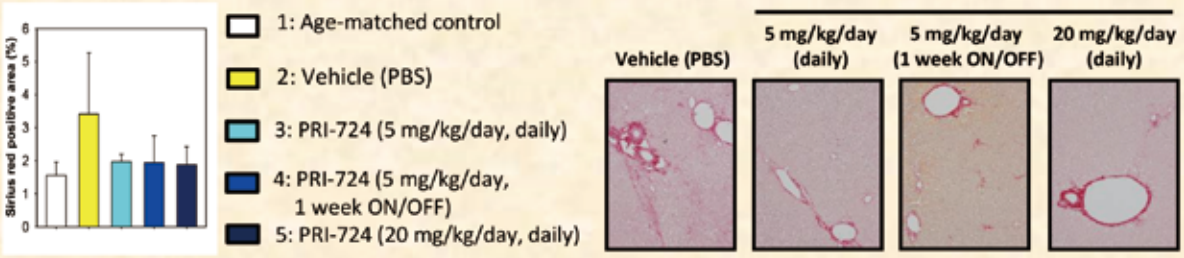
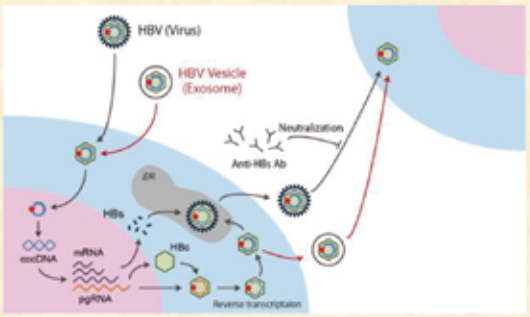


Figure. PRI-724ameliorates hepatitis C virus-induced liver fibrosis.

Transmission of HBV DNA Mediated by Ceramide-Triggered Extracellular Vesicles

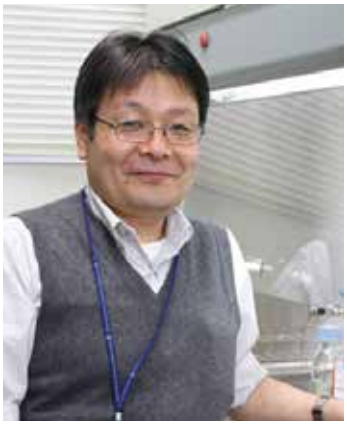
Extracellular vesicle is a nanovesicle that shuttles proteins, nucleic acids, and lipids, thereby influencing cell behavior. We showed that ceramide-triggered extracellular vesicles work as DNA cargo for hepatitis B virus-DNA and are capable of trasmitting to naive hepatocytes. Further, we demonstrated 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
Kenzaburo Yamaji
Naoki Yamamoto
Takahiro Ohtsuki
Yuko Tokunaga
Takahiro Sanada
Tomoko Honda

Viral Infectious Diseases



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

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Yamayoshi S, Koike S. (2011) "Identification of the Human SCARB2 Region That Is Important for Enterovirus 71 Binding and Infection." ***J. Virol.***, 85: (10) 4937-4936

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Project Leader **Satoshi Koike** Neurovirology Project

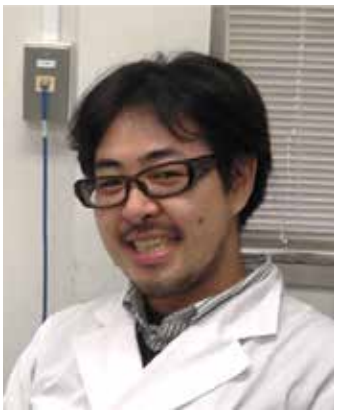
Protect the Central Nervous System from infectious Diseases

"The development of vaccine and anti-viral drugs and that of experimental models for the evaluation of these agents are important for controlling emerging and re-emerging viral infections. We will study the basic principles of neurotropic enterovirus infection and provide knowledge and technologies to control infectious diseases."

Enterovirus 71 (EV71) is a 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

Kyosuke Kobayashi

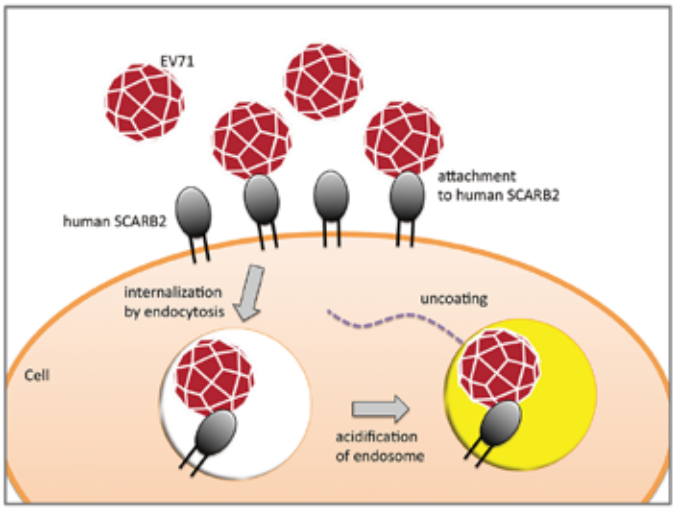


Neurovirology

Research Topics

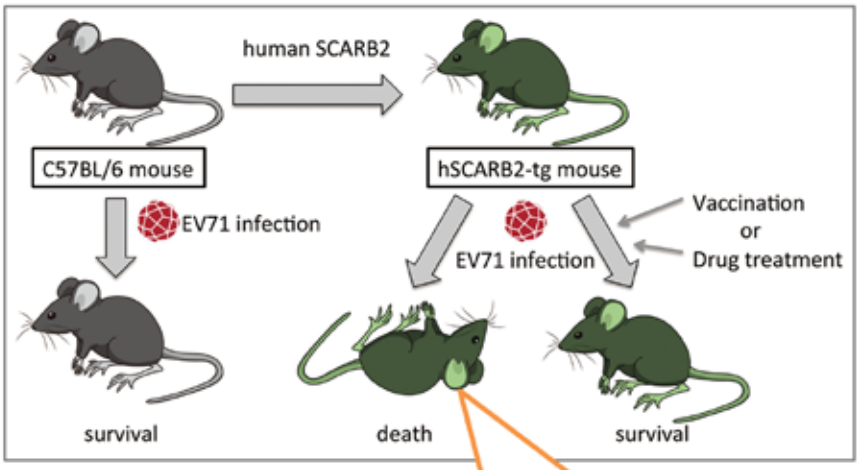
Mechanism of Enterovirus 71 infection

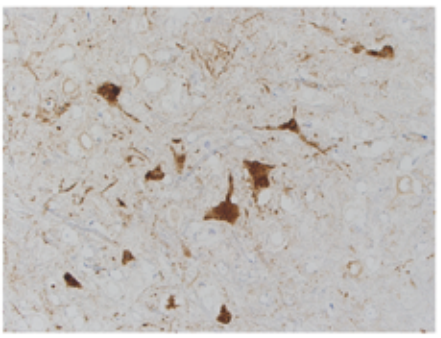
We recently found that Scavenger receptor B2 (SCARB2) is a receptor for EV71. SCARB2 plays a central role in early stages of EV71 infection. SCARB2 is able to mediate binding of the virus at the cell surface, internalization of the virus and initiation of uncoating.



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.





EV71 antigens in the spinal cord of SCARB2 tg mice

Neurovirology

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.

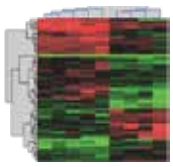
Japanese cedar pollen allergy is the major allergic disease in Japan, and the approximately 35% of Japanese people are affected. In recent years, sublingual immunotherapy has been recognized as an effective curative treatment for the allergic diseases.

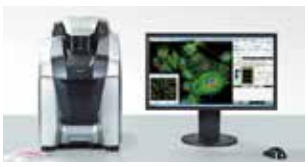
However, the molecular mechanisms of mucosal tolerance still remain unclear. In our laboratory, we focus on the following subjects.

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

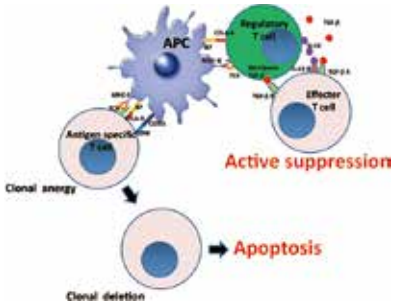
1. Search for effective biomarkers of SLIT

- 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.

Gotoh M, Kaminuma O, Nakaya A, Katayama K, Motoi Y, Watanabe N, Saeki M, Nishimura T, Kitamura N, Yamaoka K,Okubo K, and Hiroi T. (2017) "Identification of biomarker sets for predicting the efficacy of sublingual immunotherapy against pollen-induced allergic rhinitis." ***International Immunology*** 29: 291-300.

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.

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.

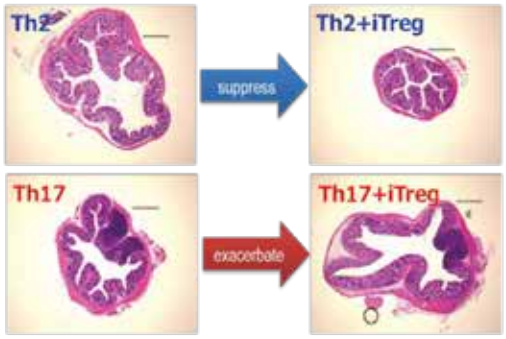
Kaminuma O, Kitamura F, Miyatake S, Yamaoka K, Miyoshi H, Inokuma S, Tatsumi H, Nemoto S, Kitamura N, Mori A, and Hiroi T. (2009) "T-box 21 transcription factor is responsible for distorted TH2 differentiation in human peripheral CD4+ T cells." ***J. Allergy Clin. Immunol.*** 123: 813-823.

Yokoyama S, Watanabe N, Sato N, Filkoski L, Tanaka T, Miyasaka M, Waldmann TA, 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.

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.

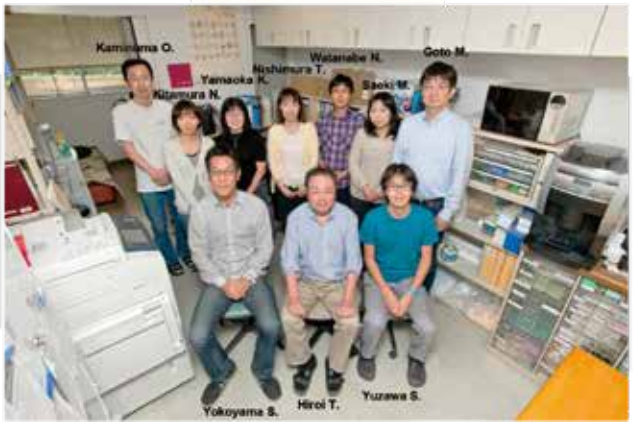
(Watanabe N, et al. (2016) *PLOS ONE*, 11: e0150244.)

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.)

Members



Allergy and Immunology

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

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

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

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

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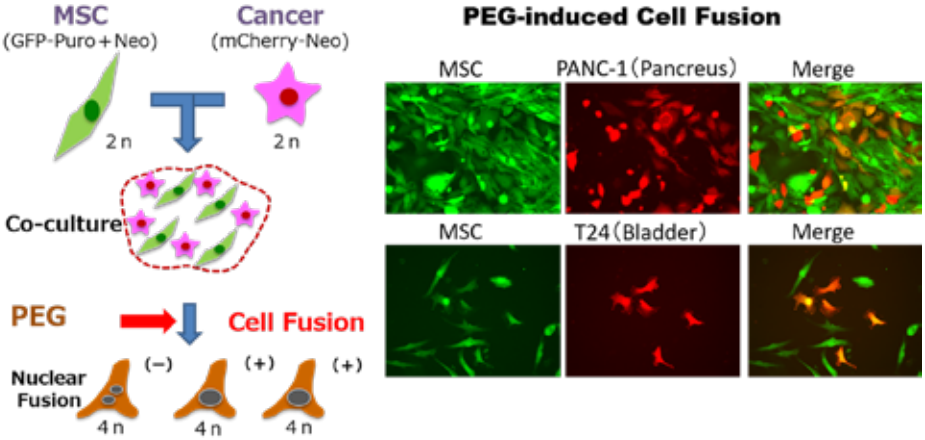
Li Chen, et al. (2007) "Mammalian Tumor Suppressor Int6 Specifically Targets HIF-2alfa To Degradation by Hypoxia- And pVHL- Independent Regulation." ***J. Biol. Chem.*** 282. 12707.

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

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

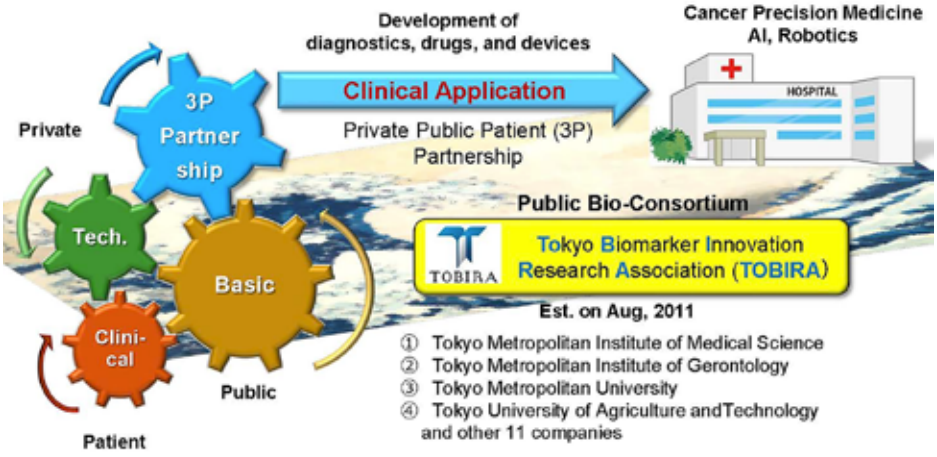
Translational Research for Cancer and Infectious Diseases: Basic to Applied Science

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 research, we have been focusing on the mechanisms of cancer angiogenesis and the drug development using siRNA, and on malignant transformation and metastasis caused by cell fusion. In addition, the novel mechanisms 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).

Our specific aims are to perform the basic science and be to develop the new findings to the translational research.

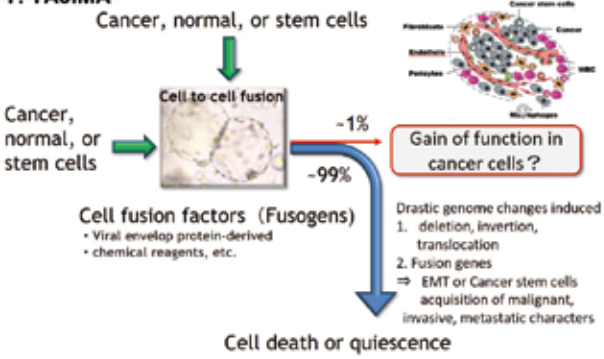


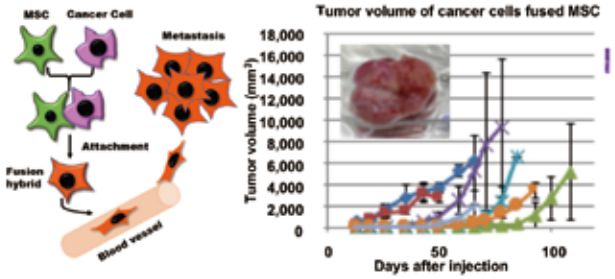
Molecular Medical Research

Malignant cancer progression after cell fusion with stem cells

Y. TAJIMA

Cancer cells fused with mesenchymal stem cell (MSC) in the micro-environment, changes the original character, and often promote dormant, malignant, or metastatic tendency.





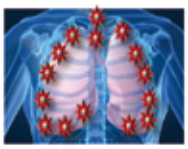
Fused cancer/MSCs promote metastasis than originals

Development of drugs for highly pathogenic H5N1 influenza viruses

N. KAJIWARA

H5N1 has multiple basic amino acids at HA cleavage site.

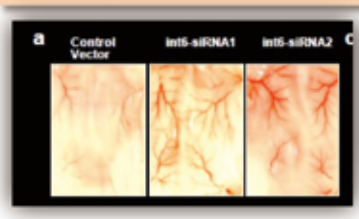
H1N1 Cleavage site
KYVRSTKLRMVTGLRNIPSIQYR----/GLF
H3N2
KYVKQNTLKLATGMRNVPEKQTR----/GLF
H5N1
HA KYVKSNRLVLATGLRNSPQRERRRKKR/GLF

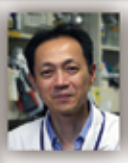


H5N1 highly pathogenic avian influenza virus causes severe pneumonia and multiple organ failure. The mortality rate is about 60%.

We focus on the mechanism of basic amino acid sequence of the split region for discovering new model of the virus entry. The goal of our research is to provide new insights into the molecular mechanism of highly pathogenic avian influenza (H5N1) infection as well as the development of novel antiviral drugs.

Drug development of Int6-siRNA



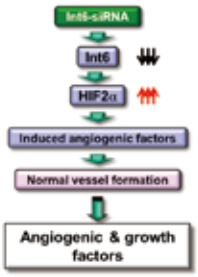


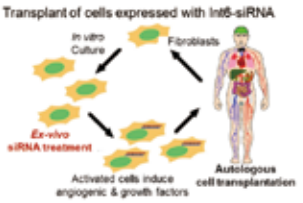
A. IRIE

S. GOTO

Int6 is a key factor to negatively regulate HIF2α-induced angiogenesis and cell protection. The specific siRNA against *int6* would be a possible candidate for cell therapy to treat emic diseases of heart, brain, lower limb, and degenerative and atrophic diseases.

Cell Therapy with *Ex vivo*-siRNA treated Cells





for Ischemia, Degeneration, Atrophy

Diagnostics and device development through Private Public Patient Partnership

Fluoro-IC Chip & Reader

IC Reader

With high sensitive fluoro-beads <15 min, >100 folds sensitive

① **Seasonal A, B Influ IC**
PMDA-approved in 2014
(100 fold higher sensitivity)

② **H5N1 Avian Influ IC**
under development

Rapid & Easy IC Chip

Rapid Colored

Semi-Quantification

Launched in 2016 from LSI Medience

① **Kits for detecting neutralizing Ab in Fabry**

② **Seasonal A, B Influ color IC**
PMDA Approved in 2014
Now on sale

③ **Kits for Cervical Cancer (Plan for sale in 2018)**

Rapid Gene Amp. Devices

Superspeed PCR & Chips

Ver.1 Ver.2 Ver.3

Rapid PCR <8 min for 40 cycles

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

Molecular Medical Research

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

Hasegawa M, Nonaka T, and Masuda-Suzukake M. (2016) "α-Synuclein: Experimental Pathology." ***Cold Spring Harb Perspect Med.*** 6. pii: a024273.

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

Tanaka Y, Nonaka T, Suzuki G, Kametani F, and Hasegawa M. (2016) "Gain-of-function profilin 1 mutations linked to familial amyotrophic lateral sclerosis cause seed-dependent intracellular TDP-43 aggregation." ***Hum. Mol. Genet.*** 25:1420-1433.

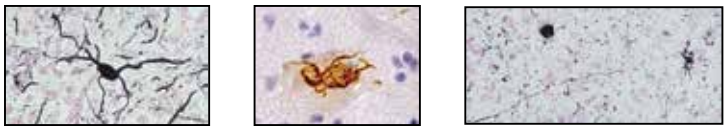
Shimonaka S, Nonaka T, Suzuki G, Hisanaga S, and Hasegawa M. (2016) "Templated Aggregation of TAR DNA-binding Protein of 43 kDa (TDP-43) by Seeding with TDP-43 Peptide Fibrils." ***J. Biol. Chem.*** 291:8896-8907.

