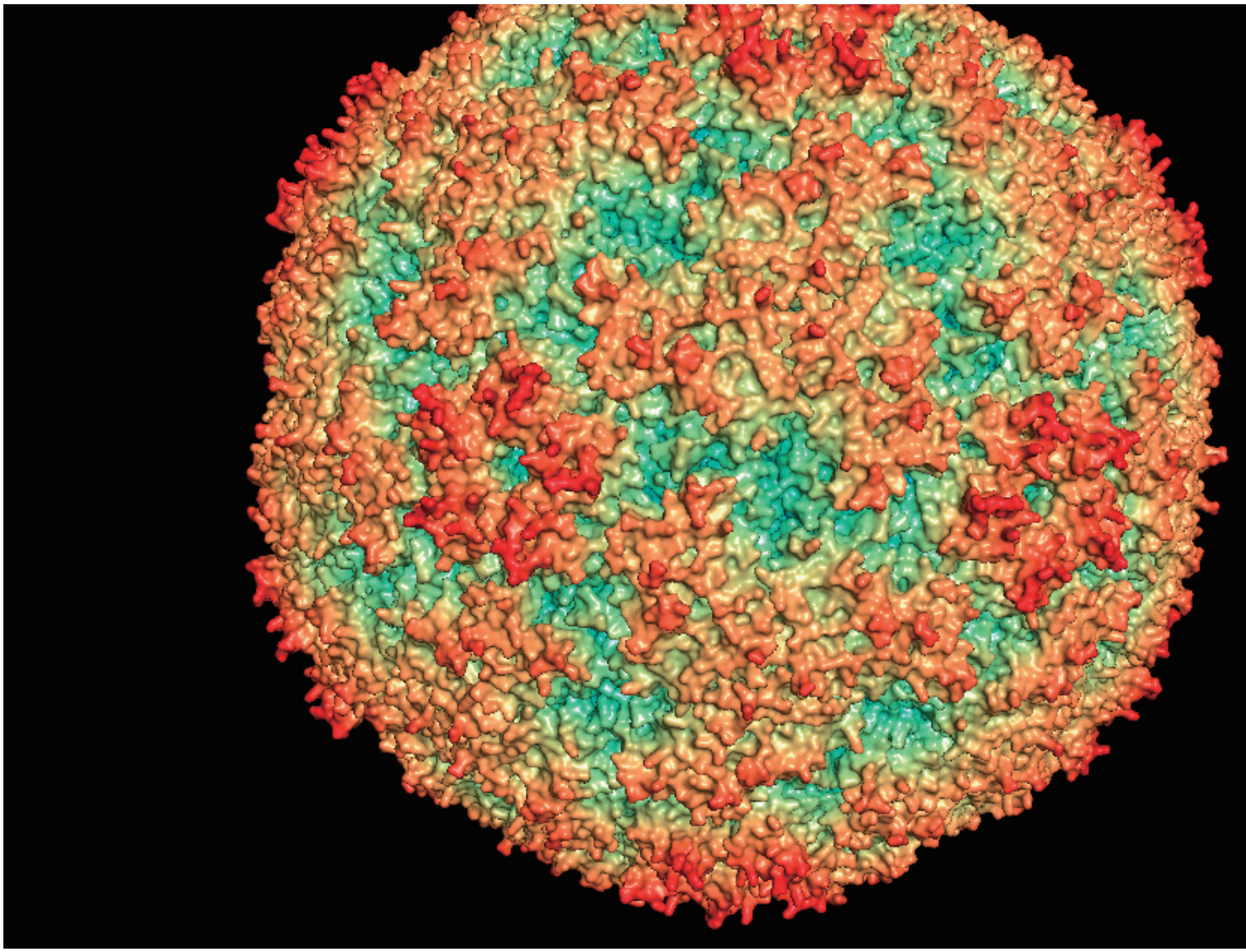


A particle structure model of Enterovirus 71 generated from the Protein Data Base 4AED. Red and green indicate surface and interior compartments, respectively.

