Annual Report of Institute of Brain Science

(Vol.1)

Institute of Brain Science

Nagoya City University Graduate School of Medical Sciences

(FY2019-2021)

Contents

Preface

I have been appointed as the Director of the Institute of Brain Science since April 2021. This institute was established in October 2019 under the leadership of Dr. Makoto Michikawa, former Dean of the Graduate School of Medical Sciences (the first Director). In addition to the Department of Glial Cell Biology, Neurotoxicology, and Developmental and Regenerative Neurobiology, which had been active since its predecessor, the Institute for Molecular Medicine, the Department of Neurocognitive Science and Neurodevelopmental Disorder Genetics have been newly established. In addition, an endowed laboratory in Cognitive Function and Pathology was established in 2021 with support from the City of Nagoya.

A year and a half have passed since the establishment of the Institute, and we have gradually built up a structure as a research institute engaged in basic neuroscience, especially in the elucidation of the pathology of brain diseases and the development of prevention and treatment. The number of researchers is gradually increasing, and we are receiving more competitive research grants and publishing more papers. We would like to promote the exchange of information and joint research within the institute by designing ways for researchers to interact with each other, which is often lacking in the COVID-19 related crisis. Furthermore, we need to further strengthen our research capabilities by collaborating not only with researchers on campus including those at our affiliated hospitals but also with other research institutions and companies in Japan and abroad.

In the Core Laboratory, which is located in the building of the Institute, the latest imaging equipment as well as equipment for analyzing cognitive and motor functions of mice will be installed as shared equipment of the university. The Biobank, scheduled to open in FY2021, will be able to store biological samples such as blood along with medical information and utilize them for medical research. These facilities are expected to be used not only for neuroscience, but also for a variety of medical and life science research at Nagoya City University, as well as for collaborative research with researchers outside the university.

We aim to promote basic research in neuroscience and to translate the results into clinical applications. We also hope to provide education and research guidance in neuroscience to young scientists, and to foster internationally active neuroscientists.

We will make a concerted effort to provide a place where researchers can enjoy their research, demonstrate their abilities, and grow, and to contribute to the development of neuroscience.

We sincerely appreciate your cooperation and support for the development of the Institute of Brain Science.

Ⅰ. Philosophy and our goals

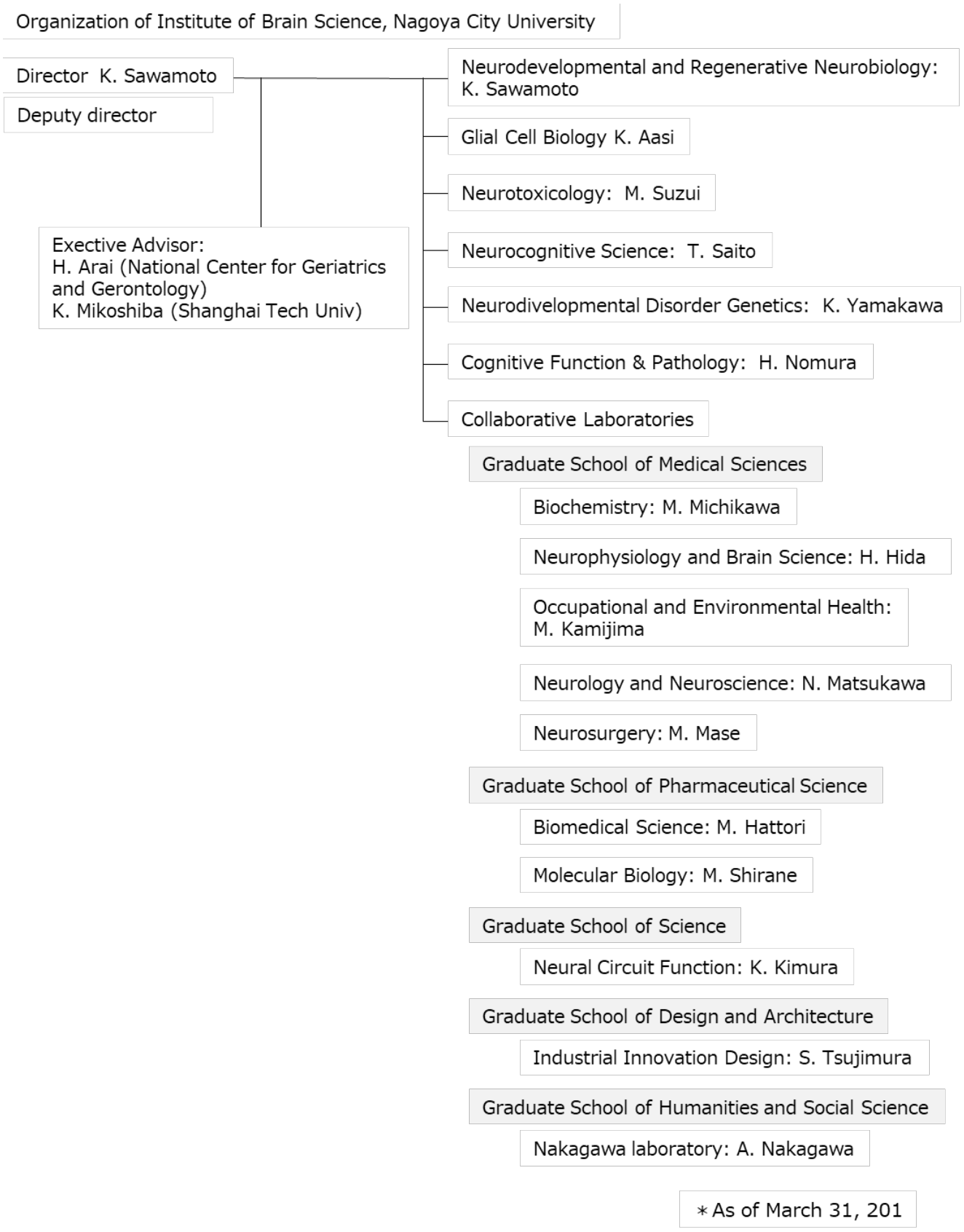
The Institute of Brain Science was established in October 2019 to promote basic research in the field of neuroscience. In addition to elucidating the developmental mechanisms and functions of neurons and neural circuits, we are working on elucidating the pathology and etiology of various neurological diseases, studying diagnostic and preventive methods, and developing therapeutic methods such as drug discovery and regenerative medicine. Through multidisciplinary and high-level neuroscience research at the molecular, cellular, and individual levels, we aim to overcome aging brain diseases such as dementia and stroke, which are increasing in our super-aging society, as well as neurodevelopmental and psychiatric disorders, which are of great social concern.

【Research】 We provide high-level education and research guidance in neuroscience to young scientists including graduate and undergraduate students and train internationally active neuroscientists.

【Education】 We provide high-level education and research guidance in neuroscience to young scientists including graduate and undergraduate students and train internationally active neuroscientists.

【Social contribution】 We make social contributions by promoting translational research and industry-academic collaboration with internal and external research institutions and hospitals to link the results of basic research to clinical and practical application.

II. Organization



＊As of March 31, 201

III. Research Activities from laboratories

Department of Developmental and Regenerative Neurobiology
Since Establishment (October 2019) to FY2021

1. Laboratory members

Full-time Staff

Kazunobu Sawamoto (Professor)
Naoko Kaneko (Associate Professor)
Masato Sawada (Associate Professor)
Chikako Nakajima (Assistant Professor)
Kazuya Kuboyama (Assistant Professor)
Shoko Takemura (Assistant Professor)
Rie Kakei (Technical Manager)

Part-time Staff

Mami Matsumoto (Researcher)
Koya Kawase (Researcher)
Takashi Ogino (Researcher)
Sayuri Nakamura (Research Assistant)
Maiko Tanaka (Research Assistant)
Chisato Suzuki (Secretary/Technical Staff)

Graduate School Students

Yuya Ohno (PhD Course)
Yasuhisa Nakamura (PhD Course)
Takukya Miyamoto (PhD Course)
Daijiro Kojima (PhD Course)
Erika Umeda (Master's Course)
Miho Furuta (Master's Course)
Tamami Nonomura (Master's Course)
Sakura Gokenya (MD-PhD Course)
Yuri Ishido (MD-PhD Course)
Yuma Takagi (MD-PhD Course)
Jiro Nagase (MD-PhD Course)
Ayato Hamaguchi (MD-PhD Course)
Chihiro Kurematsu (MD-PhD Course)
Satoaki Yamamoto (MD-PhD Course)
Norihiko Nakashima (School of Biology and Integrated Sciences)
Akari Saito (Faculty of Pharmaceutical Sciences)
Takehiro Ando (MD-PhD Course)
Yukina Sakakibara (MD-PhD Course)

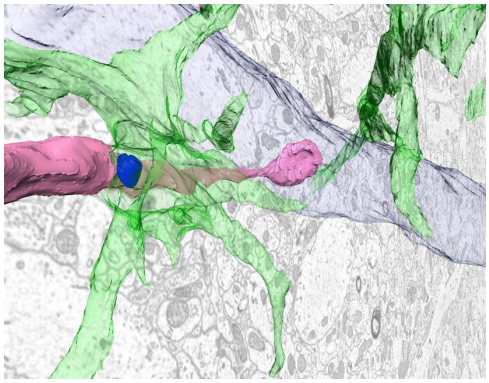
Riko Sinmoto (MD-PhD Course)

Naoya Kawamura (MD-PhD Course)

Hitomi Hujiyama (School of Biology and Integrated Sciences)

2. Research to date

New neurons are continuously generated throughout life, not only at the embryonic and neonatal stages. Recent studies using experimental animals indicate that several regions of the adult brain have the capacity to regenerate injured neural tissues. We have been studying the mechanisms for cell migration and regeneration in the postnatal brain. We aim to study the endogenous repair mechanisms in the brain and develop a new strategy to promote neuronal and glial cell regeneration after injury. Recently, we have reported our findings regarding the primary cilium of newly born neurons migrating in the postnatal brain (Matsumoto et al., J Neurosci 2019), neurogenesis in the neonatal brain of common marmosets (Akter et al., Cerebral Cortex 2020), effects of interferon-alpha treatment on neurogenesis and behavior in common marmoset (Kaneko et al., Mol Brain 2020), and the role of phosphatidylserine in synaptic pruning of newborn neurons by microglia (J Exp Med 2022). During this period, we have initiated and are continuing new projects on the adaptation and repair mechanisms of injured brain by neuronal migration (AMED-CREST) and neurogenesis in the neonatal brain and its pathogenesis (KAKENHI Grant-in-Aid for Scientific Research (S)).



Three-dimensional reconstruction of electron microscopic images showing a synaptic spine (blue) of a new neuron (pink), which forms a synapse with another neuron (light blue), engulfed by microglia (green) in the adult mouse olfactory bulb (Kurematsu et al., J Exp Med 2022).

3. Publications (original articles) (11 in total)

1. Kurematsu C, Sawada M, Ohmuraya M, Tanaka M, Kuboyama K, Ogino T, Matsumoto M, Oishi H, Inada H, Ishido Y, Sakakibara Y, Nguyen HB, Thai TQ, Kohsaka Sh, Ohno N, Yamada MK, Asai M, Sokabe M, Nabekura J, Asano K, Tanaka M, Sawamoto K: Synaptic pruning of murine adult-born neurons by microglia depends on phosphatidylserine. ***J Exp Med*** 219 (4): e20202304 (2022)
2. Yaguchi A, Oshikawa M, Watanabe G, Hiramatsu H, Uchida N, Hara C, Kaneko N, Sawamoto K, Muraoka T, Ajioka I: Efficient protein incorporation and release by a jigsaw-shaped self-assembling peptide hydrogel for injured brain regeneration. ***Nat Commun*** 12: 6623 (2021)
3. Ota Y, Kubota Y, Hotta Y, Matsumoto M, Matsuyama N, Kato T, Hamakawa T, Kataoka T, Kimura K, Sawamoto K, Yasui T: Change in the central control of the bladder function of rats with focal cerebral infarction induced by photochemically-induced thrombosis. ***PLoS***

ONE 16(11): e0255200 (2021)

4. Okada M, Kawagoe Y, Sato Y, Nozumi M, Ishikawa Y, Tamada A, Yamazaki H, Sekino Y, Kanemura Y, Shinmyo Y, Kawasaki H, Kaneko N, Sawamoto K, Fujii Y, Igarashi M: Phosphorylation of GAP-43 T172 is a molecular marker of growing axons in a wide range of mammals including primates. ***Mol Brain*** 14(1):66 (2021)
5. Ito N, Riyadh MA, Ahmad SAI, Hattori S, Kanemura Y, Kiyonari H, Abe T, Furuta Y, Shinmyo Y, Kaneko N, Hirota Y, Lupo G, Hatakeyama J, Abdulhaleem MFA, Anam MB, Yamaguchi M, Takeo T, Takebayashi H, Takebayashi M, Oike Y, Nakagata N, Shimamura K, Holtzman MJ, Takahashi Y, Guillemot F, Miyakawa T, Sawamoto K, Ohta K: Dysfunction of the proteoglycan Tsukushi causes hydrocephalus through altered neurogenesis in the subventricular zone in mice. ***Sci Transl Med*** 13; eaay7896 (2021)
6. Koyanagi I, Sonomura K, Naoi T, Ohnishi T, Kaneko N, Sawamoto K, Sato T, Sakaguchi M: Metabolic fingerprints of fear memory consolidation during sleep. ***Mol Brain*** 14(1): 30 (2021)
7. Sawada M, Matsumoto M, Narita K, Kumamoto N, Ugawa S, Takeda S, Sawamoto K: In vitro Time-lapse Imaging of Primary Cilium in Migrating Neuroblasts. ***Bio-protocol*** 10(22): e3823 (2020)
8. Kumar D, Koyanagi I, Carrier-Ruiz A, Vergara P, Srinivasan S, Sugaya Y, Kasuya M, Yu T, Vogt KE, Muratani M, Ohnishi T, Singh S, Teixeira CM, Che´ rasse Y, Naoi T, Wang S, Nondhalee P, Osman BAH, Kaneko N, Sawamoto K, Kernie SG, Sakurai T, McHugh TJ, Kano M, Yanagisawa M, Sakaguchi M: Sparse Activity of Hippocampal Adult-Born Neurons during REM Sleep Is Necessary for Memory Consolidation. ***Neuron*** 107(3):552-565.e10. (2020)
9. Kaneko N, Nakamura S, Sawamoto K: Effects of interferon-alpha on hippocampal neurogenesis and behavior in common marmosets. ***Mol Brain*** 13: 98 (2020)
10. Akter M, Kaneko N, Herranz-Pérez V, Nakamura S, Oishi H, García-Verdugo JM, and Sawamoto K: Dynamic Changes in the Neurogenic Potential in the Ventricular–Subventricular Zone of Common Marmoset during Postnatal Brain Development. ***Cerebral Cortex*** 30(7):4092-4109 (2020)
11. Matsumoto M, Sawada M, García-González D, Herranz-Pérez V, Ogino T, Nguyen HB, Thai TQ, Narita K, Kumamoto N, Ugawa S, Saito Y, Takeda S, Kaneko N, Khodosevich K, Monyer H, García-Verdugo JM, Ohno N, Sawamoto K: Dynamic changes in ultrastructure of the primary cilium in migrating neuroblasts in the postnatal brain. ***J Neurosci*** 39 (50) 9967-9988 (2019)