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, and 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

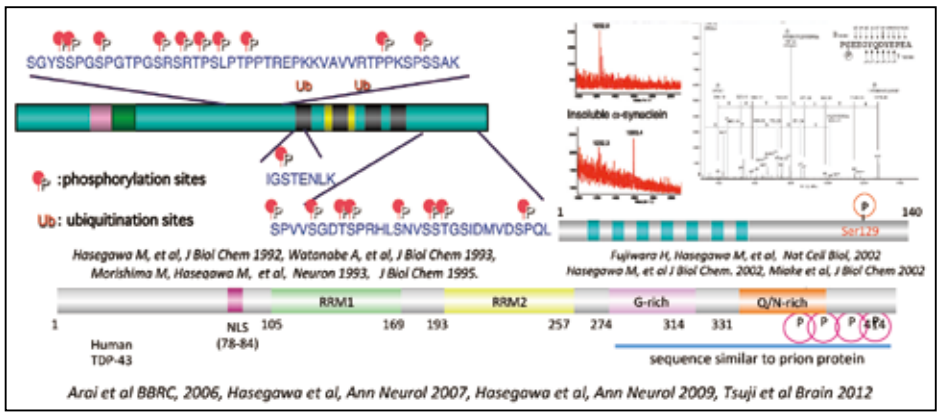
Neurodegenerative diseases are characterized by progressive degeneration of subsets of neurons and gliosis. Many of the diseases are accompanied with intracellular amyloid-like protein pathologies, such as tau in Alzheimer's disease (AD), α-synuclein in dementia with Lewy bodies (DLB) and TDP-43 in amyotrophic 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



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."

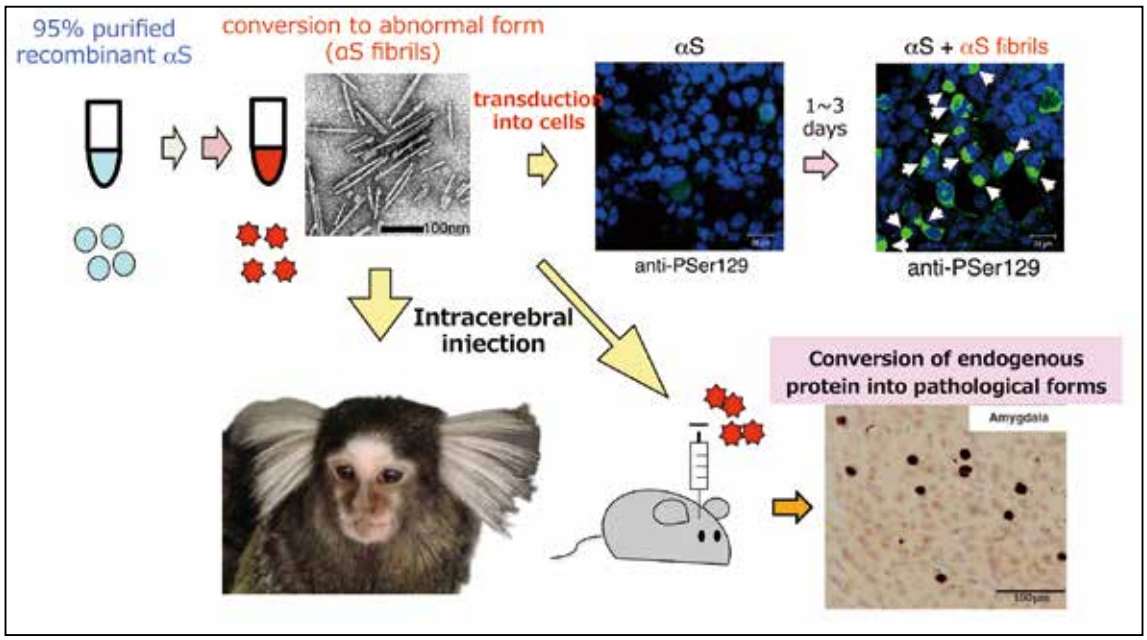
diseases.We have been investigating these intracellular abnormal proteins in brains of patients, proteinchemically using LC/MS/MS, immuno-histochemically with specific antibodies and ultrastructuraly. And we found that all of these proteins are accumulated in brains of patients as fibrous or filamentous 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 1 Triggers Mislocalization and Accumulation of TDP-43. ***J. Biol. Chem.*** 291: 5473-5483, 2016

Nonaka T, et al. Prion-like properties of pathological TDP-43 aggregates from diseased brains. ***Cell Rep.*** 4: 124-134 , 2013

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

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

Hirano Y, Ihara K, Masuda T, Yamamoto T, Iwata I, Takahashi A, Awata H, Nakamura N, Takakura M, Suzuki Y, Horiuchi J, Okuno H, and Saitoe M. (2016). "Shifting transcriptional machinery is required for long-term memory maintenance and modification in Drosophila mushroom bodies." ***Nat. Commun.*** 7: 13471.

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

Yamazaki D, Horiuchi J, Ueno K, Ueno T, Saeki S, Matsuno M, Naganos S, Miyashita T, Hirano Y, Nishikawa H, Taoka M, Yamauchi, Y, Isobe T, Honda Y, Kodama T, Masuda T, and Saitoe M. (2014). "Glial dysfunction causes age-related memory impairment in Drosophila." ***Neuron*** 84: 753-763.

Hirano Y, Masuda T, Naganos S, Matsuno M, Ueno K, Miyashita T, Horiuchi J, and Saitoe M. (2013). "Fasting Launches CRTC to Facilitate Long-term Memory Formation in Drosophila." ***Science*** 339: 443-446.

Miyashita T, Oda Y, Horiuchi J, Yin JC, Morimoto T, and Saitoe M. (2012). "$Mg2^{+}$ block of Drosophila NMDA receptors is required for long-term memory formation and CREB-dependent gene expression." ***Neuron*** 74: 887-898.

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

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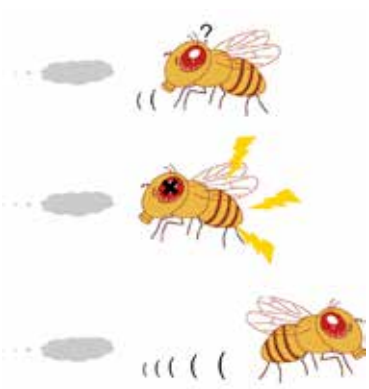
Project Leader **Minoru Saitoe** Learning and Memory Project

Investigating the Molecular Mechanisms that Generate Memory-encoding Neural Networks

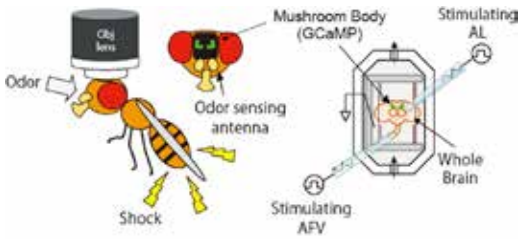
Memories mold our personalities to make us who we are. Using powerful genetic tools, numbers of genes and neural substrates underlying memory-associated behaviors have been identified in Drosophila. Given these scientific backgrounds, we have investigated when, where and how identified memory-associated 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 behavioral genetics and state-of-arts imaging techniques, we aim to understanding how our brains form, store and retrieve memory."



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

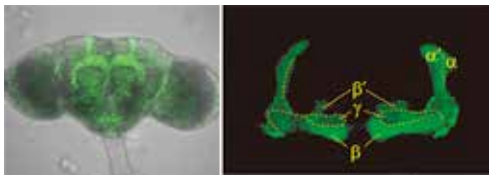


Left, in vivo imaging of fixed fly under microscope is used to investigate activity of identified neurons and network during sensory association (odor and shock), reinforcement, storage and retrieval. Right, using ex vivo imaging we attempt to make artificial memory in cultured brain, thereby elucidate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

Learning and Memory

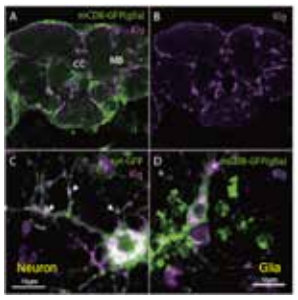
Current Research Topics

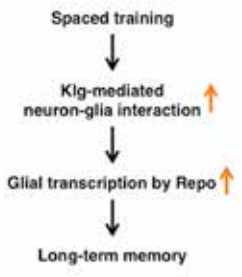
Encoding and decoding of memory: In Drosophila, the mushroom body (MB) is a neural center for olfactory memory. As described by Hermann Ebbinghaus (1885), repetitive olfactory conditioning with rest intervals, namely spaced training, stabilizes labile short-term memory (STM) into robust long-term memory (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.



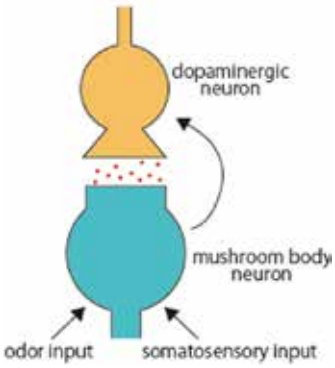


Klingon mediates neuron-glia interaction for LTM formation. A, B) Expression of Klingon (Klg) in the fly brain. C) Expression of Klg in neurons. D) Expression of Klg in glial cells.
Spaced training increases Klg-mediated neuron-glia interaction, thereby induces Repo-dependent glial transcription required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

Senior Research Scientist **Kohei Ueno**

Exploring Physiological Systems Underlying Learning and Memory

Neural plasticity in the MBs is believed to be a cellular basis of olfactory memory. To understand how odor and shock information are associated to produce plastic changes in the MB neurons, we developed ex vivo brain imaging system. Using this system, we found that simultaneous stimulation of odor and shock input pathways to the MBs produces long-term enhancement (LTE) in MB neurons in a manner dependent on activity of D1 receptor in the MBs. We further discovered a novel mode of dopamine release locally evoked by postsynaptic MB neurons which have been coincidentally activated by odor and shock input pathways. We have investigated how coincidentally activated MB neurons direct dopamine release and whether such on-demand release mode also takes place for other neuromodulators and 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

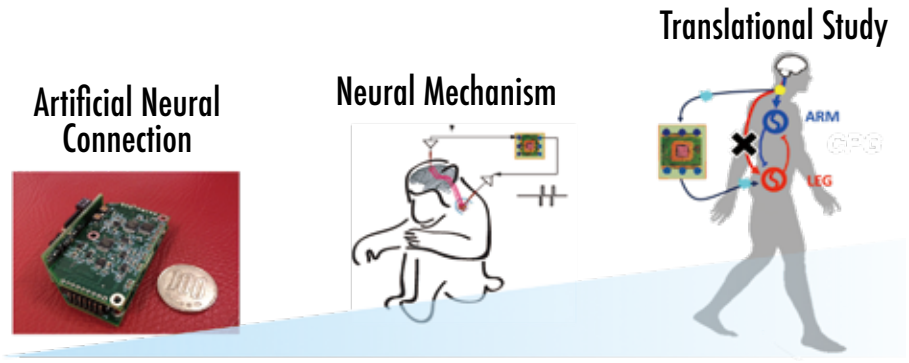
Project Leader **Yukio Nishimura** Neural Prosthesis Project

Restoring Lost Function After Neural Damage

Our research goal is to conceive innovative neuro-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 connecting cortical to spinal network, although neural circuits that locate above and below the impaired site remains their function.



Neuron 2013 | Frontiers 2013 | J Neurosci 2014

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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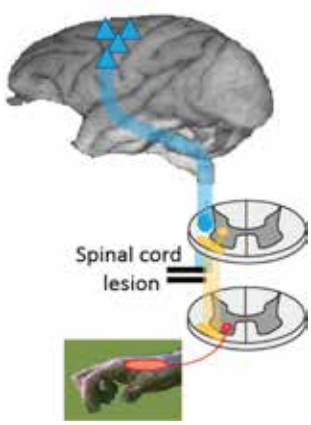
Neural Prosthesis

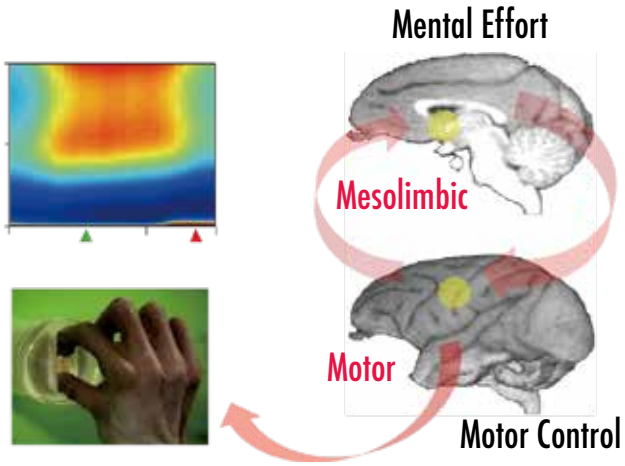
Neural Mechanisms of Functional Recovery

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 in which motor functions are reestablished 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
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Osamu Yokoyama
Nobuya Sano
Noboru Usuda
Kei Obara
Yu Shimada
Yoshihisa Nakayama
Hiroaki Ishida
Michiaki Suzuki
Miki Kaneshige
Ryoutaro Numata
Naoya Kabe

Neural Prosthesis

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.

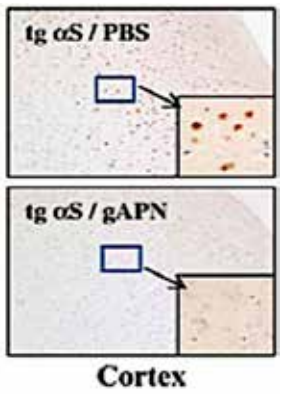

Fig. 1
Effect of adiponectin on neurodegeneration in tg mice

In our laboratory, we seek to exploit a mechanism-based disease-modifying strategy for a-synucleinopathies, such as PD and dementia with Lewy bodies. In this context, we have a particular interest in the suppressive effect of adiponectin 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 currently 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
Ryoko Wada

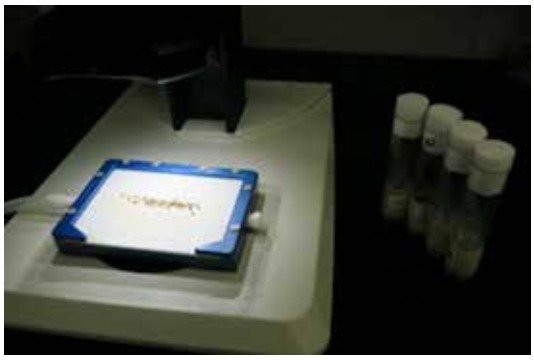

Fig. 2 Drosophila molecular genetics

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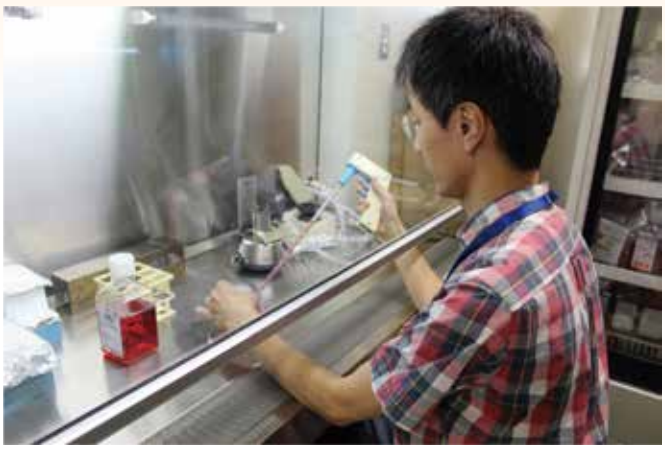
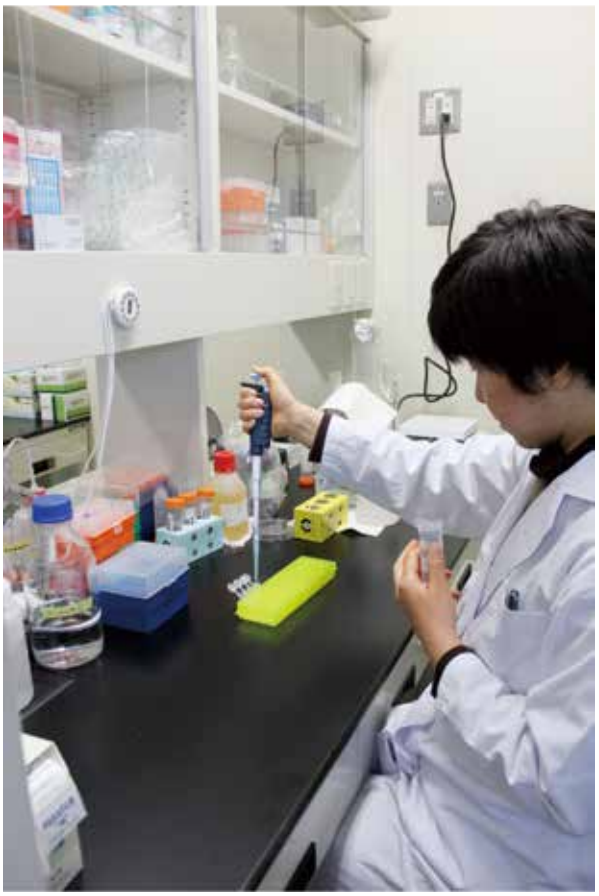
Parkinson's disease





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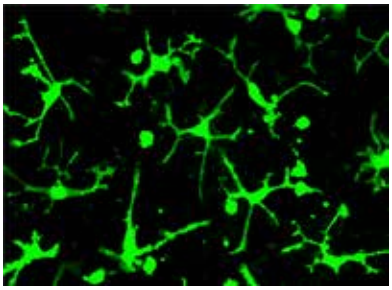
Project Leader **Hiroshi Sakuma** Developmental Neuroimmunology Project

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

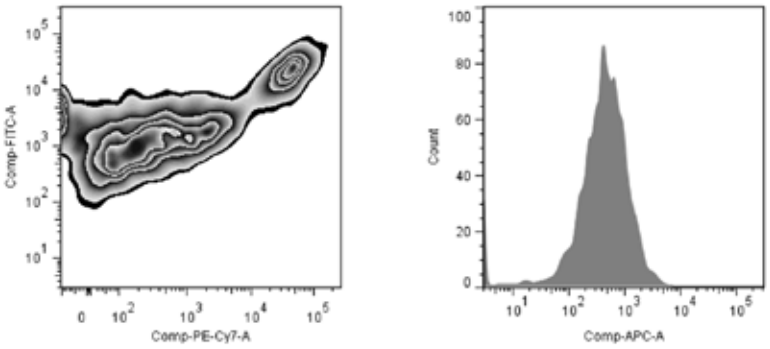


Our research focuses on the role of immune system in the developing brain. Immune and inflammatory responses not only combat pathogens but also play a variety of physiological roles in the central nervous system. Microglia are brain-resident immune cells and play multiple roles in the protection from 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



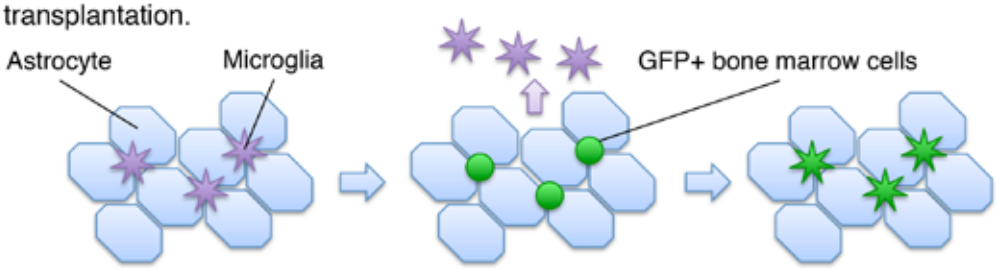
Flow cytometric analysis of microglia

Developmental Neuroimmunology

Research topic

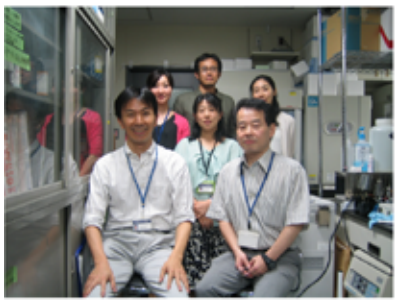
Astrocytes nurture microglia?