Diseases & Infection

Project Leader
Fumihiko YASUI

Viral Infection Control

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

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

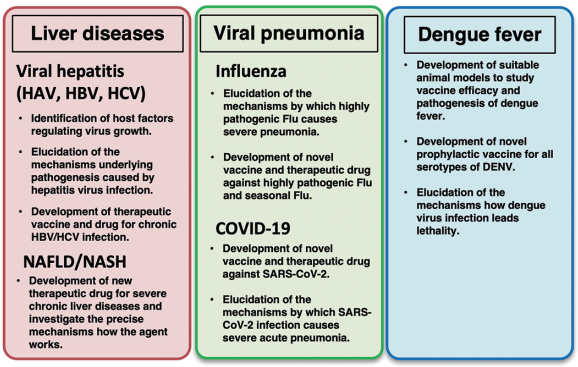
Staff

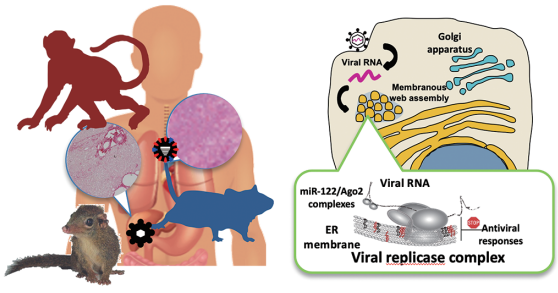
Researchers
Michinori KOHARA
Tsubasa MUNAKATA
Daisuke YAMANE
Kenzaburo YAMAJI
Yuko TOKUNAGA
Naoki YAMAMOTO
Takahiro SANADA
Yusuke MATSUMOTO
Tomoko HONDA

Research Assistants
Asako TAKAGI
Risa KONO
Masahiko HIGA

Research Summary

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





Selected Publications

Saito M, et al. In Press "Targeted macrocycles hamper hemagglutinin adsorption and fusion, and have antiviral effects in murine and macaque models of influenza." ***Nat Commun***.

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

Tokunaga Y, et al. (2017) "Selective inhibitor of Wnt/-catenin/CBP signaling ameliorates hepatitis C virus-induced liver fibrosis in mouse model." ***Sci. Rep.*** 7: 325.

Sanada T, et al. (2016) "Transmission of HBV DNA mediated by ceramidetriggered extracellular vesicles." ***Cell Mol. Gastroenterol Hepatol.*** 3:272-283.

Yasui F, et al. (2016) "Sensitization with vaccinia virus encoding H5N1 hemagglutinin restores immune potential against H5N1 influenza against H5N1 influenza virus." ***Sci. Rep.*** 6: 37915.

Sanada T, et al. (2016) "Property of hepatitis B virus replication in Tupaia belangeri hepatocytes." ***Biochem. Biophys Res. Commun.*** 469: 229-235.

Yamamoto N, et al. (2016) "Novel pH-sensitive multifunctional envelopetype nanodevice for siRNA-based treatments for chronic HBV infection." ***J. Hepatol.*** 64: 547-555

Project Leader
Satoshi KOIKE

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

Neurovirology

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

Staff

Researchers
Kyousuke KOBAYASHI
Naoki KAJIWARA

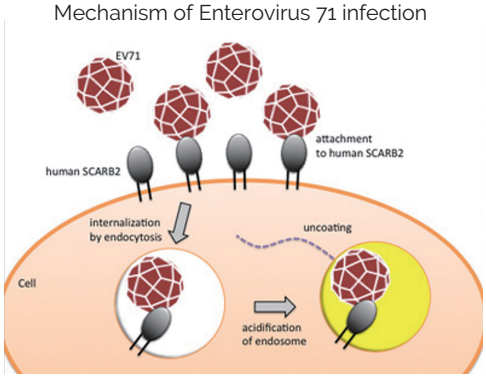
Research Assistants
Ayako TAKASHINO
Masako UKAJI
Namiko NOMURA
Tomoha NISHIZAWA
Wakako MIWATASHI
Minori ISHIDA
Sayaka ESAKI