4. Review Articles and Books (4 in total)

1. Nakajima C, Sawada M, Sawamoto K: Postnatal neuronal migration in health and disease. ***Curr Opin Neurobiol*** 66: 1-9 (2021)
2. Akter M, Kaneko N, Sawamoto K: Neurogenesis and neuronal migration in the postnatal ventricular-subventricular zone:similarities and dissimilarities between rodents and primates. ***Neuroscience Research*** 15;S0168-0102(20)30379-5 (2020)
3. Sawada M, Sawamoto K: Neuronal migration in the postnatal brain. In: Rubenstein J et al (eds.) ***Comprehensive Developmental Neuroscience: Cellular migration and formation of axons and dendrites.*** (Second edition) Academic Press. (2020)
4. Meunier A, Sawamoto K, Spassky N: Ependyma. In: Rubenstein J, Rakic P (eds.) ***Comprehensive Developmental Neuroscience: Patterning and Cell Type Specification in the Developing CNS and PNS.*** (Second edition) Elsevier. (2020)

5. Organizing academic meetings, symposiums, etc. (1 in total)

1. Imamura T & Sawamoto K: Symposium "Understanding environmental responses of neural cells towards development of brain disorder development" **The 43th Annual metting of the Japan Neuroscience Society** July/2020, Organizer and Chairman

6. Invited lectures at International Conferences, etc.（3 in total）

1. Sawamoto K: Postnatal neuronal migration in health and disease. **The International Symposium on Development and Plasticity of Neural Systems.** March/2022
2. Sawamoto K: Postnatal neuronal migration in health and disease. **Joint symposium of McGill University – National Institute of Physiological Sciences "Recent Adcances in Neuroscience"** February/2022
3. Sawamoto K: Neuronal migration for development, maintenance and repair of the postnatal brain. **"New Frontier in Neuroscience 2020"** January/2020

7. Invited lectures at Domestic Conferrences, etc. (1 in total)

1. Sawamoto K: Invited Lecture "Neuronal migration: strategies for development, maintenance and repair of the postnatal brain" **Cell Biology, Developmental Biology, and Systems Biology Course Meeting,** December/ 2019

8. Presentaion at International Conferences, etc. (7 in total)

1. Kaneko N, Akter M, Herranz-Perez V, Oishi H, Garcia-Verdugo JM, Sawamoto K: Neurogenic potential in common marmoset ventricular-subventricular zone during postnatal brain development. **ISSCR TOKYO JAPAN**, October/2021, Poster
2. Matsumoto M, Sawada M, Garcia-Gonzalez D, Herranz-Perez V, Ogino T, Nguyen HB, Thai TQ, Narita K, Kumamoto N, Ugawa S, Saito Y, Takeda S, Kaneko N, Khodosevich K, Monyer H, Garcia-Verdugo JM, Ohno N, Sawamoto K: Dynamic Changes in Ultrastructure of the Primary Cilium in Migrating Neuroblasts in the Adult Brain. **ISSCR TOKYO JAPAN**, October/2021, Poster
3. Sawamoto K, Matsumoto M, Sawada M: Dynamic changes in ultrastructure of migrating neuroblasts in the postnatal brain. **AMED-CREST International Symposium**, January/2020, Poster
4. Kaneko N, Sawamoto K: Positioning of new neurons for efficient brain repair. **AMED-CREST International Symposium**, January/2020, Poster
5. Sawada M, Sawamoto K: PlexinD1 signaling controls morphological changes and migration termination in new neurons. **AMED-CREST International Symposium**, January/2020, Poster
6. Kaneko N, Herranz-Perez V, Otsuka T, Sano H, Ohno N, Omata T, Bang Nguyen H, Quynh Thai T, Nambu A, Kawaguchi Y, Garcia-Verdugo JM, Sawamoto K: New neurons migrate through the glial meshwork using slit1 to approach the lesion for functional recovery. **Soceity for Neuroscience Annual Meeting 2019**, October/2019, Poster
7. Fujikake K, Sawada M, Hikita T, Seto Y, Kaneko N, Herranz-Perez V, Dohi N, Homma NY., Osaga S, Yanagawa Y, Akaike T, García-Verdugo JM, Hattori M, Sobue K, Sawamoto K: Fyn controls detachment of chain-forming neuroblasts by regulating cell cell adhesion in the postnatal brain. **Soceity for Neuroscience Annual Meeting 2019**, October/2019, Poster

9. Presentations at Domestic Conferences, etc. (1 in total)

1. Sawada M, Sawamoto K: Role of microglial phagocytosis of dead cells in adult neurogenesis. **The 64th Annual Meeting of the Japanese Society for Neurochemistry**, September/2021, Oral

10. Other activities (0 in total)

11. Press Release and Media Coverage (6 in total)

1. “Discovery of an 'Eat-Me' signal discovered in synaptic pruning and maturation of new neurons in the adult brain” Medical Xpress（March 22, 2022）
2. “Discovery of an 'Eat-Me' signal discovered in synaptic pruning and maturation of new neurons in the adult brain“ Mirage News（March 22, 2022）
3. “Synaptic pruning and new neuron maturation in the adult brain“ Genetic Engineering & Biotechnology News（March 18, 2022）
4. “Discovery of an 'Eat-Me' signal discovered in synaptic pruning and maturation of new neurons in the adult brain“ UK Today News（March 17, 2022）
5. “'Eat-Me' signal discovered in synaptic pruning and maturation of new neurons in the adult brain“ SciTechDaily（March 17, 2022）
6. “Discovery of an 'Eat-Me' signal involved in synaptic pruning and maturation of new neurons in the adult brain“ EurekAlert!（March 17, 2022）

12. Patent (2 in total)

1. Composition containing self-assembling peptide
   Ajioka I, Oshikawa M, Muraoka T, Sawamoto K, Kaneko N
   Kanagawa Institute of Industrial Science and Technology
   PCT/JP2021/010595
   March 16, 2021

2. Brain disease therapeutic agent and use thereof
   Sawamoto K, Sawada M, Igarashi M, Nakajima C
   Nagoya City University
   PCT/JP2020/47678
   December 21, 2020

Department of Glial Cell Biology
Since Establishment (October 2019) to FY2021

1. Laboratory members

Full-time Staff

Kiyofumi Asai (Professor)
Yohei Kawaguchi (Assistant Professor)
Seiko Ukai (Technical Manager)

2. Research to date

・Astrocyte-Neuron interactions in expression of neural function
・Molecular mechanisms of astrocyte
・The effects of neuro-protective and neuro-regenerative factors derived from glial cell
・The pathophysiology of rheumatoid arthritis

3. Publications (original articles) (10 in total)

1. Miwa S, Okamoto H, Yamada S, Kawaguchi Y, Endo K, Aiba H, Hayashi K, Kimura H, Sekiya I, Otsuka T, Tsuchiya H.
   Distribution of Solitary and Multiple Enchondromas of the Hand.
   In Vivo (2019) Nov-Dec;33(6):2235-2240.
2. Kawaguchi Y, Okamoto H, Endo K, Iwata H, Joyo Y, Nozaki M, Tamechika S, Waguri-Nagaya Y, Murakami H.
   Pyogenic tenosynovitis of the wrist due to Corynebacterium striatum in a patient with dermatomyositis: A case report.
   Medicine (Baltimore) (2020) Jan;99(3):e18761.
3. Yamamura H, Suzuki Y, Asai K, Imaizumi Y, Yamamura H.
   Oxidative stress facilitates cell death by inhibiting Orai1-mediated Ca2+ entry in brain capillary endothelial cells.
   Biochem Biophys Res Commun (2020) Feb 26;523(1):153-158.
4. Yasuma S, Nozaki M, Murase A, Kobayashi M, Kawanishi Y, Fukushima H, Takenaga T, Yoshida M, Kuroyanagi G, Kawaguchi Y, Nagaya Y, Murakami H.
   Anterolateral ligament reconstruction as an augmented procedure for double-bundle anterior cruciate ligament reconstruction restores rotational stability: Quantitative evaluation of the pivot shift test using an inertial sensor
   Knee 2020 Mar;27(2):397-405.
5. Suzuki T, Yasumoto M, Suzuki Y, Asai K, Imaizumi Y, Yamamura H.
   TMEM16A Ca^{2+}-Activated Cl^- Channel Regulates the Proliferation and Migration of Brain Capillary Endothelial Cells
   Mol Pharmacol 2020 Jul;98(1):61-71.
6. Kawanishi Y, Nozaki M, Kobayashi M, Yasuma S, Fukushima H, Murase A, Takenaga T, Yoshida M, Kuroyanagi G, Kawaguchi Y, Nagaya Y, Murakami H.
   Preoperative Knee Instability Affects Residual Instability as Evaluated by Quantitative Pivot-Shift Measurements During Double-Bundle ACL Reconstruction
   Orthop J Sports Med (2020) Oct 19;8(10):2325967120959020.
7. Oguri Y, Kawaguchi Y, Tatematsu N, Joyo Y, Mizuguchi K, Yonezu H, Okamoto H, Nozaki M, Kobayashi M, Kuroyanagi G, Aiba H, Asai K, Inoue K, Murakami H, Waguri-Nagaya Y.
   N-acetyl-seryl-aspartyl-lysyl-proline:
   A new potential serum biomarker of rheumatoid arthritis
   Medical Mass Spectrometry (2021) Vol. 5 No. 1
8. Mizuguchi K, Aoki H, Aoyama M, Kawaguchi Y, Waguri-Nagaya Y, Ohte N, Asai K .
   Three-dimensional spheroid culture induces apical-basal polarity and the original characteristics of immortalized human renal

proximal tubule epithelial cells
Exp Cell Res (2021) Jul 1;404(1):112630.

9. Kojima M, Kojima T, Waguri-Nagaya Y, Takahashi N, Asai S, Sobue Y, Nishiume T, Suzuki M, Mitsui H, Kawaguchi Y, Kuroyanagi G, Yasuoka M, Watanabe M, Suzuki S, Arai H.
   Depression, physical function, and disease activity associated with frailty in patients with rheumatoid arthritis
   Mod Rheumatol (2021) Sep;31(5):979-986.
10. Yagi K, Goto Y, Kato K, Suzuki N, Kondo A, Waseda Y, Mizutani J, Kawaguchi Y, Joyo Y, Waguri-Nagaya Y, Murakami H.
    p38 Mitogen-Activated Protein Kinase Is Involved in Interleukin-6 Secretion from Human Ligamentum Flavum-Derived Cells Stimulated by Tumor Necrosis Factor-α
    Asian Spine J 2021 Dec;15(6):713-720.

4. Review Articles and Books (4 in total)

1. Iwata H, Okamoto H, Kawaguchi Y, Endo K, Joyo Y, Aiba H, Murakami S, Murakami H.
   Insidious Onset Compartment Syndrome of the Forearm in a Teenager: A
   Case Report and Review of the Literature
   J Hand Surg Asian Pac Vol 2021 Sep;26(3):481-484.

5. Organizing academic meetings, symposiums, etc.(0 in total)

6. Invited lectures at International Conferences, etc.（0 in total）

7. Presentaion at International Conferences, etc. (2 in total)

1. Joyo Y, Kawaguchi Y, Oguri Y, Nozaki M, Asai K, Waguri-Nagaya Y.
   The JAK inhibitor (baricitinib) inhibits IFN-γ-induced gliostatin expression in human fibroblast-like synoviocytes.
   Annual European Congress of Rheumatology EULAR 2019, July/2019
2. Kawaguchi Y, Oguri Y, Nozaki M, Asai K, Waguri-Nagaya Y.
   Novel anti-angiogenic effects of tofacitinib in fibroblast-likes synoviocytes derived from patients with RA.
   Annual European Congress of Rheumatology EULAR 2019, July/2019

Department of Neurotoxicology
Since Establishment (October 2019) to FY2021

1. Laboratory members

Full-time Staff
Masumi Suzui (Professor)
Katsumi Fukamachi (Associate Professor)
Hideaki Kurachi (Technical Staff)

Part-time Staff
Atsuko Kazama (Part-time Staff)

Graduate School Students
Nahida Sultana (PhD Degree Program)

2. Research to date

While chemicals provide many benefits, many chemicals have adverse effects in some cases. Toxicology plays an important role in risk assessment of chemicals for carcinogenicity, neurotoxicity, reproductive toxicity, developmental toxicity, genetic toxicity, immunotoxicity and general toxicity. The risk assessment can help prevent health hazards and it is also utilized for risk management. In our laboratory, we are developing the method of risk assessment for new substances such as nanomaterials, which have different properties from general chemicals. In addition, we are generating new low-toxic anti-cancer drugs, which are derivatives consisting of components from natural products, using *in vitro*, *in vivo* and *in silico* analyses. We are trying to identify active components from natural products, such as plant extracts with anticancer activity (1-3). In particular, we are developing a novel anticancer compound that was originate from natural fatty acid as a lead compound derived from natural product. *In silico* docking analysis indicated that the anticancer agent we invented binds to the SH2 domain of the transcription factor STAT3. Our agent markedly inhibited the transcriptional activity of STAT3 in colon cancer cells. In animal model systems, it inhibited the growth of implanted colon cancer cells, and also induced a significant decrease in the multiplicity of precancerous lesions in the colon. It is therefore suggested that the inhibition of STAT3 by our agent affects the function of molecules that are related to the cell cycle, apoptosis, and angiogenesis, and eventually contributing to the growth inhibitory effect on tumor (2). In other studies, we established genetically engineered animal models of pancreatic cancer that can develop neoplastic lesions in a short period. The such lesions in our animal model exhibit morphological similarities to those observed in humans as nonivasive precursor lesions including pancreatic intraepithelial neoplasia (PanIN). Therefore, this model system is suitable for screening of potential biomarkers human pancreatic cancer. We are developing serodiagnostic markers using this animal model (4). In coming fiscal year (April 2022), Assistant Professor Tomoya Ozaki will join our research group and work on the discivery of therapeutic agents for the spinal injury focusing on the morphological changes of axons.