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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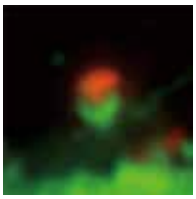
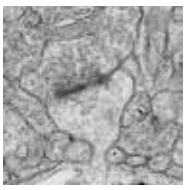
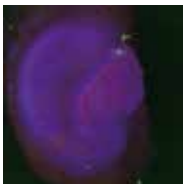
Project Leader **Kanato Yamagata** Synaptic Plasticity Project

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.

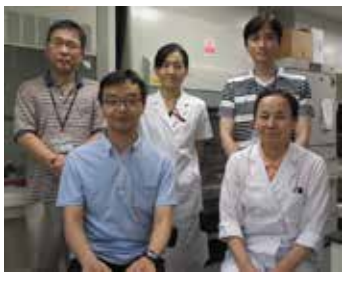






"We have clarified mechanisms of refractory epilepsy, intellectual disability and/or autism caused by impaired synaptic plasticity. Based on the novel mechanisms we found, we are trying to find new treatments for developmental brain disorders"

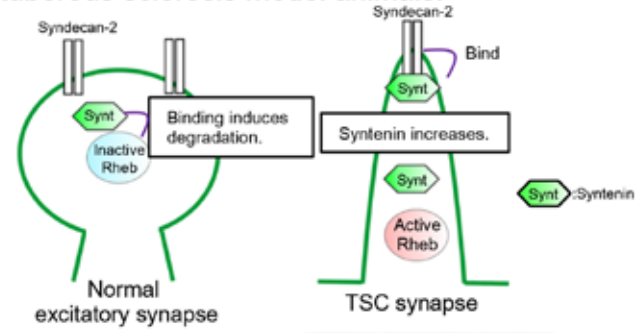
For example, COX-2 and mPGES-1 are prostaglandin synthases and exacerbate neuronal cell death after seizures, leading to intractable epilepsy. Arcadlin is a protocadherin and induces spine shrinkages after seizures, resulting in developmental delay or amnesia. Rheb regulates excitatory synapse formation 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.

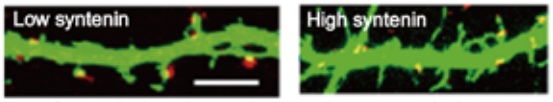


Synaptic Plasticity

Our Recent Topics

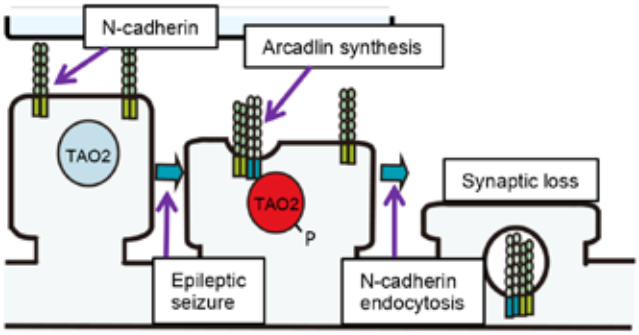
Mechanism of abnormal synapse formation in tuberous sclerosis model animals:

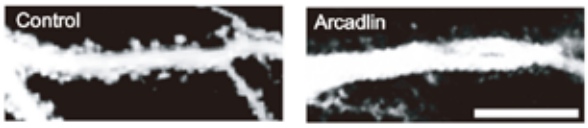




Syntenin levels regulate synapse morphology. *Nat. Commun.* 2015

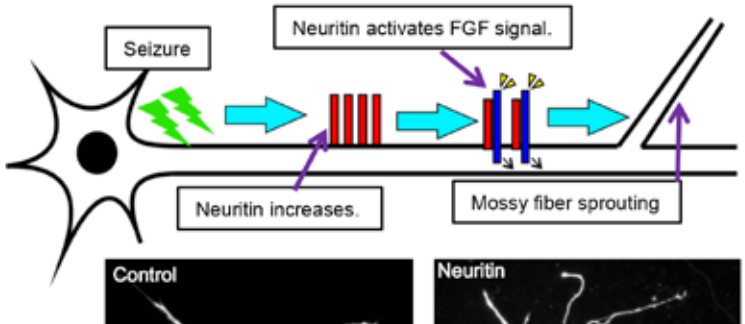
Mechanism of spine retraction after the epileptic seizure:

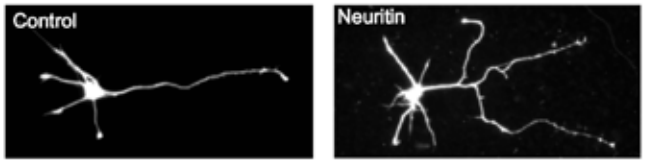




Overexpression of Arcadlin reduces spine number. *Neuron* 2007

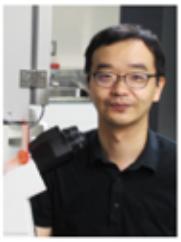
Mechanism of mossy fiber sprouting in epilepsy model animals:





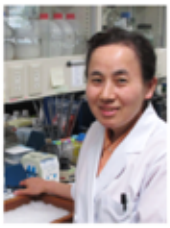
Overexpression of Neuritin promotes axonal branch formation. *J. Neurosci.* 2016

Members



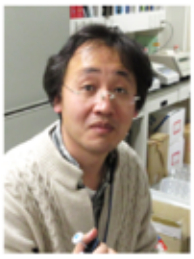
Tadayuki Shimada

Chihiro Hisatsune



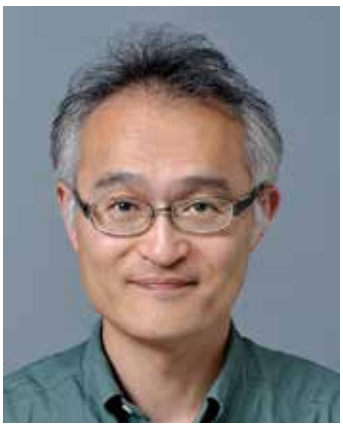
Hiroko Sugiura

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

Hirai S, Hotta K, and Okado H. (2018) "Developmental Roles and Evolutionary Significance of AMPA-Type Glutamate Receptors." ***Bioessays.*** 2018 2018 Sep;40(9):e1800028.

Hirai S, Hotta K, Kubo Y, Nishino A, Okabe S, Okamura Y, and Okado H. (2017) "AMPA glutamate receptors are required for sensory-organ formation and morphogenesis in the basal chordate." ***Proc. Natl. Acad. Sci. USA.*** 114: 3939-3944.

Nakajima K, Hirai S, Morio T, and Okado H. (2015) "Benzodiazepines induce sequelae in immature mice with inflammation-induced status epilepticus." ***Epilepsy & Behavior*** 52: 180-186.

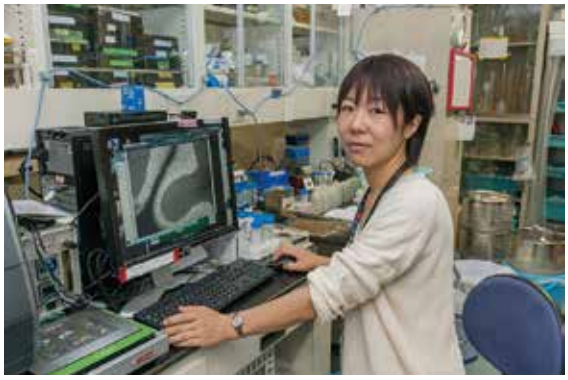
Ohtaka-Maruyama C, Hirai S, Miwa A, Heng JI, Shitara H, Ishii R, Taya C, Kawano H, Kasai M, Nakajima K, and Okado H. (2013) "RP58 regulates the multipolar-bipolar transition of newborn neurons in the developing cerebral cortex." ***Cell Rep.*** 3: 458-471.

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.

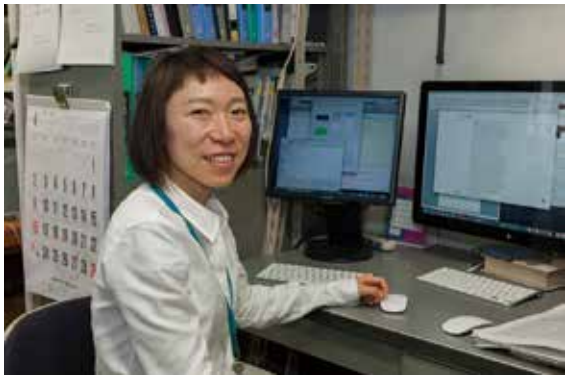
Ohtaka-Maruyama C, Hirai S, Miwa A, Takahashi A, and Okado H. (2012) "The 5'-flanking region of the RP58 coding sequence shows prominent promoter activity in multipolar cells in the sub- ventricular zone during corticogenesis." ***Neuroscience*** 201: 67-84.

Okado H, Ohtaka-Maruyama C, Sugitani Y, Fukuda Y, Ishida R, Hirai S, Miwa A, Takahashi A, Aoki K, Mochida K, Suzuki O, Honda T, Nakajima K, Ogawa M, Terashima T, Matsuda J, Kawano H, and Kasai M. (2009) "Transcriptional repressor RP58 is crucial for cell-division patterning and neuronal survival in the developing cortex." ***Dev. Biol.*** 331: 140-151.

Neural Development



Shinobu Hirai



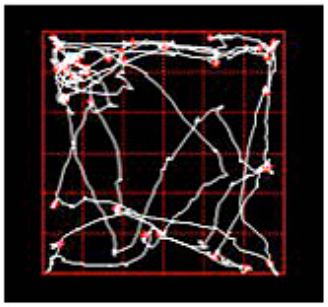
Tomoko Tanaka

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.**

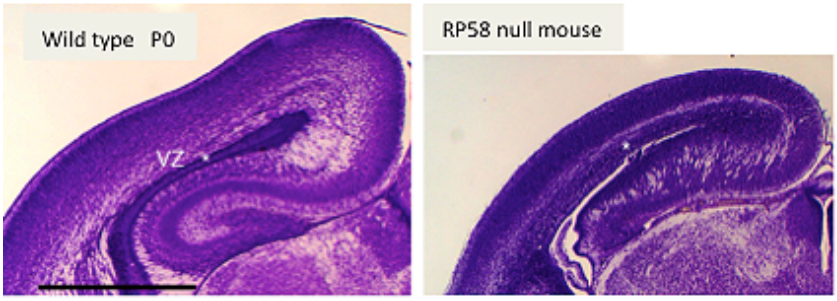
3) **Understanding the roles of environmental factors in development and ageing of brain functions.**



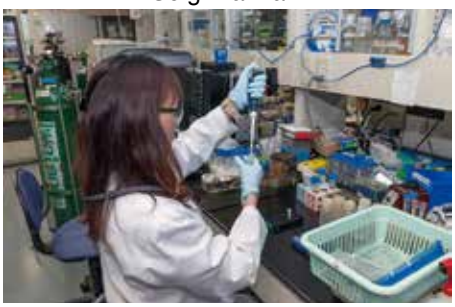
Locomotion, anxiety, memory, and sociality of mice are evaluated using the tracking system. Neuronal activity can be analyzed *in vivo* system.

Yoshie Matsumoto

Seigi 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.

Ohtaka-Maruyama C, Okamoto M, Endo K, Oshima M, Kaneko N, Yura K, Okado H, Miyata S, and Maeda N. (2018) "Synaptic transmission from subplate neurons controls radial migration of cortical neurons." ***Science*** 360: 313-317.

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

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

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.

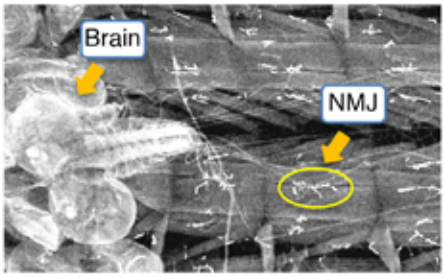
Ohtaka-Maruyama C, et al. (2013) "RP58 regulates the multipolar-bipolar transition of newborn neurons in the developing cerebral cortex." ***Cell Rep.*** 3: 458-471.

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.

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.

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.

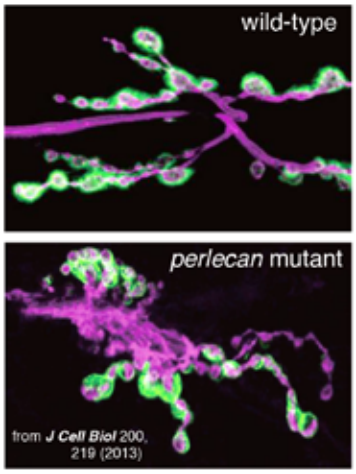
Neural Network

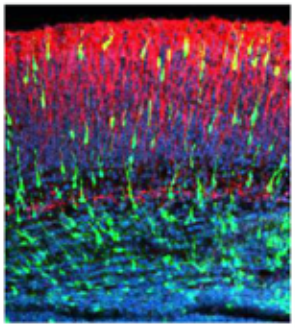


Brain and NMJ
of *Drosophila larva*

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

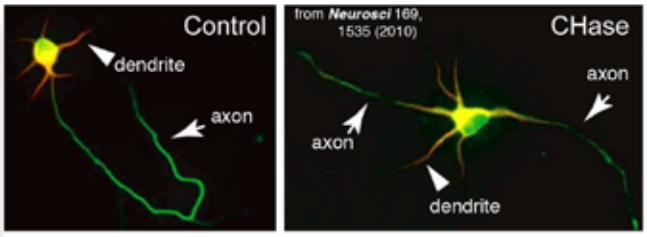
We demonstrated that Perlecan bidirectionally regulates pre- and post-synaptic Wnt signaling by precisely distributing Wnt at NMJ.





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).

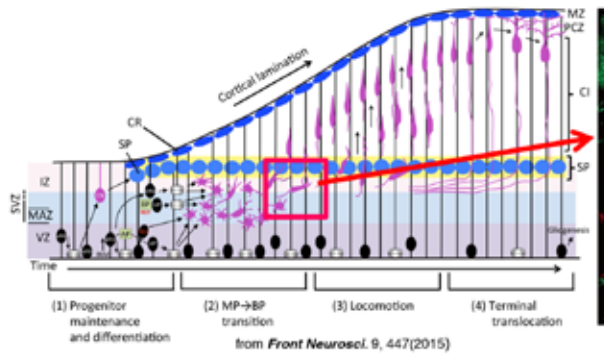


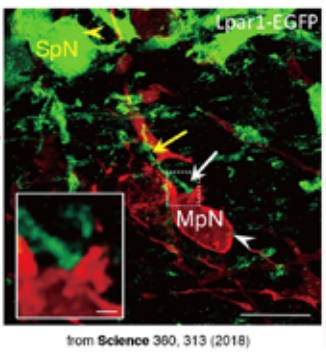
We revealed that chondroitin sulfate proteoglycans play critical roles in neuronal polarization.

Senior Research Scientist Chiaki Ohtaka-Maruyama

Subplate layer in development and evolution of 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 by forming transient glutamatergic synapses on 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.





Differentiation and radial migration of neocortical neurons

Subplate neurons (SpN) extend axons (yellow arrow), and form transient synapses (white arrow) on multipolar migrating neurons (MpN).

The synaptic transmission induces multipolar-to-bipolar transition of MpNs.

Neural Network

Nakanishi M, Niimura J, Yamasaki S, and 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.

Ando S, Koike S, Shimodera S, Fujito R, Sawada K, Terao T, Furukawa TA, Sasaki T, Inoue S, Asukai N, Okazaki Y, and Nishida A. (2017) "Lithium levels in tap water and the mental health problems of adolescents: an individual level cross-sectional survey." ***J. Clin. Psychiatry.*** 78(3):e252-e256.

Nakanishi M, Nakashima T, Shindo Y, Niimura J, and 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

Yamasaki S, Ando S, Koike S, Usami S, Endo K, French P, Sasaki T, Furukawa TA, Hasegawa-Hiraiwa M, Kasai K, and 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

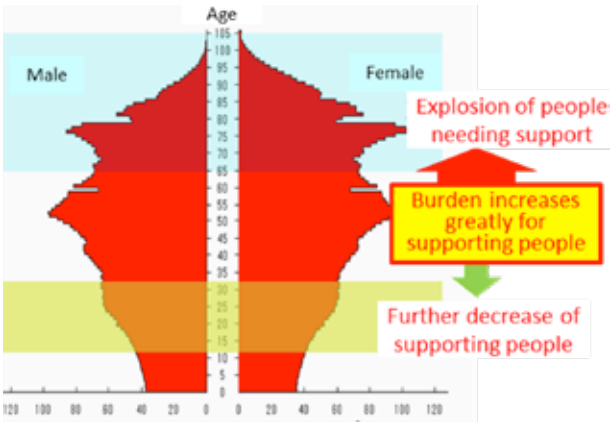
No health without Mental Health:

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

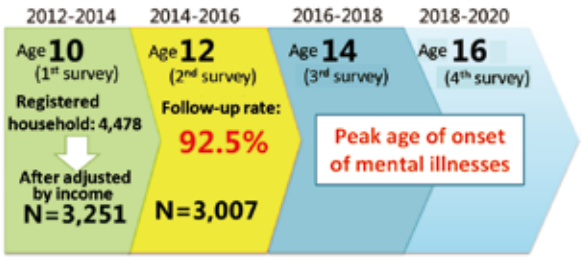
What we do

Elucidating contributing factors to adolescent mental health

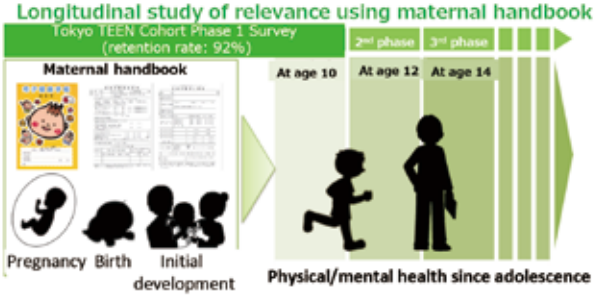
In adolescence, body and mind change significantly. Adolescents, therefore, are vulnerable to mental problems. Adolescent Health/Development Survey is a large-scale longitudinal birth cohort study included 10-year-old children and their carers living in Setagaya-ward, Chofu-city, and Mitaka-city. Currently, 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)

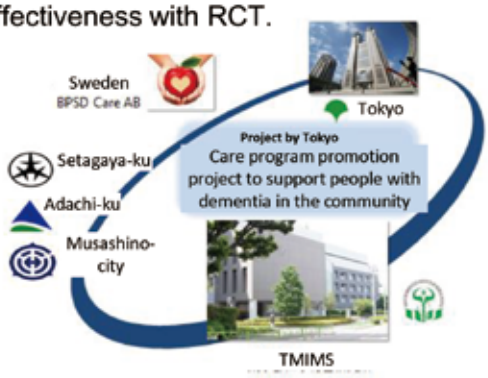


Longitudinal study of relevance using maternal handbook



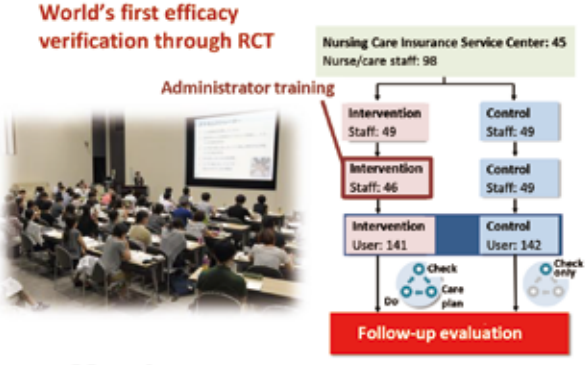
Care model development to support people with dementia at home

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



Members

Atsushi Nishida
Syudo Yamasaki
Miharu Nakanishi
Junko Niimura
Kaori Endo
Kayo Hirooka
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, and Miyata T. (2018) "Pyridoxamine: A novel treatment for schizophrenia with enhanced carbonyl stress." ***Psychiatry Clin. Neurosci.*** 72: 35-44.