Research Summary

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

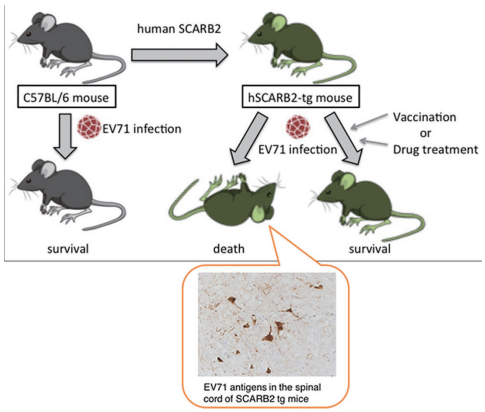
Research Topics

Mechanism of Enterovirus 71 infection



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

Development of an animal model for Enterovirus 71 infection



Transgenic mice expressing human SCARB2 are susceptible to EV71, and are a useful model for the study of EV71 pathogenesis and vaccine efficacy.

Selected Publications

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

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

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

Fujii K, et al. (2018) "VP1 Amino Acid Residue 145 of Enterovirus 71 Is a Key Residue for Its Receptor Attachment and Resistance to Neutralizing Antibody during Cynomolgus Monkey Infection." ***J. Virol.,*** 92:(15)e00682-18

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

Yamayoshi S, et al. (2009) "Scavenger receptor B2 is a cellular receptor for enterovirus 71." ***Nature Medicine*** 15:789-801

Project Leader
Takayuki HARADA

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

Visual Research

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

Staff

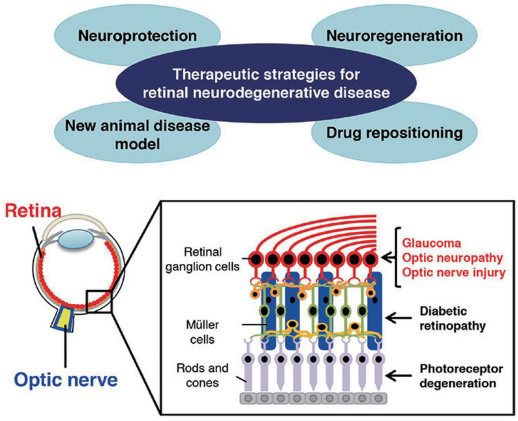
Researchers
Researchers
Kazuhiko NAMEKATA
Xiaoli GUO
Atsuko KIMURA
Chikako HARADA
Takahiko NORO
Euido NISHIJIMA
Yuta KITAMURA
Naoki KIYOTA

Research Assistants
Mayumi KUNITOMO

Students
Kaori SEGURA

Research Summary

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



The Rho-ROCK pathway regulates actin cytoskeleton and dynamics, and we have recently reported that application of the Rho-ROCK inhibitor ripasudil eyedrops promoted optic nerve regeneration and neuroprotection by suppressing phosphorylation of CRMP2 and cofilin, two proteins involved in the Rho-ROCK pathway.

We have also been examining the role of DOCK-D family proteins in neuroinflammation. DOCK proteins are atypical guanine nucleotide exchange factors, and we found that deficiencies in DOCK10 reduced neuroinflammation in an animal model of multiple sclerosis (MS). Thus, DOCK10 may be a novel therapeutic target for diseases such as MS and optic neuritis.

Finally, we have been studying the relationship between glaucoma and EAAT1, a glutamate transporter that regulates glutamate signaling. Glutamate is the major excitatory neurotransmitter in the central nervous system and we identified EAAT1 variants that are associated with glaucoma. These loss-of-function variants may contribute to pathogenesis of glaucoma.