3. Publications (original articles) (4 in total)

1. Matsumoto H, Ando S, Yoshimoto E, Numano T, Sultana N, Fukamachi K, Iinuma M, Okuda K, Kimura K, *Suzui M. Extracts of Musa basjoo induce growth inhibition and changes in the protein expression of cell cycle control molecules in human colorectal cancer cell lines. Oncol Lett. 2022;23(3):99.

2. Ando S, Fukamachi K, Yoshimoto E, Matsumoto H, Iinuma M, *Suzui M. Palmitoyl piperidinopiperidine, a novel derivative of 10 hydroxy 2 decenoic acid, as a potent and selective anticancer agent against human colon carcinoma cell lines. Int J Oncol. 2021; 58(2): 251-265.

3. Ichimaru Y, Kanaeda N, Tominaga S, Suzui M, Maeda T, Fujii H, *Nakao M, *Yoshioka H. Sasa veitchii extract induces anticancer effects via inhibition of cyclin D1 expression in MCF-7 cells. Nagoya J Med Sci. 2020; 82(3): 509-518.

4. *Fukamachi K, Hagiwara Y, Futakuchi M, Alexander DB, Tsuda H, Suzui M. Evaluation of a biomarker for the diagnosis of pancreas cancer using an animal model. J Toxicol Pathol. 2019; 32(3): 135-141.

4. Review Articles and Books (0 in total)

5. Organizing academic meetings, symposiums, etc. (0 in total)

6. Invited lectures at International Conferences, etc.（0 in total）

7. Invited lectures at Domestic Conferrences, etc. (0 in total)

8. Presentaion at International Conferences, etc. (3 in total)

1. Matsumoto H, Sultana N, Fukamachi K, Suzui M. The dried leaf extract of Musa basjoo induces growth inhibition and changes in protein expression level of cell cycle control molecules in human colon carcinoma cell lines. **The 1st Meeting of the Asian Union of Toxicologic Pathology**, January/2022, Poster

2. Sultana N, Matsumoto H, Fukamachi K, Suzui M. Palmitoyl piperidineopiperidine induces selective anticancer activity against human coloncarcinoma cell lines. **The 1st Meeting of the Asian Union of Toxicologic Pathology**, January/2022, Poster

3. Fukamachi K, Sultana N, Matsumoto H, Tsuda H, Suzui M. LRG-1 is a promising blood marker for pancreas cancer. **The 1st Meeting of the Asian Union of Toxicologic Pathology**, January/2022, Poster

9. Presentations at Domestic Conferences, etc. (10 in total)

1. Matsumoto H, Sultana N, Fukamachi K, Suzui M. The dried leaf extract of Musa basjoo induces growth inhibition and changes in protein expression level of cell cycle control molecules in human colon carcinoma cell lines. **The 38th Annual Meeting of the Japanese Society of Toxicologic Pathology,** January/2022, Poster

2. Sultana N, Matsumoto H, Fukamachi K, Suzui M. Palmitoyl piperidineopiperidine induces selective anticancer activity against human coloncarcinoma cell lines. **The 38th Annual Meeting of the Japanese Society of Toxicologic Pathology,** January/2022, Poster

3. Fukamachi K, Sultana N, Matsumoto H, Tsuda H, Suzui M. LRG-1 is a promising blood marker for pancreas cancer. **The 38th Annual Meeting of the Japanese Society of Toxicologic Pathology,** January/2022, Poster

4. Ando S, Yoshimoto E, Matsumoto H, Fukamachi K, Suzui M. Effect and mechanism of action of new anticancer agents. **The 36th Annual Meeting of the Japanese Society of Toxicologic Pathology,** February/2020, Poster

5. Ando S, Fukamachi K, Yoshimoto E, Matsumoto H, Suzui M. Development of novel anticancer agents derived from natural fatty acids. **FY2019「Advanced Animal Model Support」Outcome Presentation,** February/2020, Poster

6. Ando S, Fukamachi K, Suzui M. Discovery of novel STAT3 inhibitors as an anticancer agent. **The 78th Annual Meeting of the Japanese Cancer Association,** September/2019, Poster

7. Ando S, Yoshimoto E, Matsumoto H, Fukamachi K, Suzui M. Discovery of novel STAT3 inhibitors derived from natural fatty acids. **The 34th Research Conference of Carcinogenic Pathology,** August/2019, Oral

8. Ando S, Yoshimoto E, Matsumoto H, Fukamachi K, Suzui M. Development of novel STAT3 inhibitors derived from natural fatty acids. **The 26th Annual meeting of Japanse Association for Cancer Prevention,** June/2018, Poster

9. Ando S, Yoshimoto E, Matsumoto H, Fukamachi K, Suzui M. Cytotoxicity and mechanism of action of a novel STAT3 inhibitor derived from natural fatty acid. **The 46th Annual Meeting of the Japanese Society of Toxicology,** June/2019, Poster

10. Tominaga S, Kanaeda N, Ichimaru Y, Suzui M, Maeda T, Nakao M, Fujii H, Yoshioka H. Anticancer effect of Sasa veitchii extract toward MCF-7 human breast cancer cell lines. **The 46th Annual Meeting of the Japanese Society of Toxicology,** June/2019, Poster

10. Other activities (0 in total)

11. Press Release and Media Coverage (0 in total)

12. Patent (1 in total)

1. Suzui M, Iinuma M, Morita A. Anticancer agents. Japan Patent No. 6532730, 2019.

Department of Neurocognitive Science
Since Establishment (October 2019) to FY2021

1. Laboratory members

Full-time Staff

Takashi Saito (Professor)
Kaori Asamitsu (Associate Professor)
Masanori Hijioka (Assistant Professor)
Tatsuya Manabe (Assistant Professor)
Natsuki Dohi (Technical Manager)

Part-time Staff

Keiko Mutsuura (Secretary/Technical Staff)
Manami Tomita (Technical Staff)
Ikuma Nagura (Technical Stuff/Student Staff)
Hana Tokuda (Technical Stuff/Student Staff)
Yui Funahashi (Technical Stuff/Student Staff)

Graduate School Students

Ryohei Uenishi (Master's Course)

2. Research to date

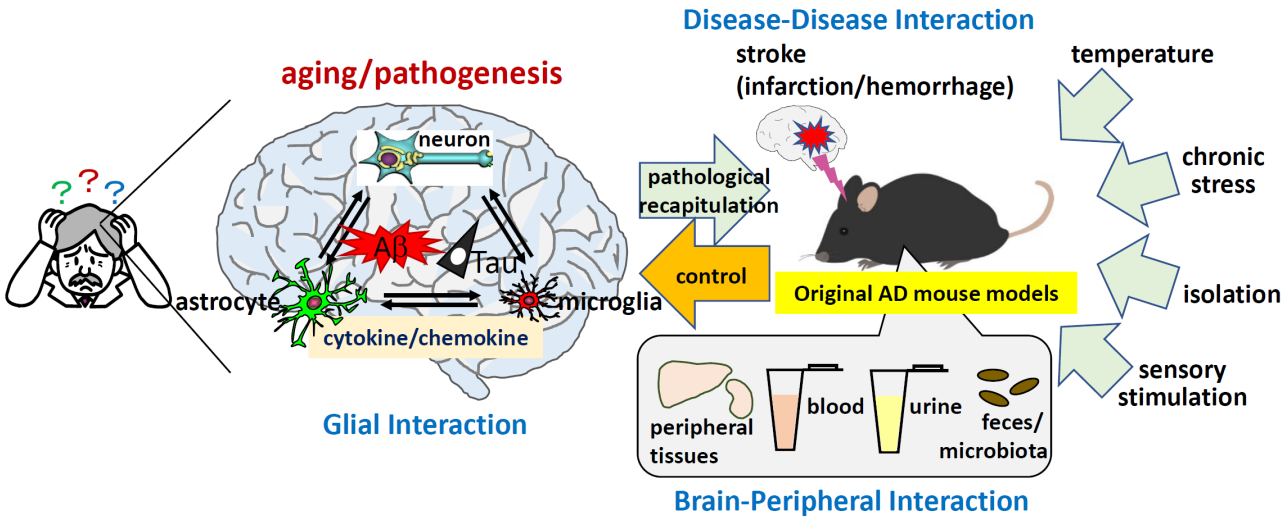
The main theme of our laboratory is to elucidate the molecular and cellular mechanisms underlying the pathogenesis of dementia, especially Alzheimer's disease (AD), which is the most common form of dementia and one of the most desired diseases to overcome in an aging society with declining birthrates, since there is still no fundamental treatment or prevention for AD. Since its opening in October 2019, we have been conducting research focusing on "Three Interactions": glial cells interaction, brain-peripheral interaction, and disease-disease interaction.

Regarding the glial interaction for pathomechanisms, we are investigating to identify glial cells that contribute specifically to pathology and pathophysiology related to neurodegenerative diseases as well as AD, and to elucidate their functions In particular, we are conducting biochemical, molecular biological, behavioral, and pathological/immunohistochemical analyses using our AD mouse model as a research resource.

Regarding the brain-periphery interaction, we regard brain diseases as one of the systemic diseases and have started research focusing on the relationship between the brain and body temperature, external stress, intestinal microflora and so on. Since FY2021, we have been a member of the team promoting the JST Moon Shot Type R&D Project Objective 2 "Toward Overcoming Dementia-Related Diseases Based on a Multi-Organ Network Analysis," and are currently conducting research toward the realization of a society that can predict and prevent diseases at a very early stage by 2050.

In the area of disease-disease ineteraction, we are analyzing the pathological interaction between dementia and stroke (cerebral infarction and intracerebral hemorrhage). Since FY2020, we have been conducting research as a member of the research team (Representative: Dr. Takashi Shichita, Team Leader of Tokyo Metropolitan Institute of Medical Science) in the area of "Understanding of Pathophysiological Processes and Discovery of Medical Technology Seeds through Spatiotemporal Research of Tissue Adaptation and Repair Mechanisms," an advanced

research & development programs for medical innovation, AMED-CREST. We are also conducting many domestic and international collaborative studies using our AD model mice.



From the development of mouse models that fully recapitulate pathological process to the control of pathological conditions from the insight of "three interactions".

3. Publications (original articles) (70 in total)

1. Palomer E, Martin-Flores N, Jolly S, Pascual-Vargas P, Benvegnù S, Podpolny M, Teo S, Vaher K, Saito T, Saido T, Whiting P, *Salinas P: Epigenetic repression of Wnt receptors in AD: a role for Sirtuin2-induced H4K16ac deacetylation of Frizzled1 and Frizzled7 promoters. ***Mol Psychiatry*** (in press)
2. Marino M, Zhou L, Rincon MY, Callaerts-Vegh Z, Verhaert J, Wahis J, Creemers E, Yshii L, Wierda K, Saito T, Marneffe C, Voytyuk I, Wouters Y, Dewilde M, Duqué SI, Vincke C, Levites Y, Golde TE, Saido TC, Muyldermans S, Liston A, Strooper BD, *Holt MG: AAV-mediated delivery of an anti-BACE1 VHH alleviates pathology in an Alzheimer's disease model. ***EMBO Mol Med*** (in press)
3. Kaneshiro N, Komai M, Imaoka R, Ikeda A, Kamikubo Y, Saito T, Saido TC, Tomita T, Hashimoto T, Iwatsubo T, Sakurai T, Uehara T, *Takasugi N: Lipid flippase dysfunction as a therapeutic target for endosomal anomalies in Alzheimer's disease. ***iScience*** (in press)
4. *Kamei N, Hashimoto A, Tanaka E, Murata K, Yamaguchi M, Yokoyama N, Kato M, Oki K, Saito T, Saido TC, Takeda-Morishita M: Therapeutic effects of anti-amyloid β antibody after intravenous injection and efficient nose-to-brain delivery in Alzheimer's disease mouse model. ***Drug Deliv Transl Res*** (in press)
5. Hao X, Li Z, Li W, Katz J, Michalek S, Barnum SR, Pozzo-Miller L, Saito T, Saido T, Wang Q, Roberson ED, *Zhang P: Periodontal infection aggravates C1q-mediated microglial activation and synapse pruning in Alzheimer's mice. ***Frontiers in Immunology*** (in press)
6. Watamura N, Kakiya N, Nilsson P, Tsubuki S, Kamano N, Takahashi M, Hashimoto S, Sasaguri H, Saito T, *Saido TC: Somatostatin-evoked Aβ catabolism in the brain: Mechanistic involvement of α-endosulfine-K_{ATP} channel pathway. ***Mol Psychiatry*** (in press)
7. Mizuno Y, Abolhassani N, Mazzei G, Saito T, Saido TC, Yamasaki R, Kira J, *Nakabeppu Y: Deficiency of MTH1 and/or OGG1 increases the accumulation of 8-oxoguanine in the brain of the $App^{NL-GF-/NL-G-F}$ knock-in mouse model of Alzheimer's disease, accompanied by accelerated microgliosis and reduced anxiety-like behavior. ***Neurosci Res*** (in press)
8. Hijioka M, Ikemoto Y, Fukao K, Inoue T, Kobayakawa T, Nishimura K, Takata K, Agata K, *Kitamura Y: MEK/ERK signaling regulates reconstitution of the dopaminergic nerve circuit in the planarian *Dugesia japonica*. ***Neurochem Res*** (in press)
9. de Jesus MSM, Macabeo APG, Ramos JDA, de Leon VNO, Asamitsu K, *Okamoto T: Voacanga globosa spirobisindole alkaloids exert antiviral activity in HIV latently infected cell lines by targeting the NF-kB cascade: in vitro and in silico investigations. ***Molecules*** 2022; 27(3): 1078
10. de Paz-Silava SLM, Victoriano-Belvis AFB, Gloriani NG, Hibi Y, Asamitsu K, Okamoto T: In Vitro Antiviral Activity of Mentha cordifolia Plant Extract in HIV-1 Latently Infected Cells Using an Established Human Cell Line. ***AIDS Res Hum Retroviruses*** 2022; 38(1): 64-72
11. Futokoro R, *Hijioka M, Arata M, Kitamura Y: Lipoxin A_4 receptor stimulation attenuates neuroinflammation in a mouse model of intracerebral hemorrhage. ***Brain Sciences*** 2022; 12(2): 162
12. McKee CA, Lee J, Cai Y, Saito T, Saido T, *Musiek ES: Astrocyte deficient in circadian clock gene Bmal1 show enhanced activation responses to amyloid-beta pathology without changing plaque burden. ***Sci Rep*** 2022; 12: 1796
13. Meier SR, Sehlin D, Roshanbin S, Lim Falk V, Saito T, Saido TC, Neumann U, Rokka J, Eriksson J, *Syvänen S: ^{11}C-PIB and ^{124}I-antibody PET provide differing estimates of brain amyloid-beta after therapeutic intervention. ***J Nucl Med*** 2022; 63: 302-309
14. Zarhin D, Atsmon R, Ruggiero A, Baeloha H, Shoob S, Scharf O, Heim LR, Buchbinder N, Shinikamin O, Shapira I, Styr B, Braun G, Harel M, Sheinin A, Geva N, Sela Y, Saito T, Saido T, Geiger T, Nir Y, Ziv Y, *Slutsky I: Disrupted neural correlates of anesthesia and sleep reveal early circuit dysfunctions in Alzheimer models. ***Cell Rep*** 2022; 38: 110268
15. Britz J, Ojo E, Dhukhwa A, Saito T, Saido TC, Hascup ER, *Hascup KN, Tischkau SA: Assessing sex-specific circadian, metabolic, and cognitive phenotypes in the AβPP/PS1 and APPNL-F/NL-F models of Alzheimer's disease. ***J Alzheimers Dis*** 2022; 85: 1077-1093
16. Mizuno Y, Abolhassani N, Mazzei G, Sakumi K, Saito T, Saido TC, Ninomiya T, Iwaki T, Yamasaki