Miyashita M, Watanabe T, Ichikawa T, Toriumi K, Horiuchi Y, Kobori A, Kushima I, Hashimoto R, Fukumoto M, Koike S, Ujike H, Arinami T, Tatebayashi Y, Kasai K, Takeda M, Ozaki N, Okazaki Y, Yoshikawa T, Amano N, Washizuka S, Yamamoto H, Miyata T, Itokawa M, Yamamoto Y, and Arai M. (2016) "The regulation of soluble receptor for AGEs contributes to carbonyl stress in schizophrenia." ***Biochem. Biophys. Res. Commun.*** 479: 447-452.

Arai M, Miyashita M, Kobori A, Toriumi K, Horiuchi Y, Hatakeyama S, and Itokawa M. (2014) "Carbonyl stress and schizophrenia." ***Psychiatry Clin. Neurosci.*** 68: 655-665.

Miyashita M, Arai M, Kobori A, Ichikawa T, Toriumi K, Niizato K, Oshima K, Okazaki Y, Yoshikawa T, Amano N, Miyata T, and Itokawa M. (2014) "Clinical Features of Schizophrenia With Enhanced Carbonyl Stress." ***Schizophr. Bull.*** 40: 1040-1046.

Arai M, Nihonmatsu-Kikuchi N, Itokawa M, Rabbani N, and Thornalley PJ. (2014) "Measurement of glyoxalase activities." ***Biochem Soc. Trans.*** 42: 491-494.

Miyashita M, Arai M, Yuzawa H, Niizato K, Oshima K, Kushima I, Hashimoto R, Fukumoto M, Koike S, Toyota T, Ujike H, Arinami T, Kasai K, Takeda M, Ozaki N, Okazaki Y, Yoshikawa T, Amano N, Miyata T, and Itokawa M. (2014) "Replication of enhanced carbonyl stress in a subpopulation of schizophrenia." ***Psychiatry Clin. Neurosci.*** 68: 83-84.

Arai M, Koike S, Oshima N, Takizawa R, Araki T, Miyashita M, Nishida A, Miyata T, Kasai K, and Itokawa M. (2011) "Idiopathic carbonyl stress in a drug-naive case of at-risk mental state." ***Psychiatry Clin. Neurosci.*** 65: 606-607.

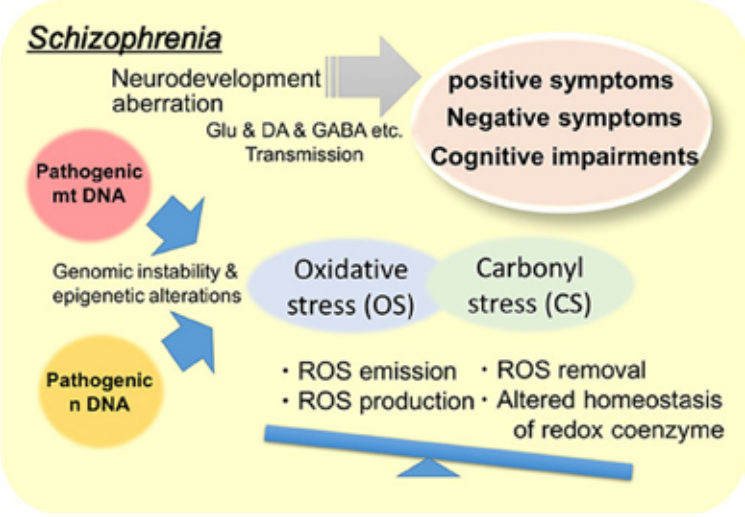
Arai M, Yuzawa H, Nohara I, Ohnishi T, Obata N, Iwayama Y, Haga S, Toyota T, Ujike H, Arai M, Ichikawa T, Nishida A, Tanaka Y, Furukawa A, Aikawa Y, Kuroda O, Niizato K, Izawa R, Nakamura K, Mori N, Matsuzawa D, Hashimoto K, Iyo M, Sora I, Matsushita M, Okazaki Y, Yoshikawa T, Miyata T, and Itokawa M. (2010) "Enhanced Carbonyl Stress in a Subpopulation of Schizophrenia." ***Arch. Gen. Psychiatry.*** 67: 589-597.

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 strategies for the prevention and treatment.
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."



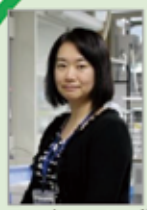
This biomarker-based approach is anticipated to become an innovative and creative strategy for elucidating the metabolic system of schizophrenia disease expression independently of conventional pathological hypotheses. Verification in cellular and animal models can shed light on the molecular mechanisms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

Schizophrenia Research

Topics of our research

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

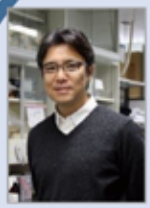
Yasue Horiuchi



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.

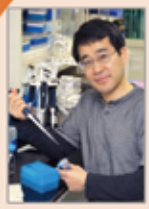
Our projects contribute to future innovation for preventive medical research in the areas of psychiatry, health, and welfare

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.

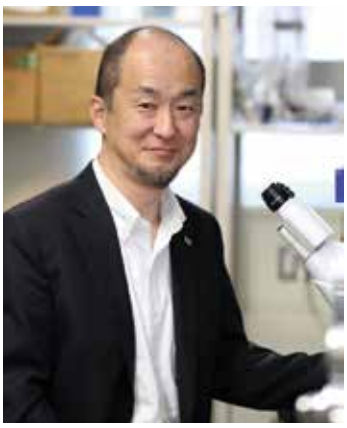
Masanari Itokawa



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



Bauer M, (64 co-authors), Tatebayashi Y et al. (2014) "Relationship between sunlight and the age of onset of bipolar disorder: an international multisite study." ***J. Affect. Disord.*** 167:104-111.

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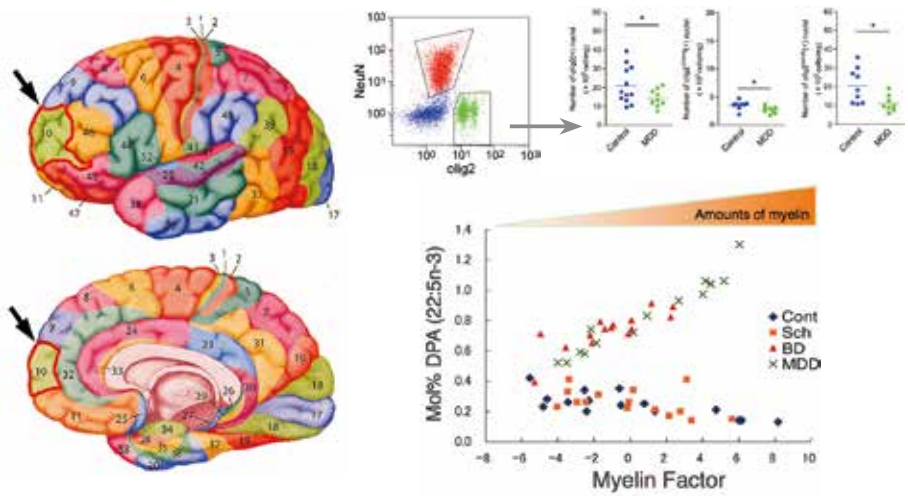
Project Leader **Yoshitaka Tatebayashi** Affective Disorders Research Project

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."



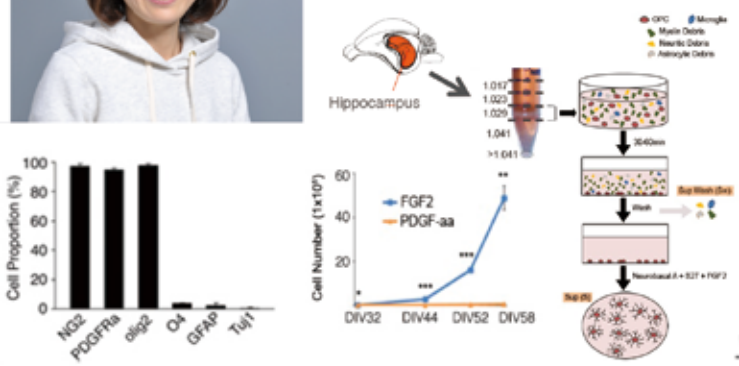
The exact functions of the human frontopolar cortex (BA10) remain enigmatic. Given that the BA10 is thought to be the most evolutionarily recent expansion of the primate prefrontal cortex, its function may uniquely reflect human adaptations in the context of selecting and updating models of reward contingency 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.

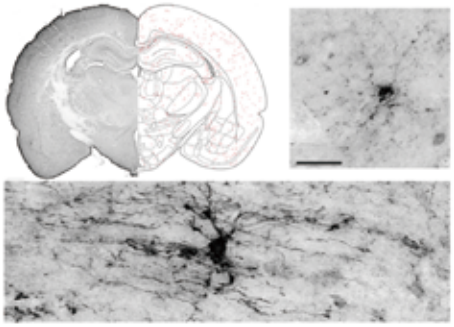
Affective Disorders Research

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

Naomi Nihonmatsu-Kikuchi

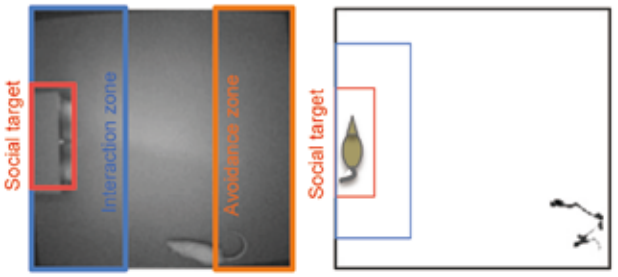
We purify and culture adult oligodendrocyte progenitor cells (aOPCs) from adult mammalian brains to understand their roles in the pathogenesis of affective disorders.

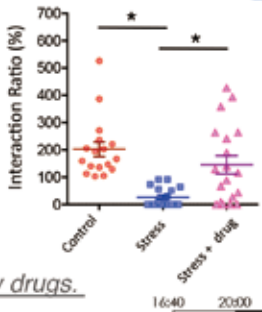


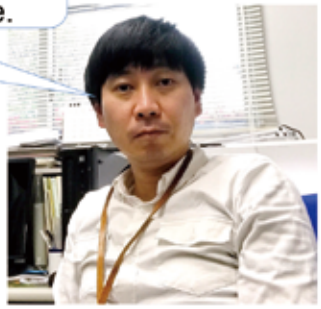


We found a novel aOPC subtype from culture.

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.

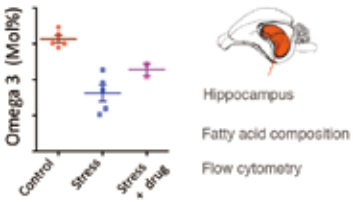






Yoshiki Matsuda

We found a therapeutic effect of anti-inflammatory drugs.

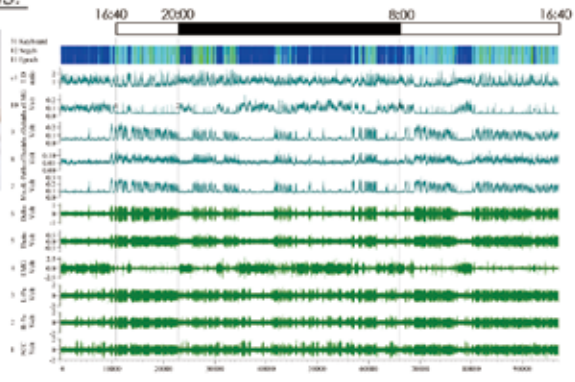


Hippocampus

Fatty acid composition

Flow cytometry

Kazuhisa Aoki



Blood

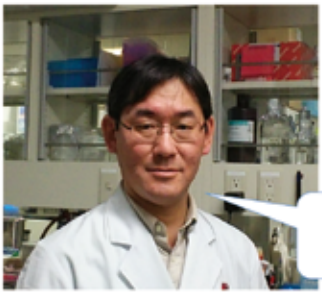
Luminex

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

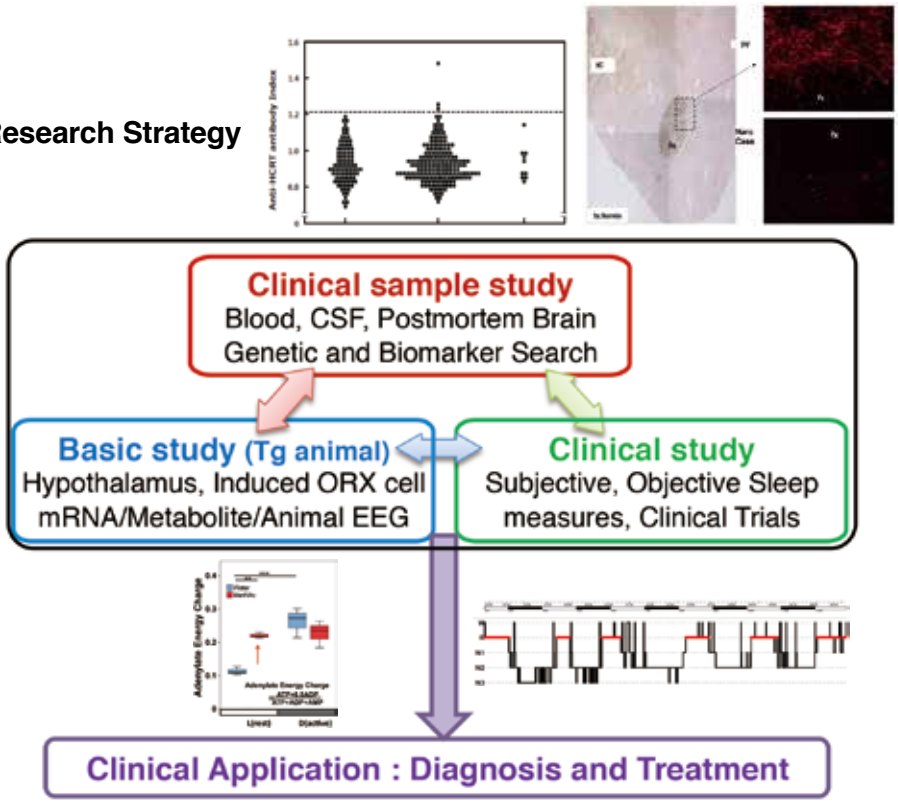
Narcolepsy and Hypersomnia:
Find the causes to develop better treatments

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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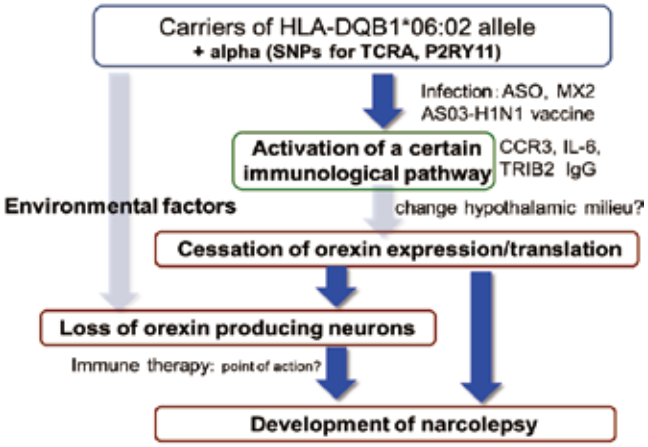
Sleep Disorders

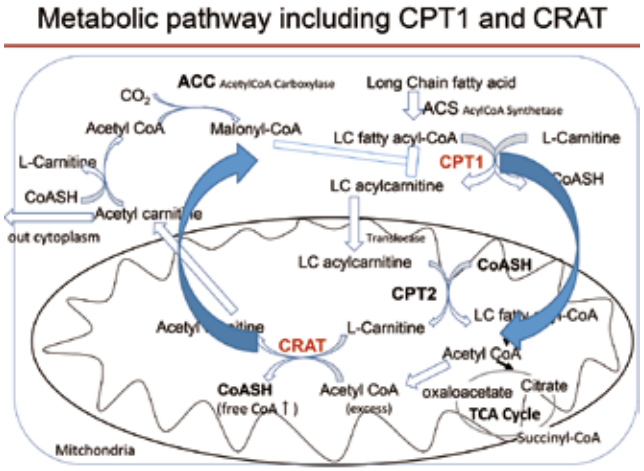
Research Interests

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.





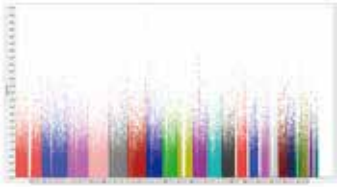
2. Metabolic aspect of narcolepsy and related hypersomnia

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)

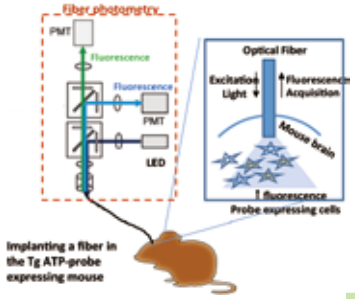
Taku Miyagawa

Understanding the genetic background and mechanism of sleep disorders.



Akiyo Natsubori

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



Sleep Disorders

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

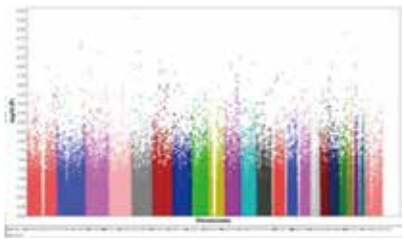
Addiction to substances (e.g. drugs, alcohol, tobacco) and behavior (e.g. internet, gambling) is a serious public health problem. Moreover, use of legal drugs has been increasing in Japan in recent years. It is important to prevent and solve problems of addictions.

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.



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Addictive Substance

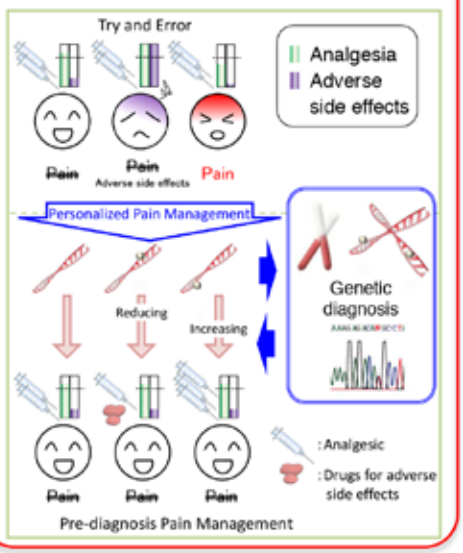
Topics of our research

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.



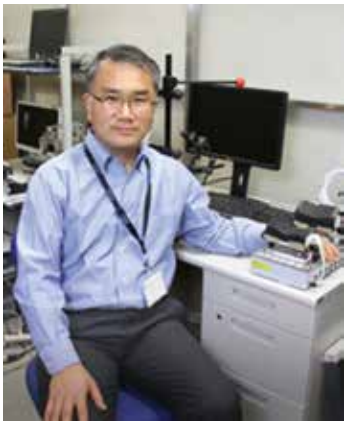
Developmental disorder research

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



Tomatsu S, Ishikawa T, Tsunoda Y, Lee J, Hoffman DS, and Kakei S. (2016) "Information processing in the hemisphere of the cerebellar cortex for motor control of wrist movement." ***J. Neurophysiol.*** 115:255-270.