Selected Publications

Namekata, K., Guo, X., Kimura, A., Azuchi, Y., Kitamura, Y., Harada, C. and Harada, T. Roles of the DOCK-D family proteins in a mouse model of neuroinflammation. ***Journal of Biological Chemistry*** 295(19), 6710-6720, 2020.

Nishijima, E., Namekata, K., Kimura, A., Guo, X., Harada, C., Noro, T., Nakano, T. and Harada, T. Topical ripasudil stimulates neuroprotection and axon regeneration in adult mice following optic nerve injury. ***Scientific Reports*** 10(1), 15709, 2020.

Harada, C., Noro, T., Kimura, A., Guo, X., Namekata, K., Nakano, T. and Harada, T. Suppression of oxidative stress as potential therapeutic approach for normal tension glaucoma. ***Antioxidants*** 9(9), 874, 2020.

Kimura, A., Noro, T. and Harada, T. Role of animal models in glaucoma research. ***Neural Regeneration Research*** 15(7), 1257-1258, 2020.

Yanagisawa, M., Namekata, K., Aida, T., Katou, S., Takeda, T., Harada, T., Fuse, N., the Glaucoma Gene Research Group, and Tanaka, K. EAAT1 variants associated with glaucoma. ***Biochemical and Biophysical Research Communications*** 529(4), 943-949, 2020.

Kikuchi, K., Dong, Z., Shinmei, Y., Murata, M., Kanda, A., Noda, K., Harada, T. and Ishida, S. Cytoprotective effect of astaxanthin in a model of normal intraocular pressure glaucoma. ***Journal of Ophthalmology*** 2020, 9539681, 2020.

Project Leader
Kazunori SANGO

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

Diabetic Neuropathy

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

Staff

Researchers
Mari SUZUKI
Hideji YAKO
Naoko NIIMI
Shizuka TAKAKU

Research Assistants
Kumi SUMIDA

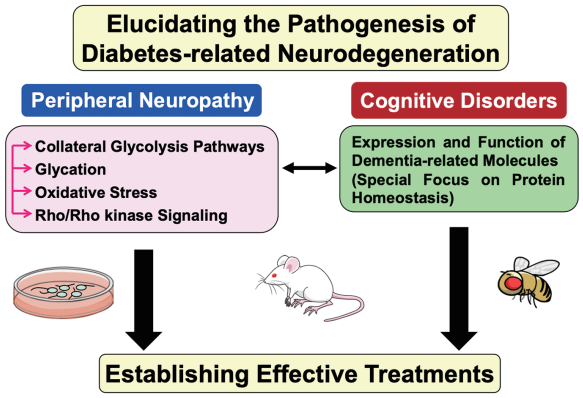
Visiting Scientists
Koichi KATO
Tatsufumi MURAKAMI
Junji YAMAUCHI
Hitoshi KAWANO
Ken MURAMATSU
Keiichiro MATOBA
Tomoyo AKAMINE
Tomoko ISHIBASHI

Students
Yosuke NAGAI
Masaki OBA
Nozomi SAKATA

Research Summary

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

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



Project1:
Therapeutic Approaches to Diabetic Peripheral Neuropathy

Using diabetic model animals and culture systems of adult rodent dorsal root ganglion (DRG) neurons and immortalized Schwann cells, we seek to establish effective pathogenesis-based treatments for peripheral neuropathy.

Project2:
Mechanistic link between Metabolic dysfunction and Neurodegenerative Diseases

By using a Drosophila model, we aim to understand the molecular mechanism by which metabolic conditions influence misfolding protein-induced neurodegeneration.

Selected Publications

Mizukami H, et al. "Role of glucosamine in development of diabetic neuropathy independent of aldose reductase pathway." ***Brain Commun***, Oct 9, 2020 (on line).

Akamine T, et al. (2020) "Glycolaldehyde induces sensory neuron death through activation of the c-Jun N-terminal kinase and p-38 MAP kinase pathways." ***Histochem. Cell Biol.*** 153:111-119.