R, Kira JI, *Nakabeppu Y: MUTYH activity contributes to microglial activation and impaired neurogenesis in the pathogenesis of Alzheimer's disease. ***Oxid Med Cell Longev*** 2021; 2021: 8635088

17. *Minamisawa M, Sato Y, Ishiguro E, Taniai T, Sakamoto T, Kawai G, Saito T, Saido TC: Amelioration of Alzheimer's disease by gut-pancreas-liver-brain interaction in an App knock-in mouse model. ***Life*** 2021; 12: 34
18. Liu X, Zhou Q, Zhang J-H, Wang X, Gao X, Wang K-Y, Saito T, Saido TC, *Azuma K: Microglia-based sex-biased neuropathology in early-stage Alzheimer's disease model mice and the potential pharmacologic efficacy of Dioscin. ***Cells*** 2021; 10: 3261
19. Pauls E, Bayod S, Mateo L, Alcalde V, Juan-Blanco T, Sánchez-Soto M, Saido TC, Saito T, Berrenguer-Llergo A, Attolini CS-O, Gay M, de Oliveira E, Duran-Frigola M, *Aloy P: Identification and drug-induced reversion of molecular signatures of Alzheimer's disease onset and progression in App^{NL-G-F}, App^{NL-F}, and 3xTg-AD mouse models. ***Genome Med*** 2021; 13: 168
20. Wu X, Saito T, Saido TC, *Barron AM, Ruedl C: Microglia and CD206+ border-associated mouse macrophages maintain their embryonic origin during Alzheimer's disease. ***Elife*** 2021; 10: e71879
21. Tanaka H, Kondo K, Fujita K, Homma H, Tagawa K, Jin X, Jin M, Yoshioka Y, Takayama S, Masuda H, Tokuyama R, Nakazaki Y, Saito T, Saido T, Murayama S, Ikura T, Ito N, Yamamori Y, Tomii K, Bianchi ME, Okazawa H: HMGB1 signaling phosphorylates Ku70 and impairs DNA damage repair in Alzheimer's disease pathology. ***Commun Biol*** 2021; 4: 1175
22. Hoshi K, Ito H, Abe E, Fuwa TJ, Kanno M, Murakami Y, Abe M, Murakami T, Yoshihara A, Ugawa Y, Saito T, Saido TC, Matsumoto K, Yamaguchi Y, Furukawa K, Arai H, Kanai M, Miyajima M, Arai H, Ogawa N, Akatsu H, Hashizume Y, Tateno H, Honda T, *Hashimoto Y: Transferrin biosynthesized in the brain is a novel biomarker for Alzheimer's disease. ***Metabolites*** 2021; 11: 616
23. Hata S, Kano K, Kikuchi K, Kinoshita S, Sobu Y, Saito H, Saito T, Saido TC, Sano Y, Taru H, Aoki J, Komano H, Tomita T, Natori S, *Suzuki T: Suppression of amyloid-β secretion from neurons by cis-9, trans-11-octadecadienoic acid, an isomer of conjugated linoleic acid. ***J Neurochem*** 2021; 159: 603-617
24. Omagari K, Asamitsu K, Tanaka Y: Application of fluorescent-based technology detecting protein-protein interactions to monitor the binding of hepatitis B virus X protein to DNA-damage-binding protein 1. ***Biophys Physicobiol*** 2021; 18: 67-77
25. Inden M, Takagi A, Kitai H, Ito T, Kurita H, Honda R, Kamotani YO, Nozaki S, Wen X, Hijioka M, Kitamura M, *Hozumi I: Kaempferol has potent protective and antifibrillogenic effects for α-synuclein neurotoxicity in vitro. ***Int J Mol Sci*** 2021; 22: 11484
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27. Sato K, Watamura N, Fujioka R, Mihira N, Sekiguchi M, Nagata K, Ohshima T, Saito T, Saido TC, *Sasaguri H: A 3rd generation mouse model of Alzheimer's disease shows early and increased cored plaque pathology composed of wild-type human amyloid β peptide. ***J Biol Chem*** 2021; 297: 101004
28. Mazzei G, Abolhassani N, Ikegami R, Haruyama N, Sakumi K, Saito T, Saido TC, *Nakabeppu Y: A high-fat diet exacerbates the Alzheimer's disease pathology in the hippocampus of the $App^{NL-F/NL-F}$ knock-in mouse model. ***Aging Cell*** 2021; e13429
29. Benitez DP, Jiang S, Wood J, Wang R, Hall CM, Peerboom C, Wong N, Stringer KM, Vitanova KS, Smith VC, Joshi D, Saito T, Saido TC, Hardy J, Hanrieder J, De Strooper B, Salih DA, Tripathi T, Edwards FA, *Cummings DM: Knock-in models related to Alzheimer's disease: synaptic transmission, plaques and the role of microglia. ***Mol Neurodegener*** 2021; 16: 47
30. Sakakibara Y, Hirota Y, Ibaraki K, Takei K, Tsubokawa Y, Saito T, Saido TC, Sekiya M, *Iijima KM: Widespread reduced density of noradrenergic locus coeruleus axons in the *App* knock-in mouse model of Aβ amyloidosis. ***J Alzheimers Dis*** 2021; 82: 1513-1530
31. *Sasai K, Tabu K, Saito T, Matsuba Y, Saido TC, Tanaka: Difference in the malignancy between *RAS* and *GLI1*-transformed astrocytes is associated with frequency of $p27^{KTP1}$-positive cells in xenograft

tissues. ***Pathol Res Pract*** 2021; 223: 153465

32. Takamura R, Mizuta K, Sekine Y, Islam T, Saito T, Sato M, Ohkura M, Nakai J, Ohshima T, Saido T, *Hayashi Y: Modality specific impairment of hippocampal CA1 neurons of Alzheimer's disease model mice. ***J Neurosci*** 2021; 41: 5315-5329
33. Bettegazzi B, Monasor LS, Bellani S, Codazzi F, Restelli L, Colombo A, Deigendesch N, Frank S, Saito T, Saido T, Lammich S, Tahirovic S, Grohovaz F, *Zacchetti D: Casein Kinase 2 dependent phosphorylation of eIF4B regulates BACE1 expression in Alzheimer's disease. ***Cell Death Dis*** 2021; 12: 769
34. Nakamura Y, Yamamoto T, Xu X, Kobayashi S, Tanaka S, Tamitani M, Saito T, Saido TC, *Yano M: Enhancing calmodulin binding to ryanodine receptor is crucial to limit neuronal cell loss in Alzheimer's disease. ***Sci Rep*** 2021; 11: 7289
35. Clayton K, Delpech JC, Herron S, Iwahara N, Ericsson M, Saito T, Saido TC, Ikezu S, *Ikezu T: Plaque associated microglia hyper-secrete extracellular vesicles and accelerate tau propagation in a humanized APP mouse model. ***Mol Neurodegener*** 2021; 16: 18
36. Maeda J, Minamihisamatsu T, Shimojo M, Zhou X, Ono M, Matsuba Y, Ji B, Ishii H, Ogawa M, Akatsu H, Kaneda D, Hashizume Y, Robinson JL, Lee VM-Y, Saito T, Saido TC, Trojanowski JQ, Zhang M-R, Suhara T, Higuchi M, *Sahara N: Distinct microglial response against Alzheimer's amyloid and tau pathologies characterized by P2Y12 receptor. ***Brain Commun*** 2021; 3: fcab011
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40. Taslima F, Jung C-G, Zhou C, Abdelhamid M, Abdullah M, Goto T, Saito T, Saido TC, *Michikawa M: Tooth loss induces memory impairment and gliosis in App knock-in mouse models of Alzheimer's disease. ***J Alzheimers Dis*** 2021; 80: 1687-1704
41. Sutoko S, Masuda A, Kandori A, Sasaguri H, Saito T, Saido TC, *Funane T: Early identification of Alzheimer's disease in mouse models: Application of deep network algorithm to cognitive behavioral parameters. ***iScience*** 2021; 24: 102198
42. Nakano M, Mitsuishi Y, Liu L, Watanabe N, Hibino E, Hata S, Saito T, Saido TC, Murayama S, Kasuga K, Ikeuchi T, Suzuki T, Nishimura M: Extracellular release of ILEI/FAM3C and Amyloid-β is associated with the activation of distinct synapse subpopulations. ***J Alzheimers Dis*** 2021; 80: 159-174
43. Salobrar-García E, López-Cuenca I, Sánchez-Puebla L, de Hoz R, Fernández-Albarral JA, Ramírez AI, Bravo-Ferrer I, Medina V, *Moro MA, Saido TC, Saito T, Salazar JJ, Ramírez JM: Retinal thickness changes over time in a murine AD model APP$^{NL-F/NL-F}$. ***Front Aging Neurosci*** 2021; 12: 625642
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45. Sobue A, Komine O, Hara Y, Endo F, Mizoguchi H, Watanabe S, Murayama S, Saito T, Saido T, Sahara N, Higuchi M, Ogi T, *Yamanaka K: Microglial gene signature reveals loss of homeostatic microglia associated with neurodegeneration of Alzheimer's disease. ***Acta Neuropathol Commun*** 2021; 9: 1
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disease pathology via angiopathy. ***Exp Neurol*** 2021; 337: 113552

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55. *Narukawa M, Takahashi S, Saito T, Saido TC, Misaka T: Analysis of taste sensitivities in App knock-in mouse model of Alzheimer's disease. ***J Alzheimers Dis*** 2020; 76: 997-1004
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62. Hongo N, Takamura Y, Nishimaru H, Matsumoto J, Tobe K, Saito T, Saido TC, *Nishijo H: Astaxanthin ameliorated parvalbumin-positive neuron deficits and Alzheimer's disease-related pathological progression in the hippocampus of $App^{NL-G-F/NL-G-F}$ mice. ***Front Pharmacol*** 2020; 11: 307
63. Tanaka H, Homma H, Fujita K, Kondo K, Yamada

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4. Review Articles and Books (4 in total)

1. Sasaguri H, Hashimoto S, Watamura N, Sato K, Takamura R, Nagata K, Tsubuki S, Ohshima T, Yoshiki A, Sato K, Kumita W, Sasaki E, Kitazume S, Nilsson P, Winblad B, *Saito T, Iwata N, Saido TC: Recent advances in the modeling of Alzheimer's disease. ***Front Neurosci*** (in press)
2. *Nagata K, Saito T, Saido TC, Morihara T: Biology of splicing in Alzheimer's disease research. ***Prog Mol Biol Tansl Sci*** 2019; 168: 79-84
3. *Saito T: Aβ, Tau and ApoE in mouse models of Alzheimer's Disease. ***Dementia Japan*** 2021; 35: 18-25
4. *Saito T: Development and application of the next generation mouse models for Alzheimer's disease. ***Nagoya Med J*** 2020; 56: 247-254

5. Organizing academic meetings, symposiums, etc.(6 in total)

1. Saito T & Tomiyama T: Symposium "Academia-bioventure aiming to overcome neurodegenerative and psychiatric diseases" **The 40th Annual metting of Japan Society for Dementia Research** November/2021, Organizer and Chairman
2. Saito T & Nonaka T: Symposium "Viewing and Controlling Neuroinflammation - Glial Technology" **The 39th Annual metting of Japan Society for Dementia Research** November/2020, Organizer and Chairman
3. Saito T: **The 1st Biomarker metting for Dementia** October/2020, Organizer and Chairman
4. Saito T & Tomita T: Symposium "Mechanobiology and Physical Medicine" **The 38th Annual metting of Japan Society for Dementia Research** November/2019, Organizer and Chairman
5. Saito T & Muramatsu R: Symposium "Brain Infrastructure- Functional Maintenance Structures for Homeostasis and Logistical Systems in Brain Cell Societies" **The 92nd Annual Meeting of the Japanese Biochemical Society** September/2019, Organized and Chairman

6. Saito T & Tomita T: Symposium "Understanding the homeostatic maintenance mechanisms and logistics of cellular community in the brain-Brain Infrastructure" **Neuro2019** July/2019, Organized and Chairman

6. Invited lectures at International Conferences, etc.（0 in total）

7. Invited lectures at Domestic Conferrences, etc. (6 in total)

1. Saito T: Educational lecture "Generation of mouse models of Alzheimer's disease, their problems, and future developments."**The 55th Annual meeting of Japanese Association for Experimental Animal Technologists**, October/2021
2. Saito T: Special lecture "Understanding the brain environment in Alzheimer's disease"**The 73rd Seinan Regional Meeting of the Japanese Pharmacological Society**, November/2020
3. Saito T: Lecture "Towards overcoming Alzheimer's disease-Development and application of the disease model"」**The 68th Meeting of the Medical and Biological Society for the Brain**, February/2020
4. Saito T: Lecture "Toward understanding the pathogenesis of Alzheimer's disease" **The 3rd Future Conference Medical-Scientific-Industrial Collaboration**, November/2019
5. Saito T: Lecture "Propagation model for the pathophysiologically abnormal protein accumulation in Alzheimer's disease" **The 41st Annual meeting of Japanese Association of Neural Tissue Culture**, November/2019
6. Saito T: Lecture "Development of applications from the generation of Alzheimer's disease model mice" **The 29th Annual Meeting of the Japanese Society of Pharmaceutical Health Care and Science**, November/2019