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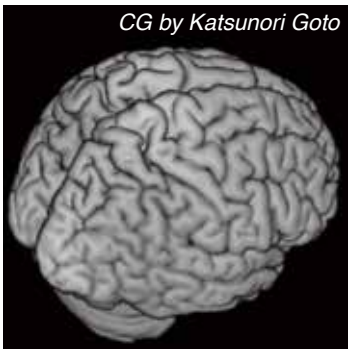
Project Leader **Shinji Kakei** Motor Disorders Project

From Neuron to Action and its Disorders

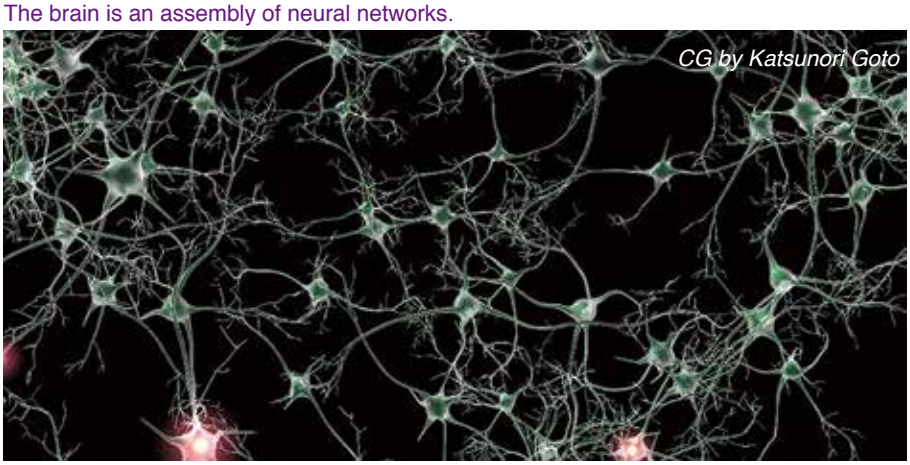
We try to understand how the brain controls our movements in the real world. We study the process of action generation at a single neuron level using animal models to understand how the movement is processed in the brain. We also study actions of healthy people, as well as those with neurological disorders, 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."



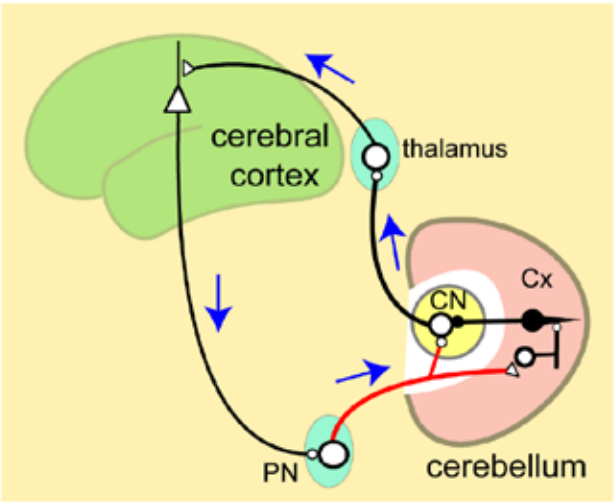
"The brain mechanism for motor control must provide a basic framework to understand higher brain functions."

The brain is an assembly of neural networks.

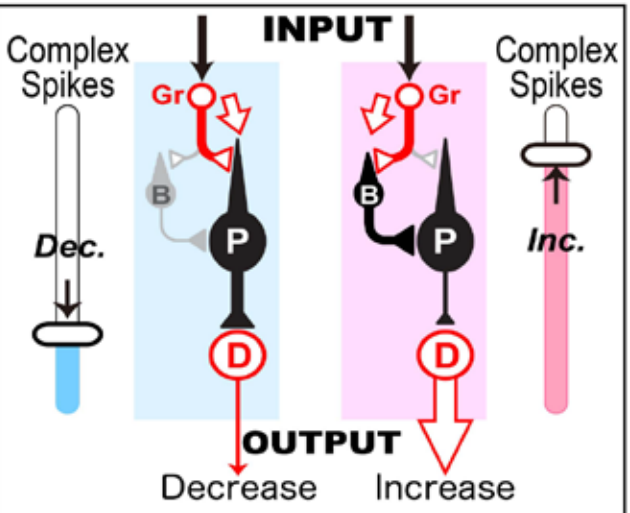


Motor Disorders

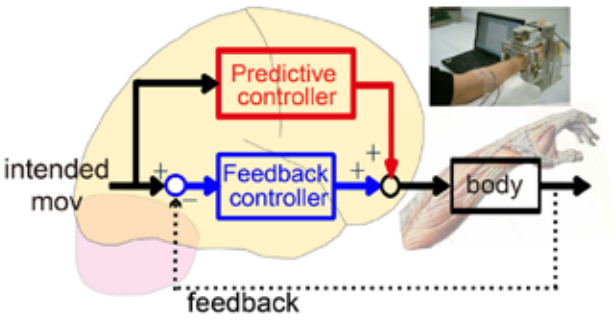
Hot Topics of Our Research



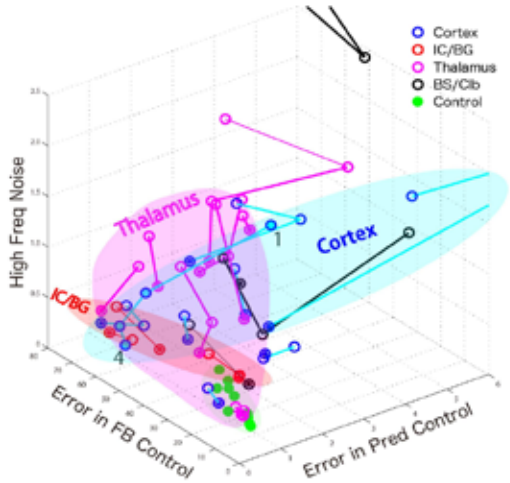
The cerebro-cerebellar communication loop plays essential roles to organize both motor control and higher brain functions such as thought and speech.



We found two modes of cerebellar input-output relationship that explain generation of precise motor commands.



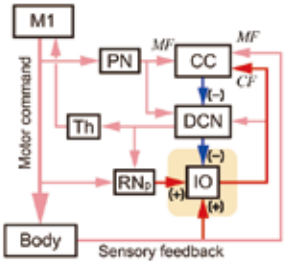
We were the first group in the world to build a system (*inset*) to dissociate predictive motor control and feedback motor control (below) in patients with neurological disorders. This system provides quantitative parameters that characterize the two controllers.



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

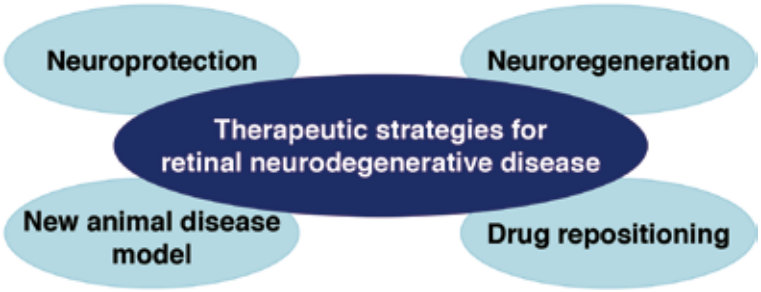
Project Leader **Takayuki Harada** Visual Research Project

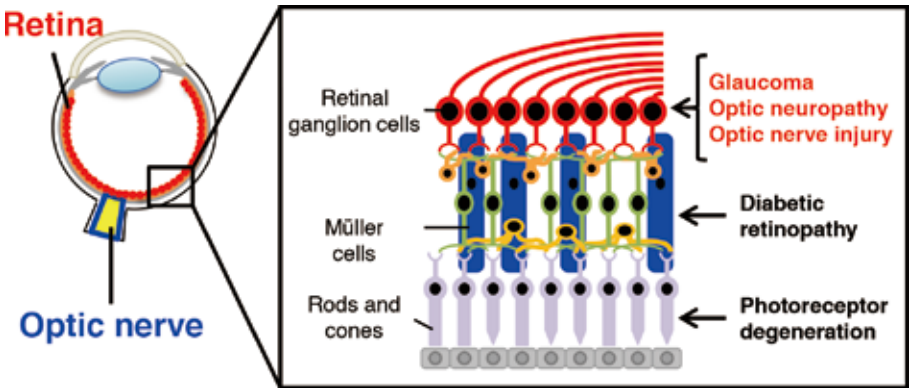
Elucidation of Pathology and Development of Therapeutic Strategies for Retinal Neurodegenerative Diseases

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.

Our objectives

“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.”





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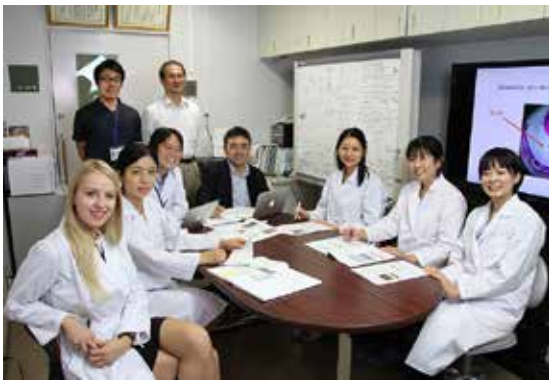
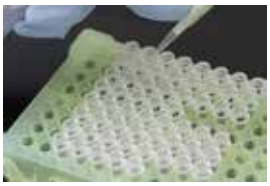
Our major aim

- **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**



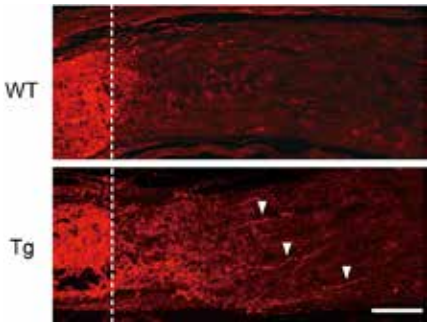




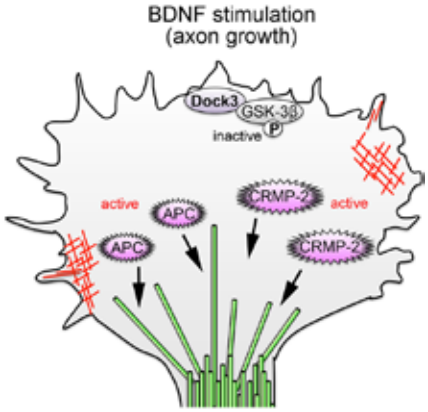
Senior Research Scientist **Kazuhiko Namekata**

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 protein (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)



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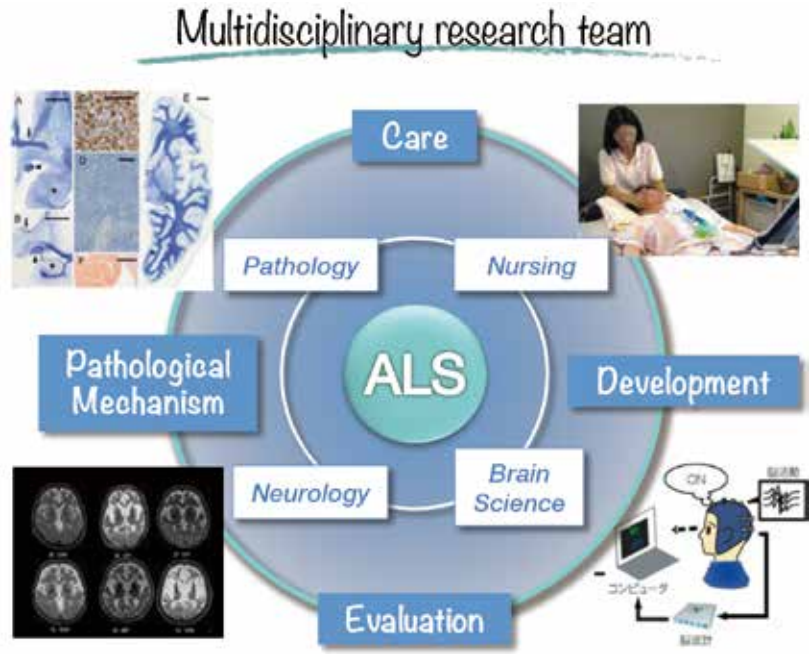
Visual Research

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."



Matsuda C, Shimizu T, Nakayama Y, and Haraguchi M. (2018) "Cough peak flow decline rate predicts survival in patients with amyotorophic lateral sclerosis." ***Muscle Nerve.*** 2018 Aug 14.

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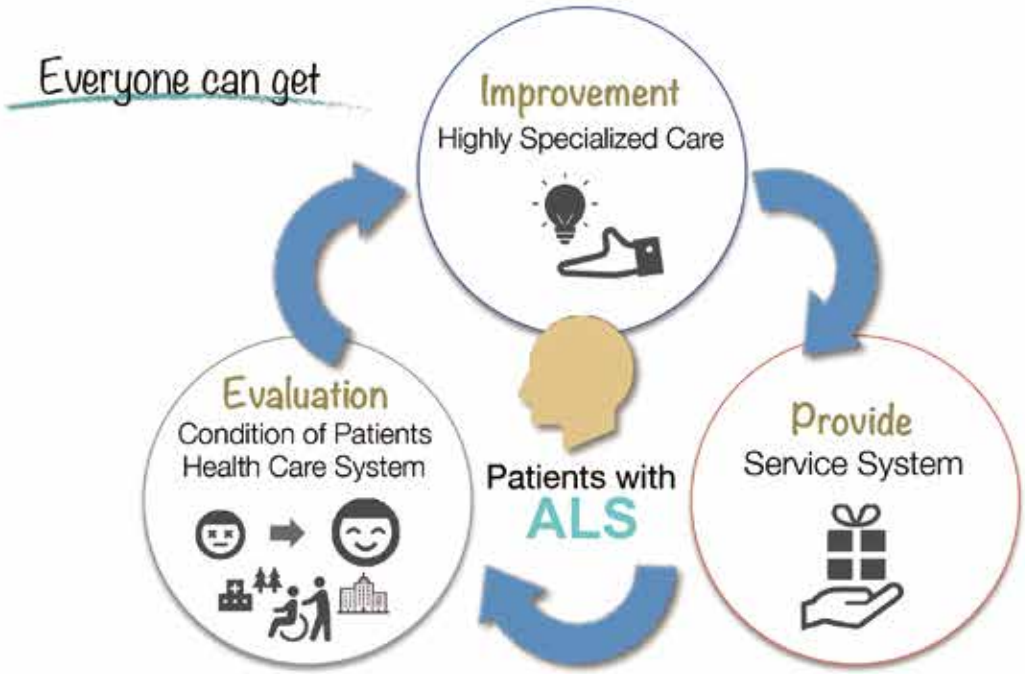
Nakayama Y, Shimizu T, Mochizuki Y, Hayashi K, Matsuda C, Nagao M, Watabe K, Kawata A, Oyanagi K, Isozaki E, and Nakano I. (2016) "Predictors of impaired communication in amyotrophic lateral sclerosis patients with tracheostomy invasive ventilation." ***Amyotroph. Lateral Scler. Frontotemporal Degener.*** 17(1-2):38-46.

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

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.

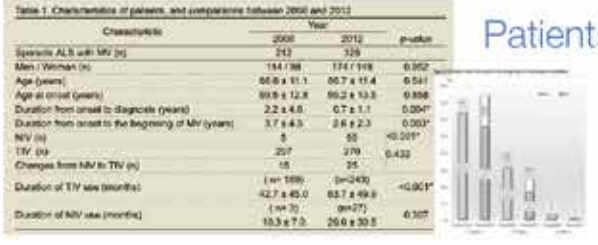
Michiko Haraguchi, Ph.D.

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	1.653	1.150–2.370	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



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

Yumi Itagaki, M.S.

ALS Nursing Care

Takaku S, Yako H, Niimi N, Akamine T, Kawanami D, Utsunomiya K, and Sango K. (2018) "Establishment of a myelinating co-culture system with a motor neuron-like cell line NSC-34 and an adult rat Schwann cell line IFRS1." ***Histochem. Cell Biol.*** 149: 537-543.

Yoshida S, Hasegawa T, Suzuki M, Sugeno N, Kobayashi J, Ueyama M, Fukuda M, Ido-Fujibayashi A, Sekiguchi K, Ezura M, Kikuchi A, Baba T, Takeda A, Mochizuki H, Nagai Y, and Aoki M. (2018) "Parkinson's disease-linked DNAJC13 mutation aggravates alpha-synuclein-induced neurotoxicity through perturbation of endosomal trafficking." ***Hum. Mol. Genet.*** 27: 823-836.

Niimi N, Yako H, Takaku S, Kato H, Matsumoto T, Nishito Y, Watabe K, Ogasawara S, Mizukami H, Yagihashi S, Chung SK, and Sango K. (2018) "A spontaneously immortalized Schwann cell line from aldose reductase-deficient mice as a useful tool for studying polyol pathway and aldehyde metabolism." ***J. Neurochem.*** 144: 710-722.

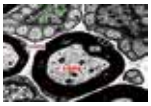
Sango K, Mizukami H, Horie H, and Yagihashi S. (2017) "Impaired axonal regeneration in diabetes. Perspective on the underlying mechanism from in vivo and in vitro experimental studies." ***Front. Endocrinol.*** 8: 12.

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.

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."

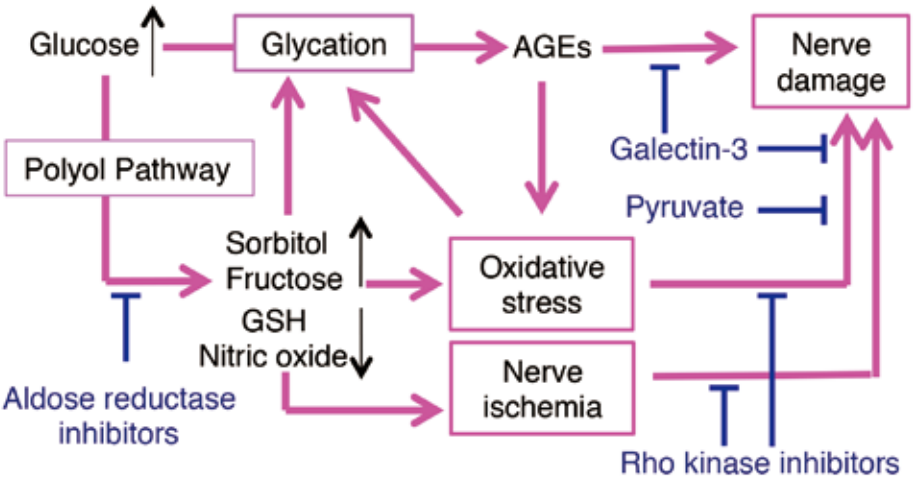
The goals of our project are as follows: 1) Establishing effective pathogenesis-based treatments for diabetic peripheral neuropathy. 2) Elucidating mechanistic link between metabolic dysfunction and neurodegenerative diseases.