Lee JS, et al. (2019) "Arylsulfatase A, a genetic modifier of Parkinson's disease, is an α -synuclein chaperone. " ***Brain*** 142:2845-2859.

*Nakamura S, *Oba M, et al. (2019) "Suppression of autophagic activity by Rubicon is a signature of aging." ***Nat. Commun.*** 10:847. (*co-first authors)

Takaku S, et al. (2018) "Establishment of a myelinating co-culture system with a motor neuron-like cell line NSC-34 and an adult rat Schwann cell line IFRS1." ***Histochem. Cell Biol.*** 149:537-543.

Niimi N, et al. (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, et al. (2017) "Impaired axonal regeneration in diabetes. Perspective on the underlying mechanism from in vivo and in vitro experimental studies." ***Front. Endocrinol.*** 8:12.

Project Leader
Yuichiro MIYAOKA

Yuichiro Miyaoka has been the leader of the Regenerative Medicine Project since 2016.
He received his Ph.D. from the Institute of Molecular and Cellular Biosciences, the University of Tokyo under the supervision of Dr. Atsushi Miyajima in 2009. After receiving his Ph.D., he worked as a staff scientist in the Dr. Atsushi Miyajima's lab from 2009 to 2011. Then, he did his postdoctoral training in the Bruce Conklin's lab at Gladstone Institutes, USA from 2011 to 2015, where he developed the first digital PCR-based method to detect genome editing outcomes. He applied this method to isolate genome-edited cells without antibiotic selection. His current interest is to apply genome editing in human iPS (induced pluripotent stem) cells to cure genetic disorders by disease modeling, cell transplantation therapy, and direct genetic manipulation in patients' cells. For these therapeutic applications, genome editing should be precise. Therefore, he also aims to improve the accuracy and predictability of genome editing.

Regenerative Medicine

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

Staff

Researchers
Tomoko KATO-INUI
Gou TAKAHASHI

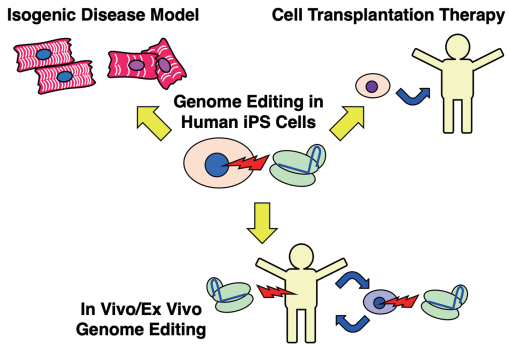
Research Assistants
Szuyin HSU

Students
Daiki KONDO
Ittetsu NAKAJIMA
Terumi ONO
Anri SAITOH
Minato MAEDA

Research Summary

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

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



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

Selected Publications

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

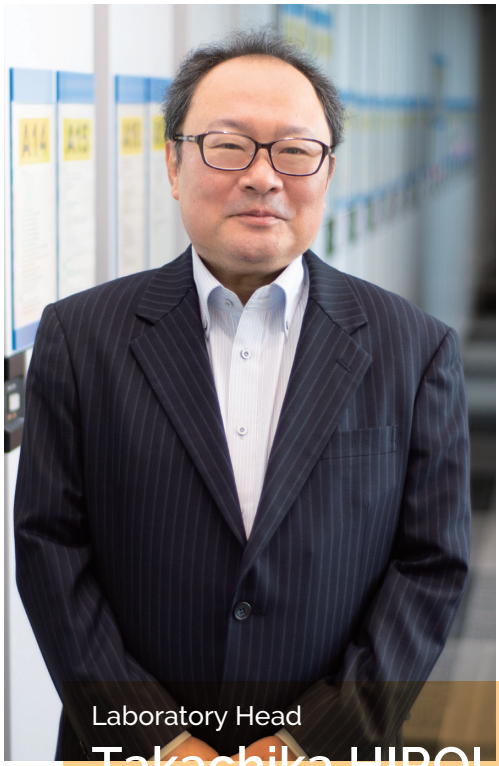
Miyaoka Y, et al. (2018) "Detection and Quantification of HDR and NHEJ Induced by Genome Editing at Endogenous Gene Loci Using Droplet Digital PCR." ***Methods Mol. Biol.*** 1768: 349-362.