8. Presentaion at International Conferences, etc. (6 in total)

1. Hart DW, Saito T, Saido TC, Lesné SE: Novel inhibitory network remodeling in knock-in models of Alzheimer's disease. **AD/PD2022**, March/2022, Poster
2. Andersson E, Saito T, Saido TC, Blennow K, Zetterberg H, Hansson O: Reduced CSF Ab42 and Ab42/Ab40 ratio during early cerebral amyloid deposition in the *App*$^{NL-F}$ knock-in mouse model of Alzheimer's disease. **AD/PD2022**, March/2022, Poster
3. Morrissey ZD, Zhan L, Ajilore O, Saido T, Saito T, Leow A, Lazarov O Age-related changes in mice with a single copy insertion of human *App* with familial Alzheimer's disease mutations using diffusion tensor imaging. **SFN2022**, November/2022, Poster
4. Salobrar-García E, Sánchez-Puebla L, López-Cuenca I, Fernández-Albarral JA, Rojas P, de Hoz R, Ramírez AI, Salazar JJ, Bravo-Ferrer I, Medina V, Moro MA, Saido TC, Saito T, Ramirez JM: Retinal changes in the App$^{NL-F/NL-F}$ mouse model: a SD-OCT study from 6 months to 20 months of age. **GLIA 2021**, July/2021, Poster
5. Sutoko S, Masuda A, Kandori A, Sasaguri H, Saito T, Saido TC, Funane T: Use of deep neural network algorithm on cognitive behavioral parameters to early identify Alzheimer's disease: An animal study. **SFN2021**, January/2021, Poster
6. Nieraad H, de Bruin N, Arne O, Josephine Hofmann MC, Schmidt M, Saito T, Saido TC, Gurke R, Schmidt D, Till U, Parnham MJ, Geisslinger G: Impact of hyperhomocysteinemia and different dietary interventions on cognitive performance in a knock-in mouse model for Alzheimer's disease. **The 33rd ECNP Congress**, September/2020, Poster

9. Presentations at Domestic Conferences, etc. (30 in total)

1. Saito Y, Kobayashi Y, Saito T, Saido TC: Analysis of neuronal primary cilia dynamics using a next-generation mouse model of Alzheimer's disease. **The 95th Annual Meeting of the Japanese Pharmacological Society**, March/2022, Poster
2. Masanori H, Futokoro R, Arata M, Katsuki H, Kitamura Y: Effect of the regulation of leukotriene B_4 and lipoxin A_4 production in intracerebral hemorrhage. **The 142nd Annual Meeting of the Pharmaceutical Society of Japan**, March/2022, Poster
3. Saito T: Glial response/Neuroinflammation and Alzheimer's disease. **The 40th Annual Meeting of Japan Society for Dementia Research**,

November/2021, Oral

4. Tanaka T, Hirai S, Hosokawa M, Saito T, Saido TC, Sakuma K, Hasegawa M, Okado H: Developmental factors in age-related brain dysfunction. **The 40th Annual Meeting of Japan Society for Dementia Research**, November/2021, Poster
5. Kitazume S, Saito T, Saido TC: Origin of Aβ and related molecules in blood. **The 40th Annual Meeting of Japan Society for Dementia Research**, November/2021, Poster
6. Iwata Y, Ito S, Kaneko Y, Ogata S, Saito T, Saido TC, Masuda G, Ohtsuki S: Drug metabolism and transport-telated protein expression changes in the liver of an App-knock-in mouse model of Alzheimer's disease. **The 36th Annual Meeting of the Japanese Society for the Study of Xenobiotics**, November/2021, Poster
7. Iwashita N, Nozaki S, Hijioka M, Wen X, Kitamura Y: Effect of galantamine on the clearance of α-synuclein protein aggregates. **The 71st Annual Meeting of the Kansai Branch of the Pharmaceutical Society of Japan**, October/2021, Poster
8. Ochi S, Saito T, Saido TC, Iinuma K, Azuma K, Kubo K 「The potential role of early tooth loss in the pathogenesis of the App knock-in mouse model of Alzheimer's disease.」 **The 44th Annual Meeting of the Japan Neuroscience Society**, July/2021, Poster
9. Nozaki S, Hijioka M, Iwashita N, Namba J, Wen X and Kitamura Y「Galantamine inhibits the accumulation of α-synuclein by autophagy activation」**The 44th Annual Meeting of the Japan Neuroscience Society**, July/2021, Poster
10. Furukawa N, Uruno A, Saito R, Mieda D, Saito T, Saido TC, Motohashi H, Yamamoto M: Glutathione and amino acid metabolism in the brain in Alzheimer's disease. **The 87th Meeting of The Japanese Biochemical Society, Tohoku Branch**, May/2021, Oral
11. Matsumaru D, Uruno A, Ryoke R, Saito R, Kadoguchi S, Mieda D, Saito T, Saido TC, Kawashima R, Yamamoto M: Activation of KEAP1-NRF2 regulatory system and Alzheimer's disease. **The 141st Annual Meeting of the Pharmaceutical Scoiety of Japan**, March/2021, Oral
12. Asamitsu K, Okamoto T, Hirokawa T: The development of novel anti-HIV drug targeting on Tat-specific CDK9 hidden cavity. **The 43th Annual Meeting of the Molecular Biology Society of Japan**, December/2020, Poster
13. Sobue A, Komine O, Endo F, Murayama S, Saito T, Saido TC, Yamanaka K: Neuroinflammation modulation through microglial cannabinoid receptor type 2 in Alzheimer's disease. **The 39th Annual Meeting of Japan Society for Dementia Research**, November/2020, Poster
14. Ting W, Sobue A, Komine O, Saito T, Saido T, Yamanaka K「Effect of Dimethyl Fumarate on the neuroinflammation in App Knock-in mouse」**The 39th Annual Meeting of Japan Society for Dementia Research**, November/2020, Poster
15. Shimokawa R, Komine O, Ito A, Sobue A, Saito T, Saido TC, Suganami T, Yamanaka K: Investigating the effects of systemic inflammation on neuroinflammation in an Alzheimer's disease model. **The 39th Annual Meeting of Japan Society for Dementia Research**, November/2020, Poster
16. Sakakibara Y, Ibaraki K, Takei Y, Saito T, Saido TC, Sekiya T, Iijima K: Analysis of changes in locus coeruleus nucleus nerve projection and neurovascular coupling in knock-in mice. **The 39th Annual Meeting of Japan Society for Dementia Research**, November/2020, Poster
17. Alam Shahnur, Nakano M, Ishihara S, Miyasaka T, Kakuda N, Saito T, Saido TC, Nishimura M, Funamoto S: Why is Aβ deposition greater in the cerebrum and less in the cerebellum? -Active Aβ efflux from the cerebellum. **The 39th Annual Meeting of Japan Society for Dementia Research**, November/2020, Poster
18. Hayashi R, Hata S, Saito T, Kasuga K, Saido TC, Ikeuchi T, Suzuki T: Evaluation of p3-Alcβ functional site gene mutations. **The 39th Annual Meeting of Japan Society for Dementia Research**, November/2020, Poster
19. Abdelhamid M, Jung C-G, Kuhara T, Zhou C, Taslima F, Abdullah M, Saito T, Saido TC, Michikawa M: Effect of *Bifidobacterium breve* strain MCC1274 on Alzheimer's disease pathogenesis. **The 39th Annual Meeting of Japan Society for Dementia Research**, November/2020, Poster
20. Okue S, Takahashi M, Saito T, Saido TC, Masuzawa-Ozaki Y, Hosono T, Seki S: Fish oil prevents AD pathology via its anti-obesity effect. **The 39th Annual Meeting of Japan Society for**

Dementia Research, November/2020, Poster

21. Tanaka T, Hirai S, Hosokawa M, Saito T, Saido TC, Sakuma K, Hasegawa M, Okado H: Developmental factors in age-related brain dysfunction. **The 39th Annual Meeting of Japan Society for Dementia Research**, November/2020, Poster
22. Okue S, Takahashi M, Orihara R, Saito T, Saido TC, Miura N, Masuzawa-Ozaki Y, Hosono T, Seki S: Investigation on the preventive effect of fish oil on Alzheimer's disease. **The 25th Annual Meeting of Japanese Society of Food Factors**, November/2020, Poster
23. Tako T, Toyohara J, Soei S, Tatsuta M, Niizaki T, Yanai S, Endo S, Saito T, Saido TC, Tanaka K: Biological Evaluation of ^{18}F-labeled neopentylstyrylpyridine Amyloid-β PET probe. **The 60th Annual Scientific Meeting of the Japanese Society of Nuclear Medicine**, November/2020, Poster
24. Saito T: A role of recognition and sorting infrastructure in the pathogenesis of Alzheimer's disease. **The 93rd Annual Meeting of the Japanese Biochemical Society**, September/2020, Oral
25. Saito T: Towards prevention and treatment of Alzheimer's disease. **The 63rd Annual Meeting of the Japanese Society for Neurochemistry**, September/2020, Oral
26. Hashimoto A, Tanaka E, Murata K, Yamaguchi M, Yokoyama N, Bando H, Kamei N, Saito T, Saido TC, Takeda M: Comparative evaluation of anti-Amyloid-β antibody drug delivery routes to enhance therapeutic efficacy in Alzheimer's disease: A study using APP knock-in mice. **The 36th Annual Meeting of the Japan Society of rug Delivery System**, August/2020, Poster
27. Saito T: Recognition and communication of glial cells underlying pathogenesis of Alzheimer's disease」**The 43rd Annual Meeting of the Japan Neuroscience Society**, July/2020, Oral
28. Saito T: Aβ, ApoE and Tau in the model mouse of Alzheimer's disease. **The 38th Annual Meeting of Japan Society for Dementia Research**, November/2019, Oral
29. Kaneko Y, Ito S, Ogata S, Yagi R, Takahata T, Iwata Y, Ohtsuka K, Saito T, Saido TC, Masuda G, Ohtsuki S: Comprehensive blood protein expression variation in a next-generation mouse model of Alzheimer's disease. **The 41st Symposium on Drug Interactions with Biological Membranes**, October/2019, Poster
30. Ohtsuka K, Ito S, Ogata S, Yagi R, Uemura T, Kaneko Y, Saito T, Saido TC, Masuda G, Ohtsuki S: Comprehensive pharmacokinetics-related protein expression variation in the kidney of a next-generation mouse model of Alzheimer's disease. **The 41st Symposium on Drug Interactions with Biological Membranes**, October/2019, Poster

10. Other activities (0 in total)

11. Press Release and Media Coverage(0 in total)

12. Patent (0 in total)

Department of Neurodevelopmental Disorder Genetics
Since Establishment (October 2019) to FY2021

1. Laboratory members

Full-time Staff

Kazuhiro Yamakawa (Professor)
Toshimitsu Suzuki (Associate Professor)
Satoshi Kanazawa (Assistant Professor)
Tetsushi Yamagata (Assistant Professor)
Yurina Hibi (Technical Manager)

Part-time Staff

Yoko Miura (Researcher)
Junko Nitatouge (Technical Staff)
Satoko Ogawa (Secretary)

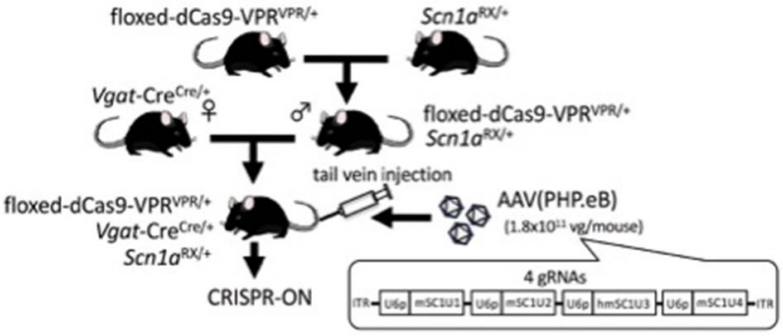
Graduate School Students

Atsushi Usami (MD-PhD Course)

2. Research to date

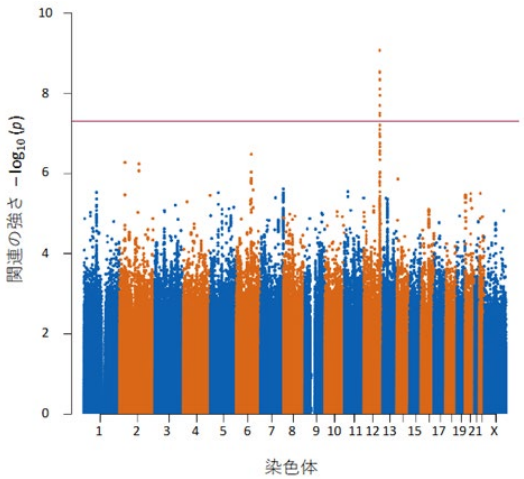
(Yamakawa group)

Dravet syndrome is an epileptic encephalopathy associated with autistic features and intellectual disability caused by loss-of-function mutations of *SCN1A* gene which encodes voltage-gate sodium channel alpha subunit type-1 Nav1.1. We applied a technique named CRISPR-ON which can accelerate tarnscription of any gene on a Dravet syndrome mouse model harboring Scn1a nosense mutation, and succeeded to increase the transcription of remained intact Scn1a gene and improve the disease phenotypes including epileptic seazures and sudden death (Figure 1) (Yamagata et al., ***Neurobiol Dis*** 141:104954,2020; Press release May 25, 2020).



[Fig.1] Inhibitory neuron-specific CRISPR-ON on *Scn1a*$^{RX/+}$ mouse

We performed whole exome and targetted sequencing on 558 patienst with developmental disorders and found multiple responsible gene candidates. We further generated knock out mice for one of those candidate genes and its homologue and found that those mice reproduce the dieases phenotypes (Suzuki et al., ***Ann Clin Transl Neurol*** 7:1117-1131,2020; Press release June 17, 2020).



[Fig.2] Genome-wide association (GWAS) on 1,825 Japanese patients of epilepsy identified a responsible locus at 12q24

We also performed genome-wide association study (GWAS) on 1,825 Japanese patients with epilepsy and

found a chromosomal locus 12q24 with a genome-wide significance (Figure 2) (Suzuki et al., ***Epilepsia*** 62:1391-1400,2021; Press release April 29, 2021).

In addition, we published 15 more papers (see Publication).

(Kanazawa group)

We have found that the induced-rheumatoid artritis-associated interstitial lung disease mouse model (iRA-ILD), in which nintedanib, a drug for ILD with progressive fibrosis, is administered, actually improves the rheumatoid lungs. The study also revealed the characteristics of invasive lung epithelial cells, which are thought to be in a precancerous state. Nintedanib, which was previously thought to improve pulmonary fibrosis by suppressing fibroblast proliferation, was also shown to eliminate these migrating lung epithelial cells (see Figure 1, Miura, Y., et al. (2021). ERJ Open Res 7(4)).