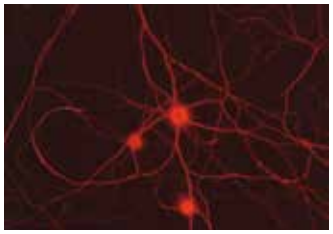
Diabetic Neuropathy

Project 1: Therapeutic Approaches to Diabetic *Peripheral Neuropathy*

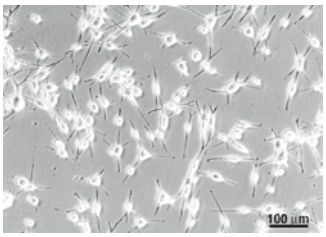
[Sango, Yako, Niimi, Takaku, Akamine]

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]

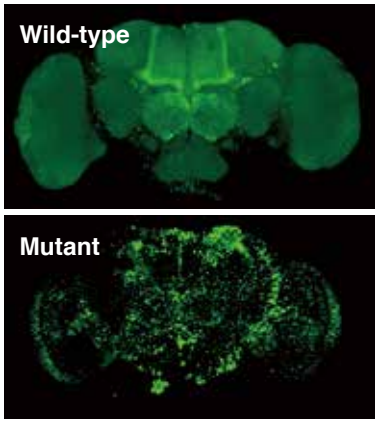
Neurodegenerative diseases are considered to share a common molecular pathogenesis involving protein misfolding and aggregation. Recently, increasing evidence suggests a relationship between metabolic syndrome and Alzheimer's disease. By using ***Drosophila* model**, we aim to understand the molecular 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, and Sorimachi H. (2016) "A Gastrointestinal Calpain Complex, G-calpain, Is a Heterodimer of CAPN8 and CAPN9 Calpain Iso-forms, Which Play Catalytic and Reg-ulatory Roles, Respectively." ***J. Biol. Chem.,*** 291: 27313-27322.

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

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, and 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, and 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.

Ono Y, Shindo M, Doi N, Kitamura F, Gregorio CC, and Sorimachi H. (2014) "The N- and C-terminal autolytic fragments of CAPN3/p94/calpain-3 restore proteolytic activity by intermolecular complementation." ***Proc. Natl. Acad. Sci. USA,*** 111: E5527-5536.

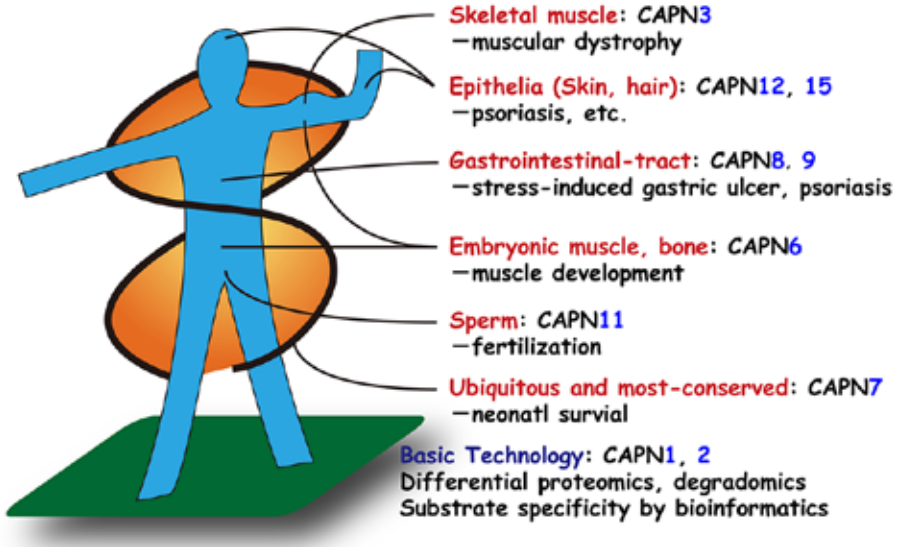
Tonami K, Hata S, Ojima K, Ono Y, Kurihara Y, Amano T, Sato T, Kawamura Y, Kurihara H, and Sorimachi H. (2013) "Calpain-6 deficiency promotes skeletal muscle development and regeneration." ***PLoS Genet.,*** 9: e1003668.

Project Leader **Yasuko Ono** Calpain Project

Calpain: Structure-Function Relationships

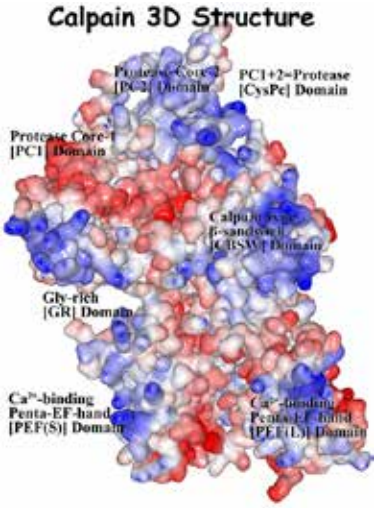
Exploring calpain-mediated biological modulation

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.



"Translational research involving calpains is still at the development 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).

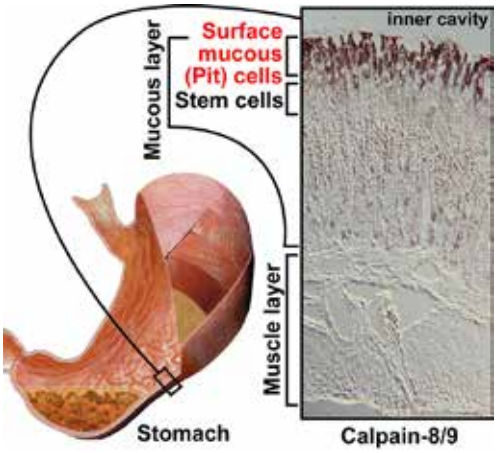
In this project, we aim to understand biology of calpains with wide scope of interest, and translate the knowledge to the development of our health as well as science.



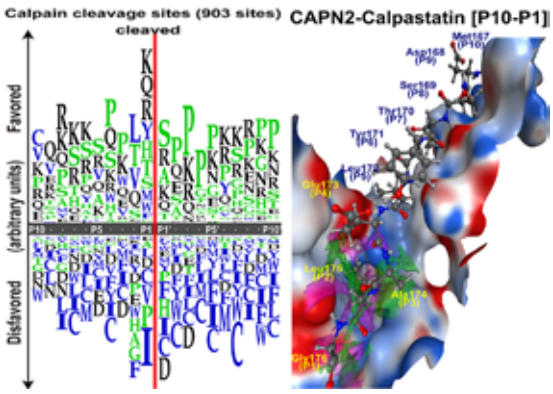
Calpain

Calpains in health and disease

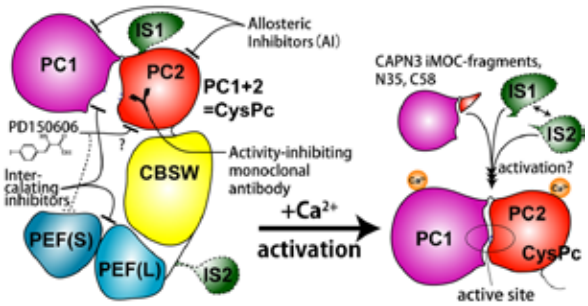
Some calpains predominantly expressed in specific tissue(s) are responsible for genetic diseases; *e.g.*, defects in *CAPN3* cause muscular dystrophy. Other calpains with rather ubiquitous expression pattern lead to lethality if deficient. It is also important to realize that some calpain species express their activity through unique and unexpected mechanisms, such as intermolecular complementation (CAPN3), heterodimerization (CAPN8/9), etc.
To explore how calpains protect our health, analyses of cells/mice lacking the function of specific calpain species or its expected targets are being performed. We are also improving research platform for studying calpains by biochemistry including proteomics, genetics, and bioinformatics.



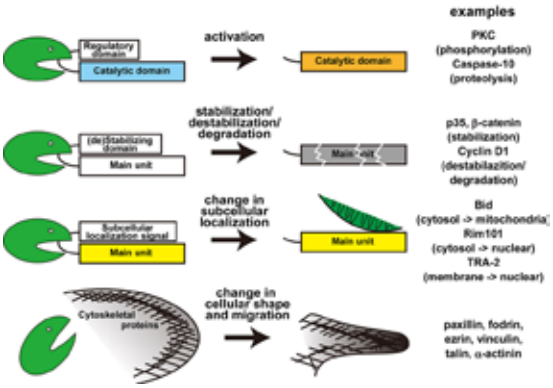
Protection of epithelial cells by heterodimeric calpain, G-calpain



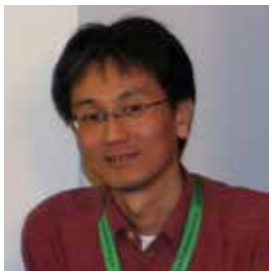
Characterization of calpain-substrate interface



Strategy for activity regulation of CAPN3



Multiplicity of calpain actions



Shoji Hata, Ph.D.
Calpains in epithelial function and tissue development

Fumiko Shinkai-Ouchi, Ph.D.
Proteomic analysis of muscular dystrophy and calpain substrate specificities

Aya Noguchi, Ph.D.
Cross talk of calpain and other proteolytic systems

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.

Yamano K, Wang C, Sarraf S, Münch C, Kikuchi R, Noda N, Hizukuri Y, Kanemaki M, Harper W, Tanaka K, Matsuda N, and Youle R. (2018) "Endosomal Rab cycles regulate Parkin-mediated mitophagy." ***eLife*** 7: e31326

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

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.

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).

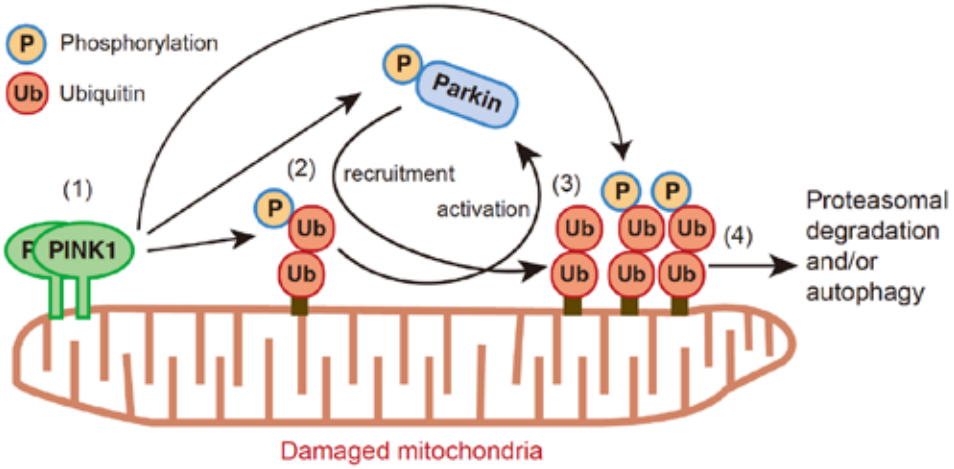
Matsuda N, Sato S, Shiba K, Okatsu K, Saisho K, Gautier C, Sou Y-S, Saiki S, Kawajiri S, Sato F, Kimura M, Komatsu M, Hattori N, and Tanaka K. (2010) "PINK1 stabilized by mitochondrial depolarization recruits Parkin to damaged mitochondria and activates latent Parkin for mitophagy." ***J. Cell Biology***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

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.

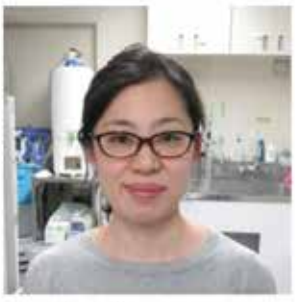
"We believe that big mystery in mitochondrial quality control has been unraveled, and our work can establish new principles of how a simple ubiquitin tag plays more varied roles than expected."



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

Tanegashima K, Takahashi R, Nuriya H, Iwase R, Naruse N, Tsuji K, Shigenaga A, Otaka A, and Hara T. (2017) "CXCL14 acts as a specific carrier of CpG DNA into dendritic cells and activates Toll-like receptor 9-mediated adaptive immunity." ***EBioMed.*** 24: 247-256.

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

Suzuki T, Kazuki Y, Oshimura M, and Hara T. (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.

Kodaka Y, Tanaka K, Kitajima, Tanegashima K, Matsuda R, and Hara T.(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.

Tanaka K, Kondo K, Kitajima K, Muraoka M, Nozawa A, and Hara T. (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.

Kitajima K, Minehata K, Sakimura K, Nakano T, and Hara T. (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.

Stem Cell

Project Leader **Takahiko Hara** Stem Cell Project

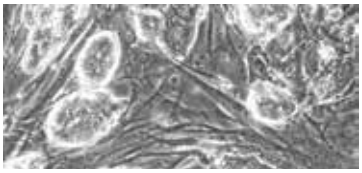
Blood regeneration from ESC/iPSC and development of novel anti-cancer drugs

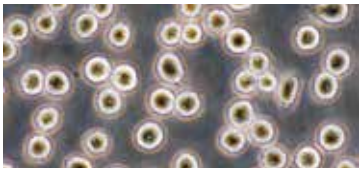
Dr. Yamanaka's inducible pluripotent stem cell (iPSC) technology has opened a new avenue to overcome incurable diseases by transplantation of missing cells. In 2011, we discovered that overexpression of Lhx2 in hemogenic mesodermal cells resulted in *ex vivo* expansion of transplantable hematopoietic 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.

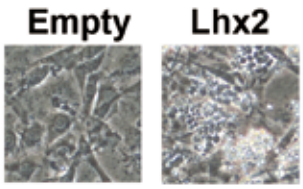
"We are making efforts to derive HSCs from human iPSCs in vitro. We are also challenging to develop novel anti-leukemia drugs and chemokine-based anti-cancer drugs."

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.

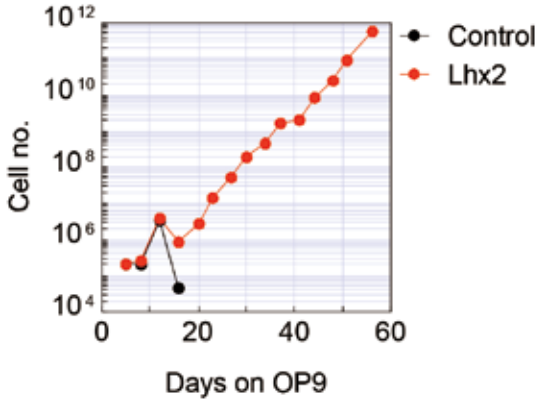
In 2007, we discovered that CXCL14, a CXC-type chemokine, is one of the causative factors for obesity-associated diabetes. In contrast, CXCL14 is known to possess tumor-suppressive activity against lung and oral carcinomas. Recently, we discovered that CXCL14 binds to CXCR4 with high affinity, thereby 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.

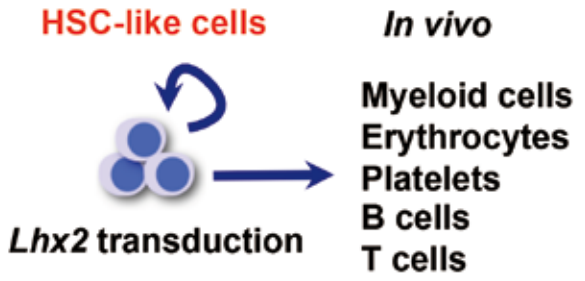




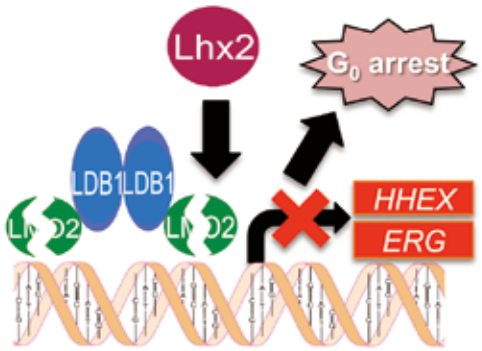


<Topic 1>
Enforced expression of *Lhx2* leads to robust *ex vivo* production of HSC-like cells from mouse ESCs/iPSCs.

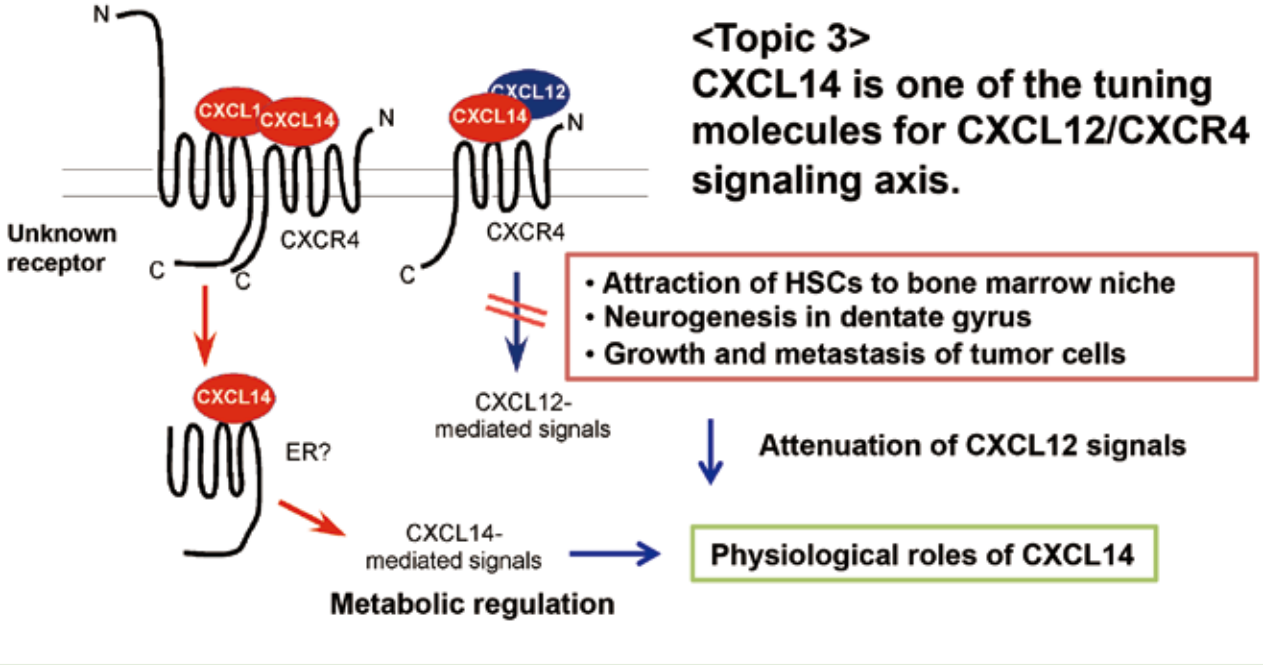




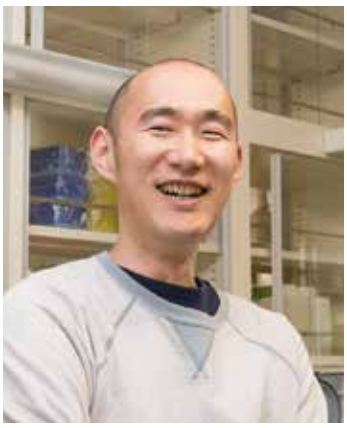
<Topic 2>
Lhx2 induces degradation of Lmo2 protein, thereby inhibiting proliferation of human T-cell acute lymphoblastic leukemia (T-ALL) cells.



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



Stem Cell



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

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

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, and Wells JM. (2017) "Engineered human pluripotent-stem-cell-derived intestinal tissues with a functional enteric nervous system." ***Nat. Med.*** 23: 49-59.

Miyaoka Y, Chan AH, and Conklin BR. (2016) "Using Digital Polymerase Chain Reaction to Detect Single-Nucleotide Substitutions Induced by Genome Editing." ***Cold Spring Harb. Protoc.*** 2016:688-692.

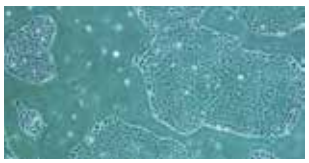
Miyaoka Y, Berman JR, Cooper SB, Mayerl SJ, Chan AH, Zhang B, Karlin-Neumann GA, and Conklin BR. (2016) "Systematic quantification of HDR and NHEJ reveals effects of locus, nuclease, and cell type on genome-editing." ***Sci. Rep.*** 6: 23549.