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

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

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

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



Laboratory Head
Takachika HIROI

Takachika Hiroi has been the leader of the laboratory of allergy and immunology since 2005. After graduation from Nihon university school of dentistry at Matsudo in 1986 (D.D.S.), he completed graduate school at Nihon university in 1990 (Ph.D). He started to work on mucosal immunology under the supervision of Dr. Hiroshi Kiyono at University of Alabama at Birmingham, Vaccine center, Alabama, USA, in 1992. After returning to Japan, he worked at Osaka University in 1995-2003 and at University Tokyo in 2003-2005. His current research is the study for effective bio-markers of sublingual immunotherapy (SLIT) for Japanese cedar pollen allergy . Further, the molecular mechanisms of mucosal tolerance still remain unclear. I want to elucidate this immune mechanism and develop drugs for some mucosal diseases in the future.

Allergy and Immunology

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

Staff

Researchers
Mayumi SAEKI
Masanobu WATANABE
Tomoe NISHIMURA

Research Assistants
Noriko KITAMURA

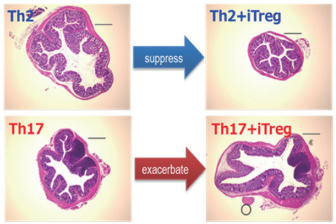
Students
Eriko ANDO
Kohei FUSANO
Satoshi UNO

Research Summary

Recent Topics of Mucosal Immunology

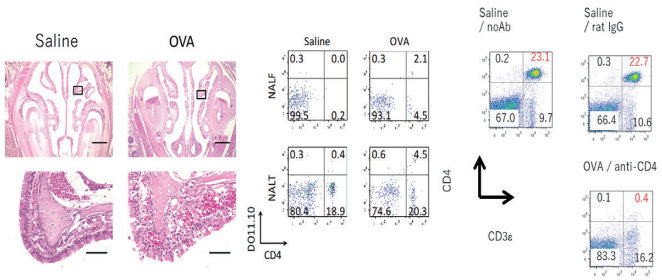
1. Antigen-specific iTreg cells stimulate Th17-mediated colon inflammation

$CD4^+$ 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.



2. Essential Contribution of $CD4^+$ T Cells to Antigen-Induced Nasal

Hyperresponsiveness in Experimental Allergic Rhinitis.
Recently, we have reported that $CD4^+$ T cells play a crucial role in the pathogenesis of AR via induction of NHR, independent of IgE-, mast cell-, and eosinophil-mediated responses. (A) (B) Antigen-induced NHR in T cell-transferred mice. (C) Administration of an anti-CD4 mAb to immunized mice depleted peripheral $CD4^+$ T cells almost completely.



Selected Publications

Tachibana M, et al. (2020). "Ablation of IL-17A leads to severe colitis in IL-10-deficient mice: implications of myeloid-derived suppressor cells and NO production." ***Int Immunol.*** 32: 187-201.

Kitamura N, et al (2020). "Identification of novel interacting regions involving calcineurin and nuclear factor of activated T cells." ***FASEB J.*** 34: 3197-3208.

Takaiwa, F, et al. (2019). "Development of rice-seed-based oral allergy vaccines containing 2 hypoallergenic Japanese cedar pollen allergen derivatives for immunotherapy." ***J Agric Food Chem.*** 67: 13127-13138.

Kaminuma O, et al. (2018). "Downregulation of NFAT3 due to lack of T-box transcription factor TBX5 is crucial for cytokine expression in T cells." ***J Immunol.*** 200: 92-100.

Yokoyama S, et al. (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.