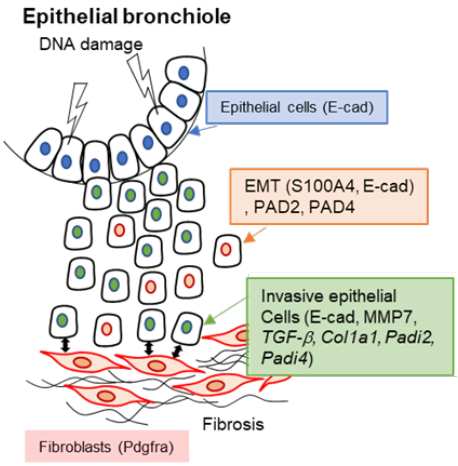


Figure 1 Characterization of pulmonary epithelial cells that have acquired migratory properties, associated with interstitial pneumonia.

We have also created a new iUIP mouse model (induced-usualintesstitial pneumonia). This model is the first model in the world to develop an intractable disease, idiopathic pulmonary fibrosis. The model shows a very severe pulmonary fibrosis state called the honeycomb lung structure, and it is expected that tracing the development of the disease in this model will lead to the evaluation and development of new therapeutic agents (see Figure 2, Miura, Y., et al. (2022). Life Sci Alliance 5(1): e202101059., Press Release February 22, 2022, in collaboration with the Faculty of Pharmacy, Monash University, Australia). Analysis of these mice has revealed the mechanism of severe interstitial pneumonia during SARS-CoV-2 infection, and this aspect of the disease is currently under investigation.

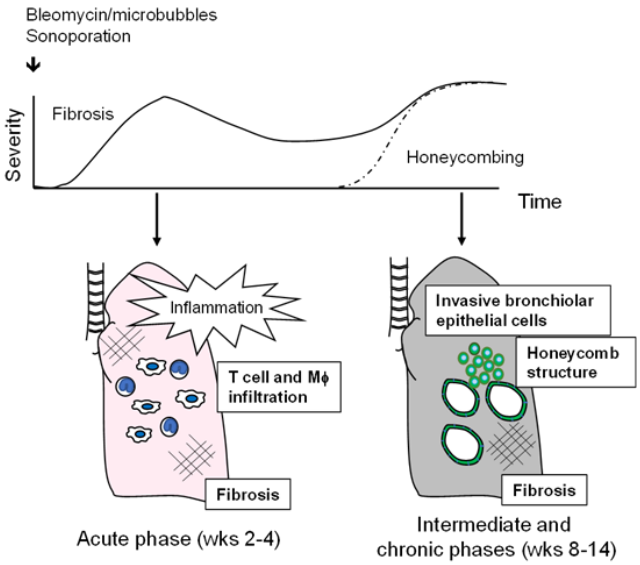


Figure 2. iUIP mouse model shows a severe fibrotic state (acute and chronic biphasic called bimodal fibrosis) characterized by honeycombing. Using these mice, we are currently evaluating and developing new therapeutic agents for pulmonary fibrosis.

3. Publications (original articles) (21 in total)

(Yamakawa Group)

1. Epi25 Collaborative (including Suzuki T, Yamakawa K). Sub-genic intolerance, ClinVar, and the epilepsies: A whole-exome sequencing study of 29,165 individuals. ***Am J Hum Genet.*** 2021; 108(10): 2024.
2. Koko M, Krause R, Sander T, Bobbili DR, Nothnagel M, *May P, *Lerche H; Epi25 Collaborative (including Suzuki T, Yamakawa K). Distinct gene-set burden patterns underlie common generalized and focal epilepsies. ***EBioMedicine.*** 2021; 72: 103588.
3. Nakajima K, Ishiwata M, Weitemier AZ, Shoji H, Monai H, Miyamoto H, Yamakawa K, Miyakawa T, McHugh TJ, *Kato T. Brain-specific heterozygous loss-of-function of ATP2A2, endoplasmic reticulum Ca2+ pump responsible for Darier's disease, causes behavioral abnormalities and a hyper-dopaminergic state. ***Hum Mol Genet.*** 2021; 30(18): 1762-1772.
4. Stevelink R, *Luykx JJ, Lin BD, Leu C, Lal D, Smith AW, Schijven D, Carpay JA, Rademaker K, Rodrigues Baldez RA, Devinsky O, Braun KPJ, Jansen FE, Smit DJA, Koeleman BPC; International League Against Epilepsy Consortium on Complex Epilepsies; Epi25 Collaborative (including Suzuki T, Yamakawa K). Shared genetic basis between genetic generalized epilepsy and background electroencephalographic oscillations. ***Epilepsia.*** 2021; 62(7): 1518-1527.
5. Epi25 Collaborative (including Suzuki T, Yamakawa K). Sub-genic intolerance, ClinVar, and the epilepsies: A whole-exome sequencing study of 29,165 individuals. ***Am J Hum Genet.*** 2021; 108(6): 965-982.
6. Suzuki T, Koike Y, Ashikawa K, Otomo N, Takahashi A, Aoi T, Kamatani N, Nakamura Y, Kubo M, Kamatani Y, Momozawa Y, Terao C, *Yamakawa K. Genome-wide association study of epilepsy in a Japanese population identified an associated region at chromosome 12q24. ***Epilepsia.*** 2021; 62(6): 1391-1400.
7. Shimizu R, *Ishihara K, Kawashita E, Sago H, Yamakawa K, Mizutani KI, Akiba S. Decrease in the T-box1 gene expression in embryonic brain and adult hippocampus of down syndrome mouse models. ***Biochem Biophys Res Commun.*** 2021; 535: 87-92.
8. Suzuki T, Inoue I, *Yamakawa K. Epilepsy protein Efhc1/myoclonin1 is expressed in cells with motile cilia but not in neurons or mitotic apparatuses in brain. ***Sci Rep.*** 2020; 10(1): 22076.
9. Kato H, *Kushima I, Mori D, Yoshimi A, Aleksic B, Nawa Y, Toyama M, Furuta S, Yu Y, Ishizuka K, Kimura H, Arioka Y, Tsujimura K, Morikawa M, Okada T, Inada T, Nakatochi M, Shinjo K, Kondo Y, Kaibuchi K, Funabiki Y, Kimura R, Suzuki T, Yamakawa K, Ikeda M, Iwata N, Takahashi T, Suzuki M, Okahisa Y, Takaki M, Egawa J, Someya T, Ozaki N. Rare genetic variants in the gene encoding histone lysine demethylase 4C (KDM4C) and their contributions to susceptibility to schizophrenia and autism spectrum disorder. ***Transl Psychiatry.*** 2020; 10(1): 421.
10. *Hayase Y, Amano S, Hashizume K, Tominaga T, Miyamoto H, Kanno Y, Ueno-Inoue Y, Inoue T, Yamada M, Ogata S, Balan S, Hayashi K, Miura Y, Tokudome K, Ohno Y, Nishijo T, Momiyama T, Yanagawa Y, Takizawa A, Mashimo T, Serikawa T, Sekine A, Nakagawa E, Takeshita E, Yoshikawa T, Waga C, Inoue K, Goto YI, Nabeshima Y, Ihara N, Yamakawa K, Taya S, Hoshino M. Down syndrome cell adhesion molecule like-1 (DSCAML1) links the GABA system and seizure susceptibility. ***Acta Neuropathol Commun.*** 2020; 8(1): 206.
11. Arimura N, Okada M, Taya S, Dewa KI, Tsuzuki A, Uetake H, Miyashita S, Hashizume K, Shimaoka K, Egusa S, Nishioka T, Yanagawa Y, Yamakawa K, Inoue YU, Inoue T, Kaibuchi K, *Hoshino M. DSCAM regulates delamination of neurons in the developing midbrain. ***Sci Adv.*** 2020; 6(36): eaba1693.
12. Arima-Yoshida F, Raveau M, Shimohata A, Amano K, Fukushima A, Watanave M, Kobayashi S, Hattori S, Usui M, Sago H, Mataga N, Miyakawa T, *Yamakawa K, *Manabe T. Impairment of spatial memory accuracy improved by Cbr1 copy number resumption and $GABA_B$ receptor-dependent enhancement of synaptic inhibition in Down syndrome model mice. ***Sci Rep.*** 2020; 10(1): 14187.
13. Heyne HO, Baez-Nieto D, Iqbal S, Palmer DS, Brunklaus A, May P; Epi25 Collaborative (including Suzuki T, Yamakawa K), Johannesen KM, Lauxmann S, Lemke JR, Møller RS, Pérez-Palma E, Scholl UI, Syrbe S, Lerche H, Lal D, Campbell AJ, Wang HR, Pan J, *Daly MJ. Predicting functional effects of missense variants

in voltage-gated sodium and calcium channels. ***Sci Transl Med.*** 202; 12(556): eaay6848.

14. Niestroj LM, Perez-Palma E, Howrigan DP, Zhou Y, Cheng F, Saarentaus E, Nürnberg P, Stevelink R, Daly MJ, Palotie A, *Lal D; Epi25 Collaborative (including Suzuki T, Yamakawa K). Epilepsy subtype-specific copy number burden observed in a genome-wide study of 17 458 subjects. ***Brain.*** 2020; 143(7): 2106-2118.
15. Suzuki T, Suzuki T, Raveau M, Miyake N, Sudo G, Tsurusaki Y, Watanabe T, Sugaya Y, Tatsukawa T, Mazaki E, Shimohata A, Kushima I, Aleksic B, Shiino T, Toyota T, Iwayama Y, Nakaoka K, Ohmori I, Sasaki A, Watanabe K, Hirose S, Kaneko S, Inoue Y, Yoshikawa T, Ozaki N, Kano M, Shimoji T, *Matsumoto N, *Yamakawa K. A recurrent PJA1 variant in trigonocephaly and neurodevelopmental disorders. ***Ann Clin Transl Neurol.*** 2020; 7(7): 1117-1131.
16. Yamagata T, Raveau M, Kobayashi K, Miyamoto H, Tatsukawa T, Ogiwara I, Itohara S, Hensch TK, *Yamakawa K. CRISPR/dCas9-based Scn1a gene activation in inhibitory neurons ameliorates epileptic and behavioral phenotypes of Dravet syndrome model mice. ***Neurobiol Dis.*** 2020; 141: 104954.
17. Kogiso H, Raveau M, Yamakawa K, Saito D, Ikeuchi Y, Okazaki T, Asano S, Inui T, Marunaka Y, *Nakahari T. Airway Ciliary Beating Affected by the *Pcp4* Dose-Dependent $[Ca^{2+}]^{i}$ Increase in Down Syndrome Mice, Ts1Rhr. ***Int J Mol Sci.*** 2020; 21(6): 1947.
18. Leu C, Stevelink R, Smith AW, Goleva SB, Kanai M, Ferguson L, Campbell C, Kamatani Y, Okada Y, Sisodiya SM, Cavalleri GL, Koeleman BPC, Lerche H, Jehi L, Davis LK, Najm IM, Palotie A, Daly MJ, Busch RM; Epi25 Consortium(including Suzuki T, Yamakawa K), *Lal D. Polygenic burden in focal and generalized epilepsies. ***Brain.*** 2019; 142(11): 3473-3481.

(Kanazawa Group)

19. Miura Y, Lam M, Bourke JE, *Kanazawa S. Bimodal fibrosis in a novel mouse model of bleomycin-induced usual interstitial pneumonia. ***Life Sci Alliance.*** 2021; 5(1): e202101059.
20. Miura Y, Ohkubo H, Niimi A, *Kanazawa S. Suppression of epithelial abnormalities by nintedanib in induced-rheumatoid arthritis-associated interstitial lung disease mouse model. ERJ Open Res. 2021 Dec 6;7(4):00345-2021.
21. Terasaki Y, Terasaki M, Kanazawa S, Kokuho N, Urushiyama H, Kajimoto Y, Kunugi S, Maruyama M, Akimoto T, Miura Y, Igarashi T, Ohsawa I, Shimizu A. Effect of H_2 treatment in a mouse model of rheumatoid arthritis-associated interstitial lung disease. ***J Cell Mol Med.*** 2019; 23(10): 7043-7053.

4. Review Articles and Books (3 in total)

(Yamakawa Group)

1. *Yamakawa K:てんかんと自閉スペクトラム症の本態を探る ***No to Hattatsu*** 22; 54: 11-7.

(Kanazawa Group)

2. Miura Y, *Kanazawa S.: Osteochondrogenesis derived from synovial fibroblasts in inflammatory arthritis model. ***Inflamm Regen.*** 2020; 40: 7.
3. Miura Y, Kanazawa K: Interstitial pneumonia mouse model. ***Respiratory Molecular Medicine*** 2020; 24(1): 16-49.