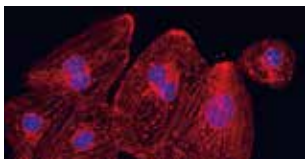
Miyaoka Y, Chan AH, Judge LM, Yoo J, Huang M, Nguyen TD, Lizarraga PP, So PL, and Conklin BR. (2014) "Isolation of single-base genome-edited human iPS cells without antibiotic selection." ***Nat. Methods*** 11: 291-293.

Project Leader **Yuichiro Miyaoka** Regenerative Medicine Project

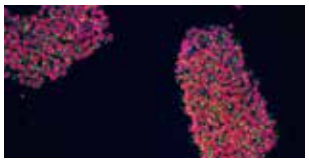
Genome Editing in Human iPS Cells: To study and cure genetic disorders

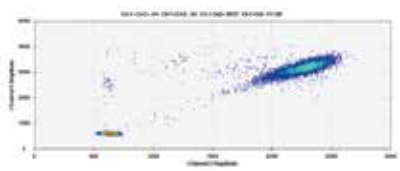
Genome editing technology allows us to rewrite the genetic information in virtually any species and any cell type including human cells. To study the pathogenesis of human diseases at the molecular level, and to develop new therapies using genome editing, we need appropriate human cellular models. Our 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."



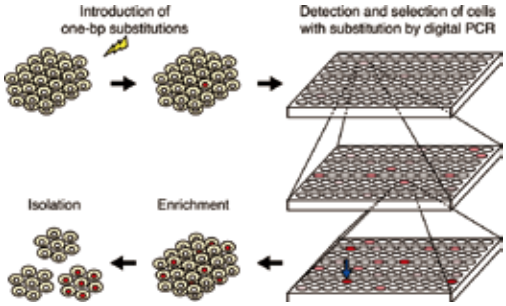


We developed an efficient method to isolate iPS cell lines containing a single nucleotide substitution. The nucleotide substitution is created by genome editing based on digital PCR, and isolation is accomplished by repeated limited dilutions in the absence of selection markers (Miyaoka, Nat. Methods 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.

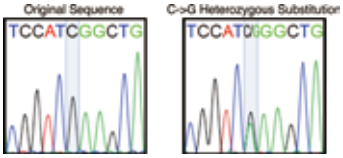
Regenerative Medicine

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

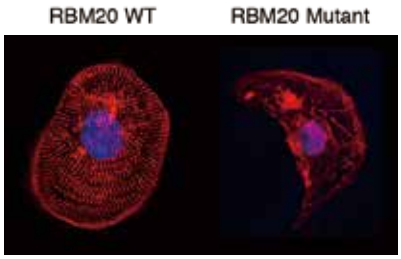


Isolated iPS cells with C→G substitution

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

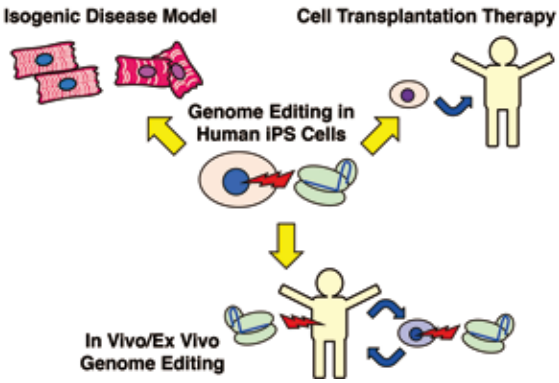
By editing the genome of iPS cells, we can study pathogenic mechanisms of genetic disorders in any cell type in a dish. For example, a point mutation in RBM20 (a cardiomyopathy mutation) introduced into iPS cells caused abnormal sarcomere structures (a functional unit of muscle contraction visualized 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

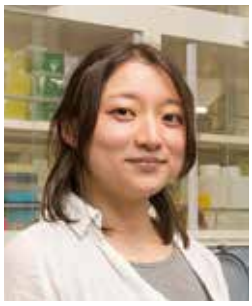
Development of Precise Ways to Edit the Genome

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.

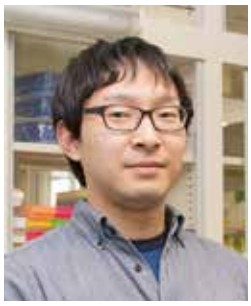


Genome editing in iPS cells to study and cure disease

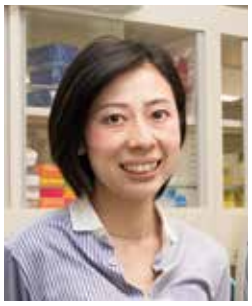
Members



Tomoko Kato-Inui



Gou Takahashi

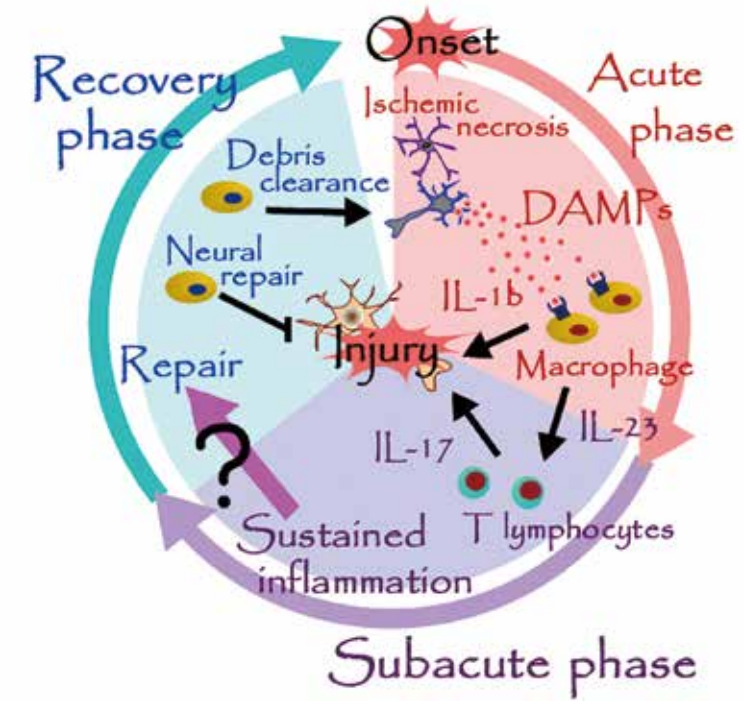


Szuyin Hsu

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.

Tsuyama J, Nakamura A, Ooboshi H, Yoshimura A, and Shichita T. (2018) "Pivotal role of innate myeloid cells in cerebral post-ischemic sterile inflammation." ***Semin. Immunopathol.***

Shichita T, Ito M, Morita R, Komai K, Noguchi Y, Ooboshi H, Koshida R, Takahashi S, Kodama T, and Yoshimura A. (2017) "Mafb prevents excess inflammation after ischemic stroke by accelerating clearance of danger signals through MSR1." ***Nat. Med.*** 23(6): 723-732.

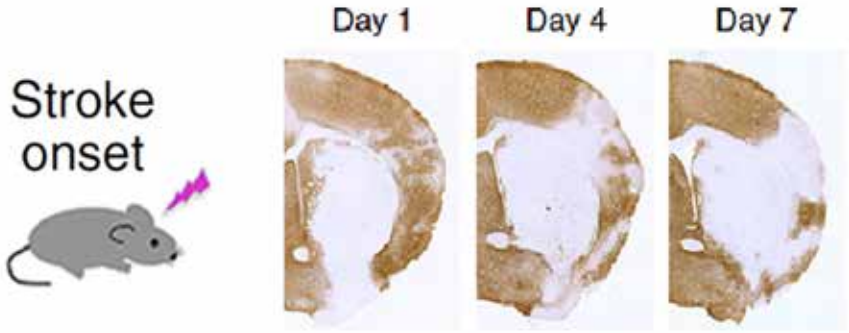
Shichita T, Hasegawa E, Kimura A, Morita R, Sakaguchi R, Takada I, Sekiya T, Ooboshi H, Kitazono T, Yanagawa T, Ishii T, Takahashi H, Mori S, Nishibori M, Kuroda K, Akira S, Miyake K, and Yoshimura A. (2012) "Peroxiredoxin family proteins are key initiators of post-ischemic inflammation in the brain." ***Nat. Med.*** 18(6): 911-917.

Shichita T, Sugiyama Y, Ooboshi H, Sugimori H, Nakagawa R, Takada I, Iwaki T, Okada Y, Iida M, Cua DJ, Iwakura Y, and Yoshimura A. (2009) "Pivotal role of cerebral interleukin-17-producing gammadelta T cells in the delayed phase of ischemic brain injury." ***Nat. Med.*** 15(8):946-950.

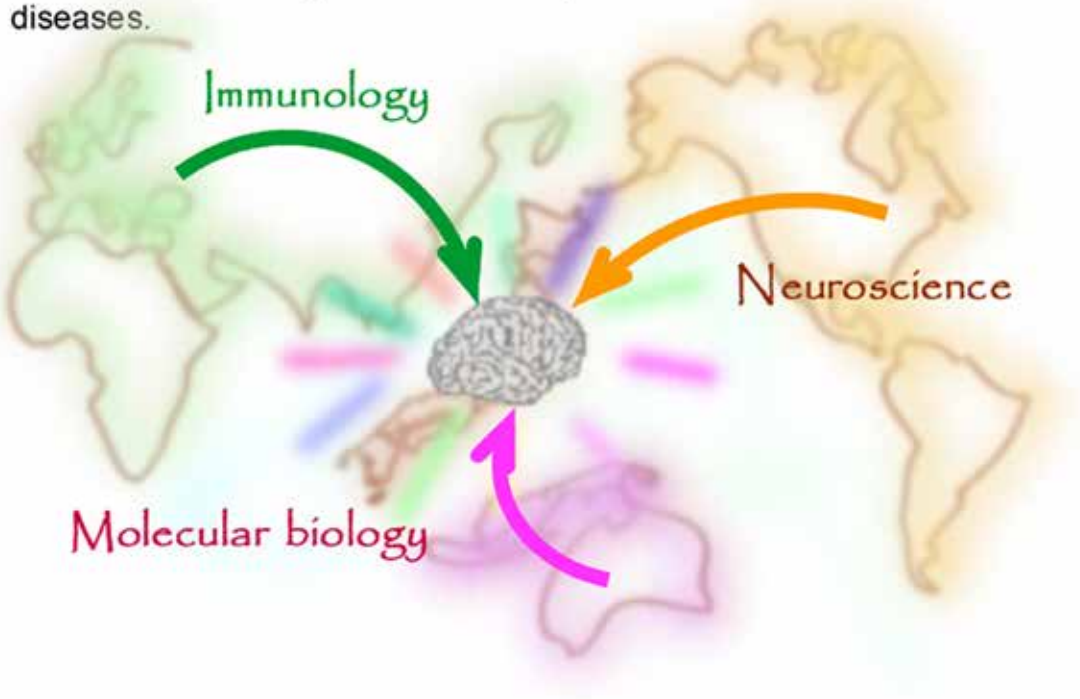
Stroke Renaissance

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.



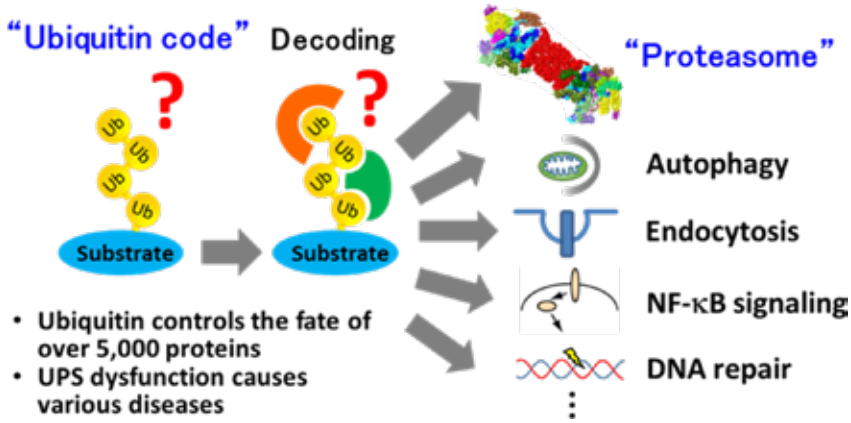
In this project, we try to clarify the detailed molecular mechanisms underlying the recovery of brain after stroke. The new research methods and techniques which have been recently developed in the field of immunology or neuroscience will enable us to investigate the precise process of inflammation and 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

Laboratory Head **Yasushi Saeki** Protein Metabolism Laboratory

The Ubiquitin-Proteasome System "Elucidation of Fundamental and Pathophysiological Mechanisms"



The ubiquitin-proteasome system (UPS) plays a pivotal role in proteostasis and controls almost all of cellular functions by selective protein degradation. As the maintenance of protein homeostasis is essential to human health, dysfunction of the UPS due to stresses, age-associated changes, or gene mutations causes various diseases such as cancers, inflammation, and neurodegeneration. However, we do not yet know the overall principle of the ubiquitin signaling, decoding mechanism, and the proteasome. We aim to elucidate the fundamental mechanisms of the ubiquitin code as well as proteasome function and to integrate it into pathophysiology, and then to develop therapeutic strategies for UPS-related diseases.

Research Projects

1. Proteasome Dynamics and Pathophysiology

The proteasome is a highly organized proteolytic machinery that degrades ubiquitylated proteins in an ATP-dependent manner. We have characterized the structure, assembly pathway, and substrate targeting mechanism of the proteasome. We also found that the proteasome dynamically changes its intracellular localization and its accessory proteins under various stresses to restore proteostasis. Currently, we are generating knock-in mice to visualize proteasome localization and activity to analyze physiological changes of the proteasome accompanying stress and aging. Furthermore, we have generated model mice of proteasomal gene mutation derived from patients with neurodevelopmental disorders. Using the mutant mice, we will elucidate the pathophysiology of the proteasome mutation at the whole-body level.

Tsuchiya H, Burana D, Ohtake F, Arai N, Kaiho A, Komada M, Tanaka K, and Saeki Y. (2018) "Ub-ProT reveals global length and composition of protein ubiquitylation in cells." ***Nature Commun.*** 9, 524.

Ohtake F, Tsuchiya H, Saeki Y, and Tanaka K. (2018) "K63 ubiquitylation triggers proteasomal degradation by seeding branched chains." ***Proc. Natl. Acad. Sci. USA.*** 115, E1401-E1408.

Xie X, Matsumoto S, Endo A, Fukushima T, Kawahara H, Saeki Y, and Komada M. (2018) "Deubiquitylases USP5 and USP13 are recruited to and regulate heat-induced stress granules through deubiquitylating activities." ***J. Cell. Sci.*** 131, jcs201856

Tsuchiya H, Ohtake F, Arai N, Kaiho A, Yasuda S, Tanaka K, and Saeki Y. (2017) "In vivo ubiquitin linkage-type analysis reveals that the Cdc48-Rad23/Dsk2 axis contributes to K48-linked chain specificity of the proteasome." ***Mol. Cell*** 66, 485-502.

Ohtake F, Saeki Y, Ishido S, Kanno J, and Tanaka K. (2016) "The K48-K63 branched ubiquitin chain regulates NF-κB signaling." ***Mol. Cell*** 64, 251-266.

Yoshida Y, Saeki Y, Murakami A, Kawawaki J, Tsuchiya H, Yoshihara H, Shindo M, and Tanaka K. (2015) "A comprehensive method for detecting ubiquitinated substrates using TR-TUBE." ***Proc. Natl. Acad. Sci. USA.*** 112, 4630-4635.

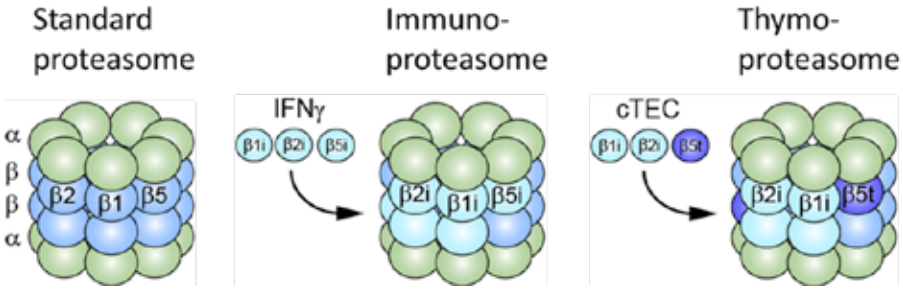
Pack Chan-Gi, Yukii H, Toh-e A, Kudo T, Tsuchiya H, Kaiho A, Sakata E, Murata S, Yokosawa H, Sako Y, Baumeister W, Tanaka K, and Saeki Y. (2014) "Quantitative live-cell imaging reveals molecular dynamics and cytoplasmic assembly of the 26S proteasome." ***Nature Commun.*** 5, 4396

Saeki Y, Toh-e A, Kudo T, Kawamura H, and Tanaka K. (2009) "Multiple proteasome-interacting proteins assist the assembly of the yeast 19S regulatory particle." ***Cell*** 137, 900-913.

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 proteasomes, which we named the "immunoproteasome" and the “thymoproteasome”. 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”. Currently, we are conducting a deep proteomic screen to validate the positive selection model.



Keiji Tanaka
(The chairperson of TMIMS)

Murata S, Takahama Y, Kasahara M, and Tanaka K. (2018) “The immunoproteasome and thymoproteasome: functions, evolution and human disease.” ***Nature Immunol.*** 19, 923-931.

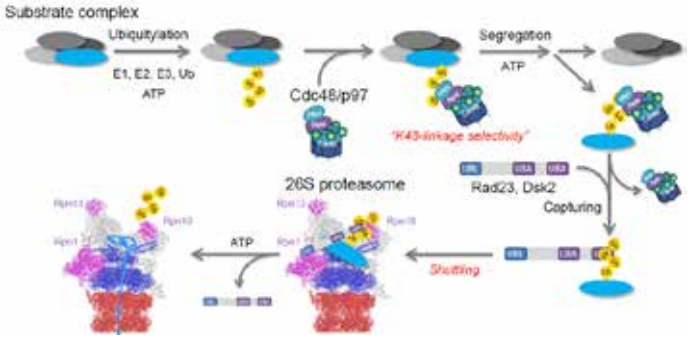
Murata S, Sasaki K, Kishimoto T, Niwa S, Hayashi H, Takahama Y, and Tanaka K. (2007) “Regulation of CD8⁺ T cell development by thymus-specific proteasomes.” ***Science*** 316, 1349-1353.

3. Deciphering the Ubiquitin Code

Different polyubiquitin chain linkages direct substrates to distinct pathways, as referred to as ‘ubiquitin code’. 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. We also identified more complexed ubiquitin chains branched at K48 and K63, which act as a unique coding signal to enhance NF-κB signaling. We are further analyzing the decoder proteins throughout the ubiquitin-mediated pathways to reveal the ubiquitin network.

Fumiaki Ohtake

Hikaru Tsuchiya



Members

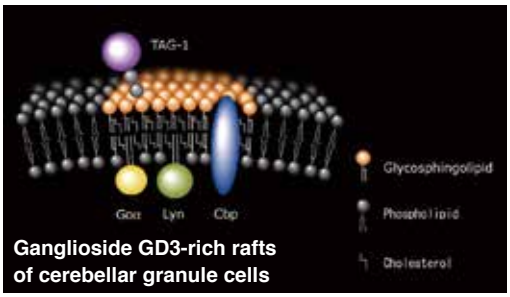
Keiji Tanaka	Ai Kaiho
Yasushi Saeki	Naoko Arai
Fumiaki Ohtake	Yuko Okamoto
Hikaru Tsuchiya	Arisa Kawano
Sayaka Yasuda	Marcel Diallo

Protein Metabolism

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.