5. Organizing academic meetings, symposiums, etc. (0 in total)

6. Invited lectures at International Conferences, etc.（1 in total）

(Yamakawa Group)

1. Yamakawa K.「Molecular genetics of epilepsy and autism: Model studies for SCN1A, SCN2A, STXBP1.」 **Xiangya International Pediatric Neurology Forum** China, November/2021

7. Invited lectures at Domestic Conferrences, etc. (6 in total)

(Yamakawa Group)

1. Yamakawa K.「てんかん・自閉症の発症機序 : SCN1A, SCN2A, STXBP1」 **脳の医学生物学研究会** November/2021
2. Yamakawa K.「てんかんと発達障害の分子遺伝学」 **茨城てんかん懇話会** July/2021
3. Yamakawa K.「てんかん・発達障害の発症神経回路」 **生理研研究会** February/2021
4. Yamakawa K. 教育講演 10「てんかんと自閉症の本態を探る」**The 62nd Annual Meeting of the Japanese Socieety of Child Neurology** October/2020
5. Yamakawa K.「てんかんと発達障害の原因遺伝子と発症メカニズム」**先端モデル動物支援発表会** February/2020
6. Yamakawa K. 招待講演「てんかんと発達障害 : 原因遺伝子と発症メカニズム」**愛知県医**

療療育総合センター発達障害研究所セミナー November/2019

8. Presentaion at International Conferences, etc. (3 in total)

(Kanazawa Group)

1. Miura Y, Kanazawa S, Ohkubo H, Niimi A, Uematsu K. 「Effects of Nintedanib on Gene Expression in Lungs of a Mouse Model of Interstitial Pneumonia: Comprehensive Analysis by Next-generation Sequencer, Shintaro Mikami1).」 **ATS 2020** Philadelphia, May/2020
2. Kanazawa S, Miura Y, Lam M, Bourke EJ. 「Bimodal fibrosis in induced-usual interstitial pneumonia mouse model (D1CC x D1BC mouse). 」**ATS 2020** Philadelphia, May/2020
3. Miura Y, Ohkubo H, Niimi A, Kanazawa S. 「Nintedanib attenuates interstitial pneumonia in a mouse model with UIP features.」 **ATS 2020** Philadelphia, May/2020

9. Presentations at Domestic Conferences, etc. (22 in total)

(Yamakawa Group)

1. Kerith-Rae Dias,.. Suzuki T, Yamakawa K, .. Tony Roscioli,et al. 「De Novo Missense and Truncating Variants in ZMYND8 Result in a Distinctive Neurodevelopmental Disorder.」 **ASHG annual meeting** Oct/2021, oral
2. Yamakawa K. 一般公演 6「側頭葉てんかん原因遺伝子同定と発症機構の解明」**The 66th Annual Meetihg of the Japan Society of Human Genetics** Oct/2021, Oral
3. Yamakawa K. セッション「てんかん症候群診断における遺伝子解析の意義:てんかんへの遺伝的背景の寄与は大きい - その理解の大切さ」**The 54th Annual Congress of the Japan Epilepsy Sciety** Sept/2021, Oral
4. Yamagata T, Yamakawa K. 「Nav1.1 分布解析と Nav1.1 発現量増加によるドラベ症候群遺伝子治療の試み」**The 54th Annual Congress of the Japan Epilepsy Sciety** Sept/2021, Oral
5. Suzuki T, Inoue I, Yamakawa K. 「若年ミオクロニーてんかん原因タンパクは神経細胞でなく運動性繊毛細胞で発現する」 **The 54th Annual Congress of the Japan Epilepsy Sciety** Sept/2021, Oral
6. Miyazaki H, Tatsukawa T, Hirai Y, Karube F, Miyasaka T, Fujiyama F, Yamakawa K, Nukina N 「Tracing and immunohistochemical study of the cortico-nigral projection in the mouse brain.」 **The 44th Annual Meeting of the Napan Neuroscience Society** July/2021, Oral
7. Suzuki T, Tatsukawa T, Hisatsune C, Mikoshiba K, Yamakawa K「Mice with Scn2a deficiency specifically in striatal medium spiny neurons displayed decreased anxiety and mild impairments of social behavior.」 **The 44th Annual Meeting of the Napan Neuroscience Society** 2021 年 7 月 July/2021, Oral
8. Suzuki T, Suzuki T, Miyake N, Tsurusaki Y, Kushima I, Aleksic B, Shiino T, Toyota T, Iwayama Y, Nakaoka K, Ohmori I, Hirose S, Kaneko S, Inoue Y, Yoshikawa T, Ozaki N, Kano M, Shimoji T, Matsumoto N, Yamakawa K.「A recurrent PJA1 hemizygous variant in trigonocephaly and neurodevelopmental disorders」 **The 65th Annual Meeting of the Japan Society of Human Genetics** 2020 年 11 月 November/2020, Oral
9. Miyazaki H, Tatsukawa T, Yamakawa K, Nukina N. 「A novel unmyelinated fiber projection to substantia nigra.」 **The 44th Annual Meeting of the Japan Neuroscience Society** July/2020, Oral
10. Suzuki T, Yamakawa K「Myoclonin1 deficiency in ependymal cells increases seizure susceptibility.」 **The 44th Annual Meeting of the Japan Neuroscience Society** July/2020, Oral

(Kanazawa Group)

11. Kanazawa K, Miura Y.「Tyrosine kinase inhibitor, nintedanib ameliorates rheumatoid arthritis associated interstitial lung disease by reducing peptidyl deiminase 4+ alveolar epithelial cells with epithelial-mesenchymal transition」 **The 44th Annual Meeting of the Molecular Biology Sciety of Japan**, December/2021, Poster
12. Miura Y, Kanazawa K.「CTLA-4 Ig suppresses antibody production by decreasing the percentage of B cells in lymph nodes.)」**The 44th Annual Meeting of the Molecular Biology Sciety of Japan**, December/2021, Poster
13. Miura Y, Kanazawa K.「Abatacept decreases B cells in lymph nodes and suppresses antibody production」 **The 42nd Annual Meeting of the Japanese Society of Inflammation and Regeneration** July/2021, Poster
14. Kanazawa K, Miura Y.「The antifibrotic drug nintedanib ameliorates pulmonary fibrosis in the rheumatoid arthritis-associated interstitial pneumonia disease model (iRA-ILD)」**The 65th**

Annual General Assembly and Scientific Meeting of the Japan College of Reumatology April/2021, Oral

15. Miura Y, Kanazawa K.「Study of fibrosis in PCLS ex vivo cultures from iUIP mouse model」 **The 61st Annual Meeting of the Japanse Respiratory Society** April/2021, Oral
16. Nakano A, Okubo H, Miura Y, Kanazawa K, Fukumitsu K, Fukuda S, Kanematsu Y、Uemura T, Tajiri T, Maeno K, Ito Y, Niimi A.「Macrophage subtypes in induced sputum in IPF after nintedanib treatment」 **The 65th Annual Meeting of The Japanese Repiratory Society** September/2020, Poster
17. Miura Y, Kanazawa K.「Analysis of fibrotic regions and inhibition of angiogenesis in idiopathic pulmonary fibrosis-like pathology of induced-UIP mouse model」 **The 65th Annual Meeting of The Japanese Repiratory Society** September/2020, Poster
18. Miura Y, Okubo H, Niimi A, Kanazawa K.「Investigation of the inhibitory effect of nintedanib treatment on idiopathic pulmonary fibrosis-like pathology in iUIP mouse model」 **The 65th Annual Meeting of The Japanese Repiratory Society** September/2020, Poster
19. Miura Y, Kanazawa K.「Nintedanib inhibit fibrosis and inflammation in rheumatoid arthritis-associated lung disease mouse model (D1CCxD1BC mice)」 **The 41st Annual Meeting of the Japanese Society of Inflammation and Regeneration** July/2020, Poster
20. Miura Y, Kanazawa K.「Pathogenesis of pulmonary fibrosis due to bronchial epithelial cell dysplasia using a novel mouse model of interstitial pneumonia (induced-UIP model)」 **MBSJ2019** December/2019, Poster
21. Takenaka T, Miura Y, Kanazawa K.「Fibroblasts from mouse model of interstitial pneumonia (iUIP mice) express high levels of PDGFRa and are involved in pathogenesis」 **MBSJ2019** December/2019, Poster
22. Miura Y, Kanazawa K.「Fibroblasts during joint inflammation have characteristics of bone and chondrocyte progenitor cells and proceed to ectopic bone differentiation」 **MBSJ2019** December/2019, Poster

10. Other activities (0 in total)

11. Press Release and Media Coverage (0 in total)

12. Patent (0 in total)

Endowed Department of Cognitive Function and Pathology
FY2021

1. Laboratory members

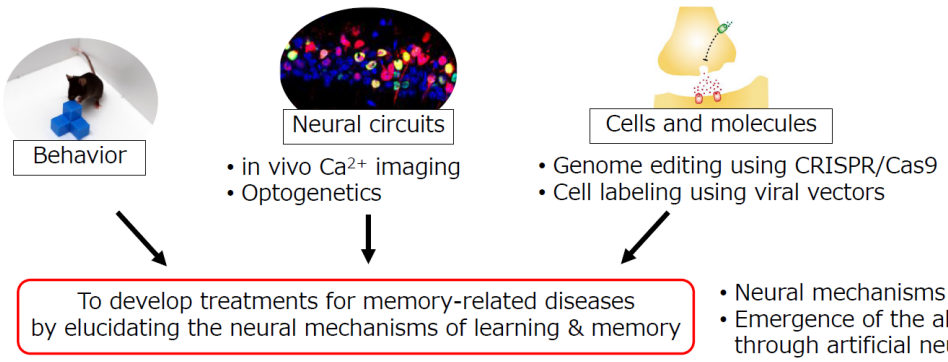
Full-time Staff
Hiroshi Nomura (Endowed Professor)
Yoshikazu Morishita (Endowed Assistant Professor)
Yuto Yokoi (Technical Staff)

Part-time Staff
Nao Nomura (Technical Staff)

Graduate School Students
Kyosuke Hirano (Ph.D. Course)
Rintaro Shimizume (Master's Course)

2. Research to date

We aim to develop treatments for memory-related diseases by elucidating the neural mechanisms of learning and memory. Patients with dementia suffer from learning and memory impairment, which interferes with their daily lives. In addition, excessive and long-term persistence of traumatic memories can trigger psychiatric disorders such as post-traumatic stress disorder (PTSD) and depression. To establish treatments for these disorders, we aim to elucidate the neural mechanisms of learning and memory, particularly by integrating behavioral, neural circuit, cellular, and molecular research approaches. The main focus of our research is on the neural mechanisms that restore memory recall and the emergence of the ability of learning and memory through artificial neural circuits. After a long time has passed since we remember something, it becomes difficult to recall that memory. However, memory traces should remain in the brain because we can recall them unexpectedly at a moment in time. We have previously shown that histamine H3 receptor antagonists can reactivate memory traces and restore memory recall. We are now further developing this research to identify the factors that modulate the recovery of memory recall and to analyze the neural mechanisms of memory recall recovery. We are also working on memory research via a synthetic approach using artificial neural circuits. Although analytical and descriptive studies measuring neural activity in the hippocampus, which is essential for learning and memory, have been conducted extensively, it has been difficult to verify the relationship between precise neural activity and memory. Therefore, we aim to elucidate hippocampal function by creating an artificial hippocampus and examining whether it acquires the learning ability. In addition to verifying the hypothesis proposed in analytical research, this project will also contribute to the proposal of a new treatment for dementia by applying the method to a mouse model of dementia.



3. Publications (original articles) (0 in total)

4. Review Articles and Books (5 in total)

1. *Nomura H, Shimizume R, Ikegaya Y: Histamine: A Key Neuromodulator of Memory Consolidation and Retrieval. ***Curr Top Behav Neurosci*** (in press)
2. *Nomura H, Amano T: Practices and challenges of online laboratory work in pharmacology. ***Nihon Yakurigaku Zasshi*** 2021; 156: 335-337
3. *Nomura H: Autonomous mouse behavioral experiments. ***Nihon Yakurigaku Zasshi*** 2021; 156: 312-312
4. * Nomura H: Histamine signaling restores retrieval of forgotten memories. ***Nihon Yakurigaku Zasshi*** 2021; 156: 292-296
5. * Nomura H: Behavioral analysis with machine learning. ***Nihon Yakurigaku Zasshi*** 2021; 156: 250-250

5. Organizing academic meetings, symposiums, etc. (0 in total)

6. Invited lectures at International Conferences, etc. (0 in total)

7. Invited lectures at Domestic Conferences, etc. (4 in total)

1. Nomura H: Manipulation of memory by controlling brain activity: Can lost memories be recovered? **The 70th Conference on Medicine and Biology of the Brain** January/2022
2. Nomura H: Brain information dynamics regulating learning and memory. **Comprehensive Brain Science Network Winter Symposium 2021 2021** December/2021
3. Nomura H: Neural mechanisms that facilitate memory retrieval **The 19th Hokkaido University Research and Education Center for Brain Science Symposium** October/2021
4. Nomura H: Can we manipulate memories to restore lost memories? **The 195th Nagoya City University Pharmaceutical Science Meeting** October/2021

8. Presentation at International Conferences, etc. (0 in total)

9. Presentations at Domestic Conferences, etc. (4 in total)

1. Nomura H, Nishimura K, Shimizume R, Takamura Y, Minami M: Activity of histamine neurons modulating learning and memory. **The 23rd Meeting of Japanese Histamine Research Society**, January/2022, Oral
2. Hirano K, Shimizume R, Minami M, Nomura H: Pitolisant, a histamine H3 receptor inverse agonist, alters the activity and synchronicity of a subset of perirhinal cortex neurons and modulates the activity of the entire neuronal population. **The 140th Kinki Branch Meeting of the Japanese Pharmacological Society**, November/2021, Oral
3. Shimizume R, Kubo A, Nishimura K, Minami M, Nomura H: Activation of histaminergic neurons in the tuberomammillary nucleus recovers retrieval of forgotten object recognition memory. The 44th Annual Meeting of the Japan Neuroscience Society, July/2021, Poster
4. Hirano K, Minami M, Nomura H: Modulation of perirhinal cortex neural activity by histamine H3 receptor inverse agonists. **The 148th Annual Meeting of The Pharmaceutical Society of Japan Hokkaido Branch**, May/2021, Oral

10. Other activities (0 in total)

11. Press Release and Media Coverage (0 in total)

12. Patent (0 in total)

IV. Research activities from collaborative laboratories

The Institute of Brain Science has established the collaborative laboratories to strengthen research activities and promote world-class research, as well as to establish a foundation for interactions among researchers and to promote research with new ideas and concepts. These laboratories are designed to accelerate research by providing a seamless platform for joint research and technology sharing.

Department of Bochemistry FY2021

1. Laboratory members

Full-time Staff
- Makoto Michikawa (Professor)
- Cha-Gyun Jung (Associate Professor)
- Kun Zou (Associate Professor)
- Maki Tujita (Junior Associate Professor)
- Eriko Inoue (Technical Manager)

Part-time Staff
- Kiyomi Yoshioka (Secretary/Technical Staff)

Graduate School Student
- Sadequl Islam (Ph.D. course)
- Ferdous Taslima (Ph.D. course)
- Mona Abdelhamid (Ph.D. course)
- Yang Sun (Ph.D. course)
- Yuan Gao1 (Ph.D. course)
- Tomohisa Nakamura (Ph.D. course)
- Chunyu Zhou (Ph.D. course)
- Yuxin Chen (Master course)
- Esraa Shaaban (Master course)

2. Research to date

1) A novel function of presenilin (PS) in apolipoprotein E secretion.

Alzheimer disease (AD) is a dementia characterized by progressive memory loss accompanied by aggregation of amyloid-β-protein (Aβ) named amyloid plaques in brain of the patient. It is known that apolipoprotein E4 (ApoE4) is the major genetic risk factor for sporadic AD (SAD) and the mutations in presenilin (PS) lead to abnormal generation of Aβ, which is the major cause of familial AD (FAD). However, whether dysfunction of PS is involved in the pathogenesis of SAD is largely unknown. We found that ApoE secretion was completely abolished in PS-deficient cells. Blockade of γ-secretase activity by a γ-secretase inhibitor, DAPT, decreased ApoE secretion, suggesting an important role of γ-secretase activity in ApoE secretion. We also found that PS deficiency enhanced nuclear translocation of ApoE and binding of ApoE to importin α4, a nuclear-transport receptor. In addition, expression of PS mutants in PS-deficient cells has less restoration effects on ApoE secretion compared with expression of wild-type PS. Our findings suggest a novel role of PS contributing to the pathogenesis of SAD by regulating ApoE secretion. These results have been published in ***J Neurosci,*** 42 (8) 1574-1586, 2022.