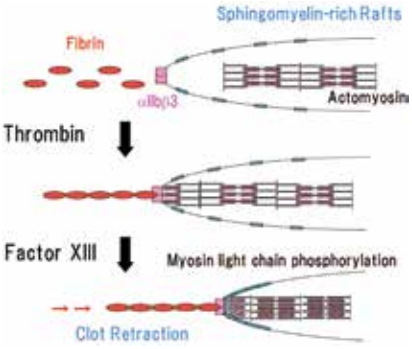


Ganglioside GD3-rich rafts of cerebellar granule cells

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

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, and Yamamoto N. (2013) "Clot retraction is mediated by factor XIII-dependent fibrin-αIIbβ3-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, and 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.

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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.

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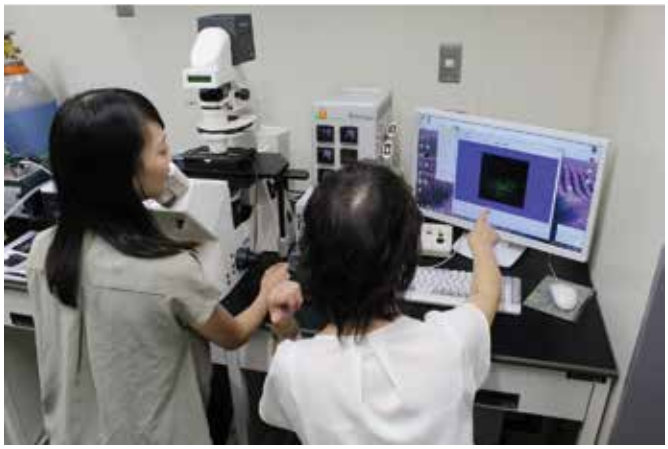
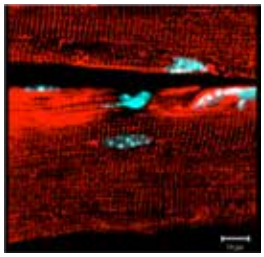
Biomembrane



Research Support

Center for Basic Technology Research

General Manager
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.

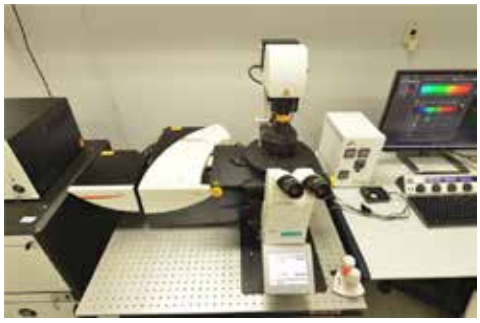
1. The Animal Research Division maintains the animal facility that is used by all the researchers who use animals for their research. It assists researchers generate knock-out or transgenic animals as well as maintain sperms and eggs of various lines of mutant animals. It also provides maximal care for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

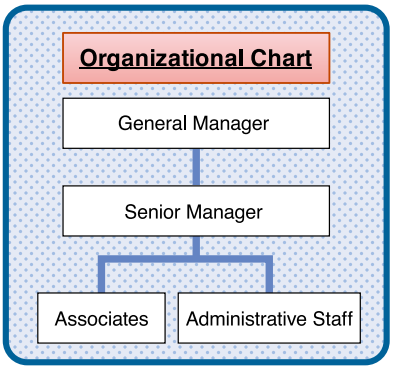
- Center for Basic Technology Research
  - Animal Research Division
    - Animal Research Control Laboratory
    - Laboratory for Transgenic Technology
  - Technology Research Division
    - Advanced Technical Support Department
      - Protein Analyses, FACS, Microarray, Confocal Microscopy, Electron 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)

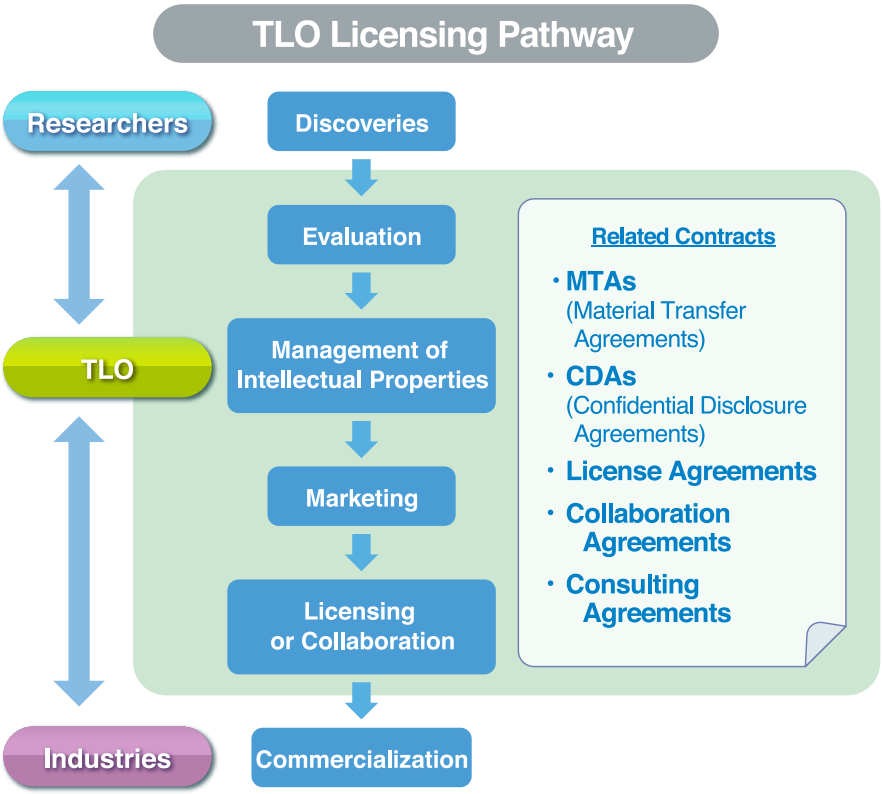
General Manager
Futoshi Shibasaki, MD, PhD

Senior Manager
Kazumasa Aoki, PhD



Who we are

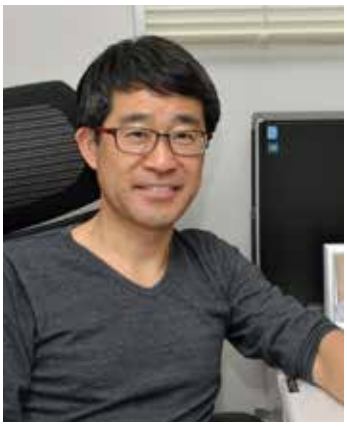
- The Technology Licensing Office (TLO) facilitates the conversion of scientific discoveries to innovative technologies with the ultimate goal of improving public health and welfare.
- We evaluate basic research findings (seeds) as intellectual property assets, and license promising candidates to industries 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, BIO-EUROPE, and BioJapan, to develop Public Private Partnership 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

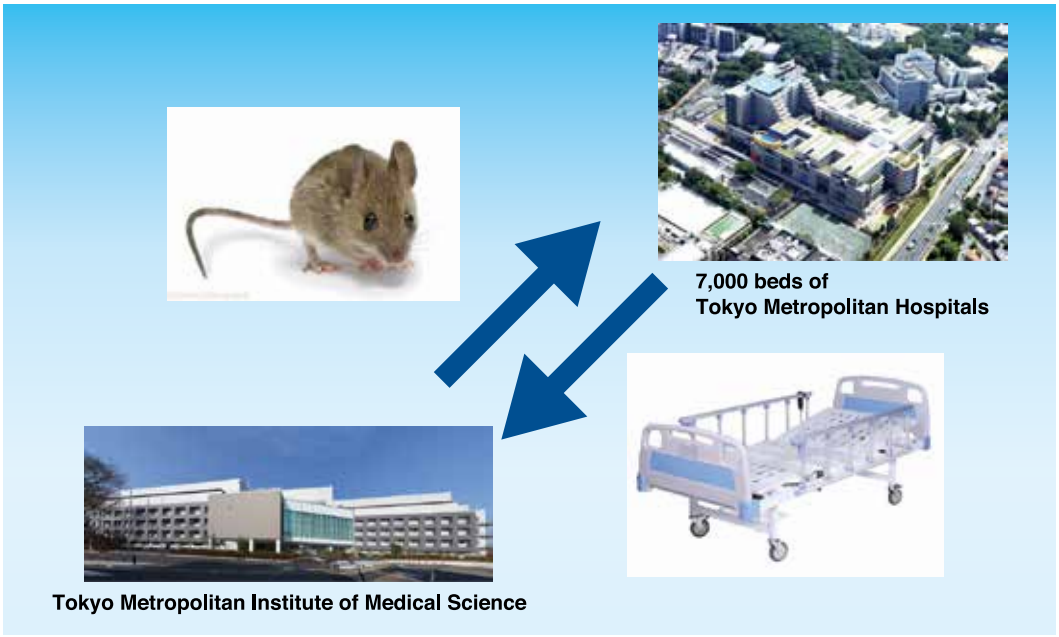


Head of Office
Masanari Itokawa MD, PhD

Making the Dream of Young Scientists Come True

– from bench to bed and back again –

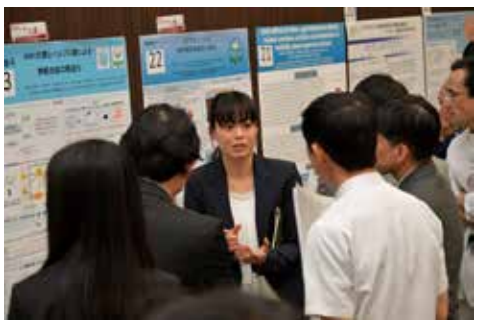
We provide---
-Consultation on statistical analyses
-Ethical issues related to human specimens
-A bridge between basic scientists and medical doctors



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.

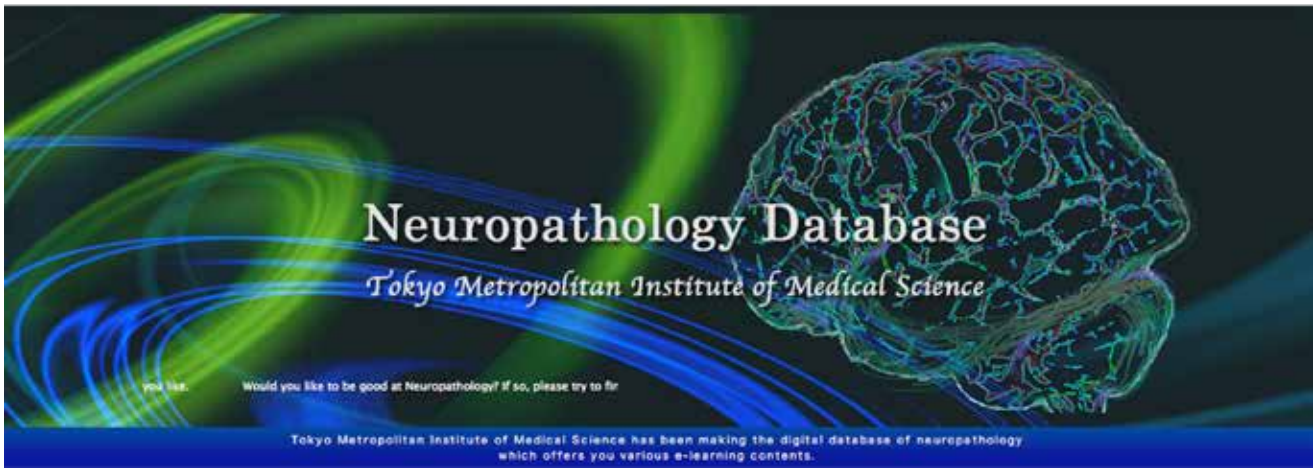


A young scientist discussing with medical doctors in a conference

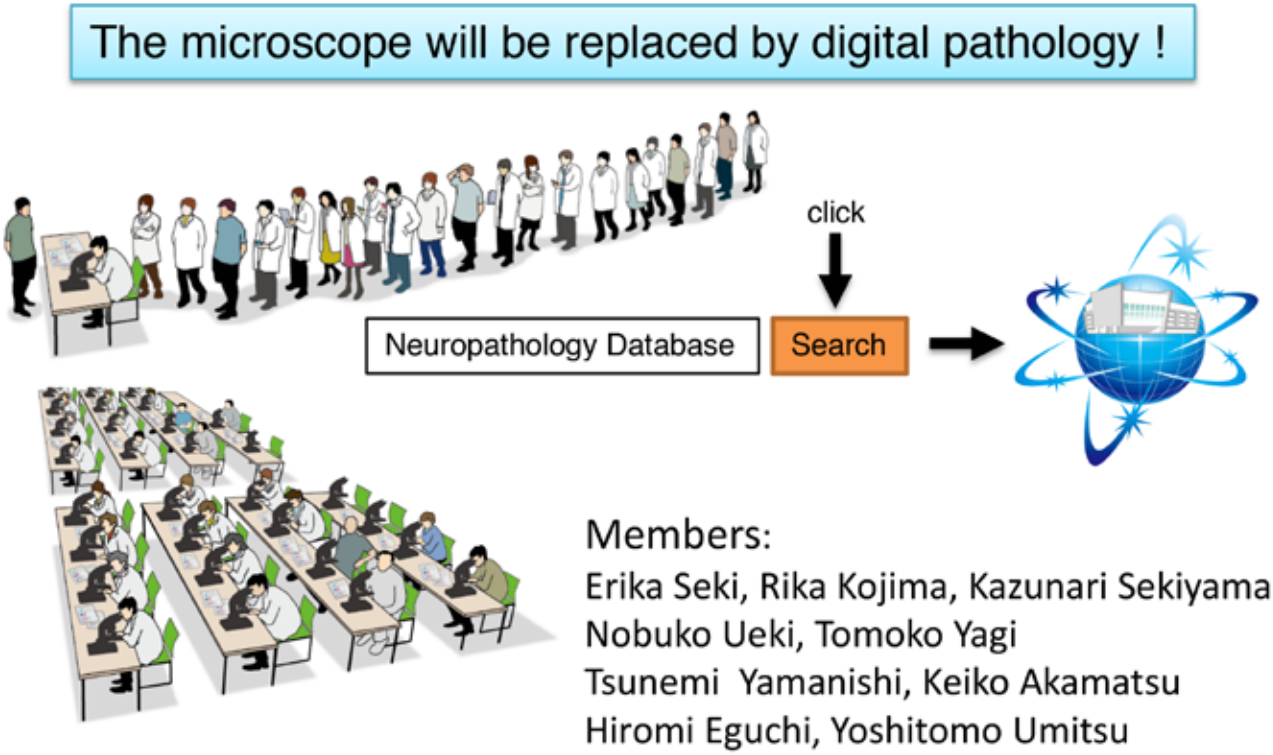
Neuropathology Laboratory

Laboratory Head
Nobutaka Arai

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



Laboratory of Neuropathology 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, we construct digital neuropathology.



Members:
Erika Seki, Rika Kojima, Kazunari Sekiyama
Nobuko Ueki, Tomoko Yagi
Tsunemi Yamanishi, Keiko Akamatsu
Hiromi Eguchi, Yoshitomo Umitsu

Neuropathology

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 subjects.

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 this field.

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.

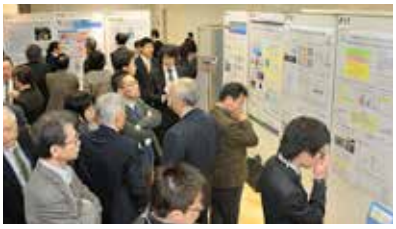
Open laboratory to graduate students:
Once a year we invite students to our institute, conduct presentation and give them opportunities to experience the laboratory.

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 and our various activities made at our institute.

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.







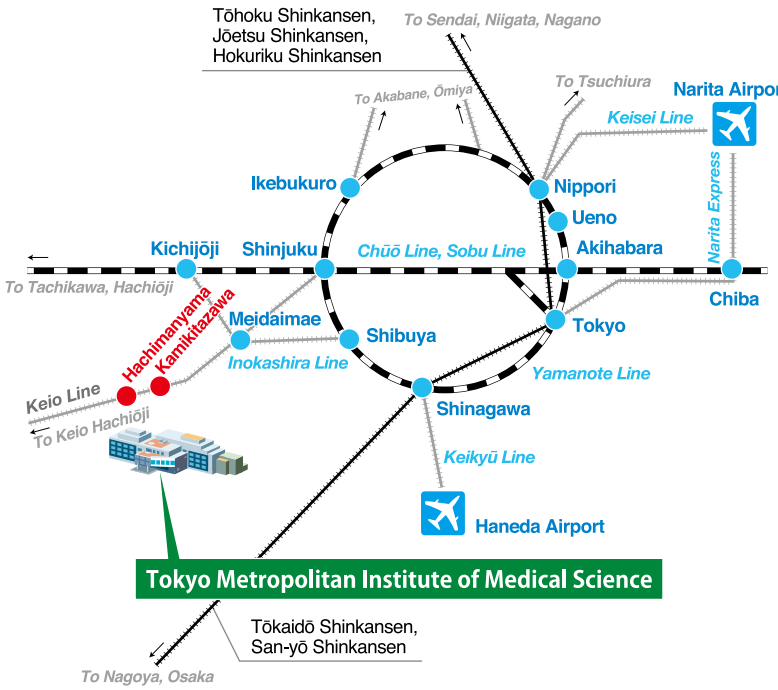

Supports for young scientists

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 fellowship with which they can attend international meetings where they will present their latest findings.

Access Map

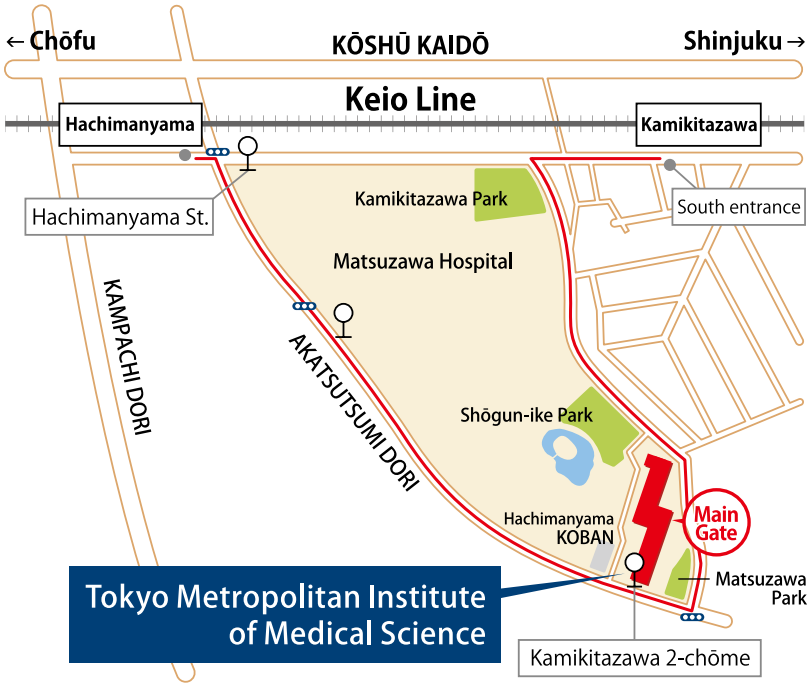
Tokyo Metropolitan Institute of Medical Science	
Address	2-1-6 Kamikitazawa, Setagaya-ku, Tokyo, 156-8506, Japan
Tel	+81-3-5316-3100
Fax	+81-3-5316-3150



AIRPORT to INSTITUTE

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

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



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

- **From Hachimanyama Station to Institute**

Hachimanyama Station - Kamikitazawa 2-chōme	Keio bus / Odakyū bus
Kamikitazawa 2-chōme - Institute	Walk

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

As of October 1, 2018