2) Effect of Probiotic *Bifidobacterium breve* on AD pathogenesis and memory impairment.

Probiotic supplementation reestablishes microbiome diversity and improves brain function in Alzheimer's disease (AD). However, mechanisms, remains to be fully illustrated. We have been investigating the effects of orally supplemented *Bifidobacterium breve* MCC1274 on cognitive function and AD-like pathologies in App^{NL-G-F} mice. We found that the oral *B. breve* MCC1 274 supplementation prevented memory impairment and reduced hippocampal Aβ levels through the enhancement of the level of ADAM10. We also found that administration of the probiotic activated the ERK/HIF-1α signaling pathway, which is responsible for increasing the ADAM10 level and attenuated microglial activation. Reduced microglia activity lead to reduced levels of mRNA expression of pro-inflammatory cytokines in the brain. *B. breve* MCC1274 supplementation increased the level of synaptic proteins in the hippocampus. Our findings support the possibility that oral *B. breve* MCC1274 supplementation may be used as a potential preventive therapy for AD progression. These results have been published in ***J Alzheimers Dis,*** 85: 1555-1571, 2022

3) Tooth loss induces memory impairment without any effects on AD pathologies, but induces neuronal losso f hippocampus.

Epidemiological studies have shown that tooth loss is associated with Alzheimer's disease (AD) and dementia. However, the molecular and cellular mechanisms by which tooth loss causes AD remain unclear. Here, we investigated the effects of tooth loss on memory impairment and AD pathogenesis in *AppNL-G-F* mice. Tooth loss induced memory impairment via an amyloid-cascade independent pathway, and decreased the neuronal activity, presynaptic and postsynaptic protein levels in both the cortex and hippocampus. Interestingly, we found that tooth loss induced glial activation, which in turn leads to the upregulation of the mRNA expression levels of the neuroinflammation cytokines tumor necrosis factor-α (TNF-α), interleukin-6

(IL-6), and IL-1β in the hippocampus. We also found that tooth loss activated a stress-activated protein kinase, c-Jun N-terminal kinase (JNK) and increased heat shock protein 90 (HSP90) levels in the hippocampus, which may lead to a glial activation. Our findings suggest that taking care of teeth is very important to preserve a healthy oral environment, which may reduce the risk of cognitive dysfunction. These results have been published in ***J Alzheimers Dis***, 80(4): 1687-1704, 2021

3. Publications (original articles) (7 in total)

1. Islam S, Sun Y, Gao Y, Nakamura T, Noorani A. A, Li T, Wong P. C, Kimura N, Matsubara E, Kasuga K, Ikeuchi T, Tomita T, Zou K*, Michikawa M*. Presenilin is essential for ApoE secretion, a novel role of presenilin involved in Alzheimer's disease pathogenesis.
   J Neurosci, 42 (8) 1574-1586, 2022
2. Abdelhamid M, Zhou C, Ohno K, Kuhara T, Taslima F, Abdullah M, Jung C-G＊, Michikawa M*. Probiotic Bifidobacterium breve decreases Aβ production via the upregulation of ADAM10 level and attenuates microglia activation I APP knock-in mouse model of Alzheimer's disease.
   J Alzheimers Dis, 85: 1555-1571, 2022
3. Abdullah, M., Nakamura, T., Ferdous, T. Gao, Y., Chen, Y., Zou, K., Michikawa M*. Cholesterol Regulates Exosome Release in Cultured Astrocytes.
   Front Immunol, 12: 722581, 2021
4. Azad A. K., Sheikh A.M., Haque M. A., Osago H., Sakai H., Shibly A. Z., Yano S., Michikawa M., Hossain S., Tabassum S., Garu A., Zhou X., Zhang Y., Nagai A*. Time-dependent analysis of plasminogens in the hippocampus of an Alzheimer's disease mouse model: A role of ethanolamine plasminogen. ***Brain Sci,*** 11: 1603, 2021
5. Tsushima, H*, Yamada, K., Miyazawa, D., Ohkubo, T., Michikawa M., Abe-Dohmae, S. Comparison of the Physical Characteristics and Behavior in ABC Transporter A1, A7 or Apolipoprotein E Knockout Mice with Lipid Transport Dysfunction
   Biol Pharm Bull, 44: 1851-1859, 2021
6. Taslima F, Jung C-G*, Zhou C, Abdullah M, Abdelhamid M, Saito T, Saido T. C, Michikawa, M*. Tooth loss iduces memory impairment and gliosis in App knock-in mouse models of Alzheiemr's disease.
   J Alzheimers Dis, 80(4): 1687-1704, 2021.
7. Sugimoto T, Sakurai T*, Akatsu H, Doi T, Fujiwara Y, Hirakawa A, Kinoshita F, Kuzuya M, Lee S, Matsuo K, Michikawa M, Ogawa S, Otsuka R, Sato K, Shimada H, Suzuki H, Suzuki H, Takechi H, Takeda S, Umegaki H, Wakayama S, Arai H. The Japan-multimodal intervention trial for prevention of dementia (J-MINT): the study protocol for an 18-month, multicenter, randomized, controlled trial.
   J Prev Alz Dis, 8 (4): 465-476, 2021.

4. Review Articles and Books (1 in total)

1. Nakamura T, Zou K, Shibuya Y, Michikawa M*. Oral dysfunctions and cognitive impairment/ dementia. ***J Neurosci Res*** , 99(2), 518-528, 2021.

Department of Occupational and Environmental Health
FY2021

1. Laboratory members

Full-time Staff

Michihiro Kamijima (Professor)
Takeshi Ebara (Associate Professor)
Yuki Ito (Associate Professor)
Kayo Kaneko (Associate Professor)
Sayaka Kato (Assistant Professor)
Kyoko Minato (Technical Manager)

Part-time Staff

Kiyoshi Sakai (Researcher)
Mio Miyake (Researcher)

Graduate School Student/ MD-PhD course

Mohanto Nayan Chandra (Ph.D. course)
Shogo Nakane (Ph.D. course)
Kazuki Sakai (Master course)
Mafu Tsunemi (Master course)
Asako Nakagawa (MD-PhD course)
Hitomi Wasada (MD-PhD course)

2. Research to date

1) Japan Environment and Children's Study (JECS).

In January 2011, a nationwide birth cohort study called as 'Japan Environment and Children's Study' started to elucidate the effects of environmental exposure, especially chemicals, on children's health. Nagoya City University Graduate School of Medical Sciences founded Center for Research of Health of Mothers and Children and Environment, and has been conducting JECS as one of the 15 Regional Centers in Japan. Pregnant women who lived in Cities of Nagoya (Kita Ward) and Ichinomiya were invited to participate in JECS between January 2011 and March 2014, and the children who were given birth from the women have been followed-up. In 2021, we published papers including the themes of 'Relationship between delivery with anesthesia and postpartum depression' and 'Relationship between physical activity and physical and mental health status in pregnant women'. In addition, we are developing human biomonitoring (BM) methods (BM is the measurement of environmental chemicals/their metabolites in biospecimens to evaluate the exposure in individuals) of chemicals that potentially affect brain/nervous system. Our research interest also covers various health/developmental outcomes of newborns/children. We aim to establish evidence that can contribute to a better environment, not only chemical context but parenting.

2) Risk assessment of health effects by chemicals.

Exposure assessment is one of the key segments of risk assessment of chemicals. In recent years, human BM has been increasingly introduced into environmental health fields. This is because BM can evaluate exposure at individual levels that vary a lot reflecting the variety of lifestyles. However, the target chemicals/metabolites need to be fixed beforehand to detect/quantify low-level environmental exposure, and non-target analysis techniques are still under development. Our laboratory is involved in this issue.

In addition to the exposure assessment, our research interest covers effects of volatile chemicals on the olfactory system and the brain. We are conducting inhalation exposure experiments using animals, and histochemically and behaviorally assessing the effects of such exposure. Our goal is to provide evidence to set an environmental standard.

3) Ergonomics for fatigue-related health disorders and stress-related diseases and improvement of labor productivity

(1) In recent years, the relationship between neck pain and use of smart phones has been a focus of attention. This is a hot topic especially in the era of the prevailing working from home in the COVID-19 pandemic. We are conducting research using originally developed apps to establish evidence of effective interventions.
(2) Use of endoscopies can cause musculoskeletal disorders in medical staffs such as doctors, nurses, and technical staffs who work in the gastrointestinal department because of their awkward posture forced during the

procedure. The problem gains increasing attention. We are doing biomechanical research to clarify effective ergonomic interventions to prevent such problems.

3. Publications (original articles) (41 in total)

1. Tamada H, Ebara T, Matsuki T, Kato S, Sato H, Ito Y, Saitoh S, Kamijima M, *Sugiura-Ogasawara M. Impact of ready-meal consumption during pregnancy on birth outcomes: The Japan Environment and Children's Study. ***Nutrients*** 2022; 14(4): 895
2. *Matsuki T, Ebara T, Tamada H, Kato S, Kaneko K, Kano H, Matsuzaki K, Sato H, Minato K, Sugiura-Ogasawara M, Saitoh S, Kamijima M, the Japan Environment and Children's Study (JECS) Group: Repeated maternal non-responsiveness to baby's crying during postpartum and infant neuropsychological development: The Japan environment and children's study. ***Child Abuse Neglect*** 2022; 105581
3. Yamada S, *Ebara T, Uehara T, Matsuki T, Kimura S, Satsukawa Y, Yoshihara A, Aoki K, Inada A, Kamijima M: Can hip-knee line angle distinguish the size of pelvic incidence? – Development of quick non-invasive assessment tool for pelvic incidence classification. ***Int J Environ Res Public Health*** 2022; 19(3):138
4. Kaneko K, *Ito Y, Ebara T, Kato S, Matsuki T, Tamada H, Sato H, Saitoh S, Sugiura-Ogasawara M, Yamazaki S, Ohya Y, Kishi R, Yaegashi N, Hashimoto K, Mori C, Ito S, Yamagata Z, Inadera H, Nakayama T, Iso H, Shima M, Kurozawa Y, Suganuma N, Kusuhara K, Katoh T, Kamijima M: Association of maternal total cholesterol with SGA or LGA birth at term: the Japan Environment and Children's Study. ***J Clin Endocrinol Metab*** 2022; 107(1): e118-e129
5. Wakayama T, *Ito Y, Miyake M, Nomasa K, Sakai K, Oya N, Sato H, Ohno H, *Kamijima M: Inhalation exposure to 2-ethyl-1-hexanol causes hepatomegaly and transient lipid accumulation without induction of peroxisome proliferator-activated receptor alpha in mice. ***Ind Health*** 2021; 59(6):383-392
6. *Suzumori N, Ebara T, Tamada H, Matsuki T, Sato H, Kato S, Saitoh S, Kamijima M, Sugiura-Ogasawara M, Japan Environment, Children's Study Group: Relationship between delivery with anesthesia and postpartum depression: The Japan Environment and Children's Study (JECS). ***BMC Pregnancy Childbirth*** 2021; 21(1): 522
7. Tsuchiyama T, *Ito Y, Oya N, Nomasa K, Sato H, Minato K, Kitamori K, Oshima S, Minematsu A, Niwa K, Katsuhara M, Fukatsu K, Miyazaki H, Ebara T, Kamijima M: Quantitative analysis of organophosphate pesticides and dialkylphosphates in duplicate diet samples to identify potential sources of measured urinary dialkylphosphates in Japanese women. ***Environ Pollut*** 2022; 298: 118799
8. Yamada Y, *Ebara T, Matsuki T, Kano H, Tamada H, Kato S, Sato H, Sugiura-Ogasawara M, Saitoh S, Kamijima M, On behalf of the Japan Environment and Children's Study (JECS) Group: Relationship between physical activity and physical and mental health status in pregnant women: A prospective cohort study of the Japan Environment and Children's Study. ***Int J Environ Res Public Health*** 2021; 18(21): 11373
9. Nomasa K, *Oya N, Ito Y, Terajima T, Nishino T, Mohanto NC, Sato H, Tomizawa M, *Kamijima M: Development of a strategic approach for comprehensive detection of organophosphate pesticide metabolites in urine: Extrapolation of cadusafos and prothiofos metabolomics data of mice to humans. ***J Occup Health*** 2021; 63(1): e12218
10. Sato H, Ito Y, Hanai C, Nishimura M, Ueyama J, *Kamijima M: Non-linear model analysis of the relationship between cholinesterase activity in rats exposed to 2, 2-dichlorovinyl dimethylphosphate (dichlorvos) and its metabolite concentrations in urine. ***Toxicology*** 2021; 450: 152679
11. Oya N, *Ito Y, Ebara T, Kato S, Ueyama J, Aoi A, Nomasa K, Sato H, Matsuki T, Sugiura-Ogasawara M, Saitoh S, *Kamijima M: Cumulative exposure assessment of neonicotinoids and an investigation into their intake-related factors in young children in Japan. ***Sci Total Environ*** 2021; 750: 141630

4. Review Articles and Books (15 in total)

1. Mohanto NC, *Ito Y, Kato S, Kamijima M: Life-time environmental chemical exposure and obesity: Review of epidemiological studies using human biomonitoring methods. ***Front Endocrinol (Lausanne)*** 2021; 12: 778737

Department of Biomedical Science FY2021

1. Laboratory members

Full-time Staff
- Mitsuharu Hattori (Professor)
- Takao Kohno (Associate Professor)
- Hitomi Tsuiji (Lecturer)

Graduate School Students
- Keisuke Ishii (PhD Course)
- Hugo Ango (Master's Course)
- Shintaro Oya (Master's Course)
- Yuta Umemura (Master's Course)

Undergraduate Students
- Nao Atsumi
- Hayataka Gotanda
- Mitsuki Hara
- Ikuma Nakagawa
- Yuto Takekoshi
- Takuto Matsuda
- Airi Taniguchi
- Muneyuki Kawase
- Shion Miyata
- Mone Sato
- Risa Ito
- Shu Tokunaga
- Haruki Matumura

2. Research to date

We study the molecular basis of brain formation and function. We expect that the results of our research will lead to the understanding and overcoming of neurodegenerative and psychiatric diseases in the future.

(1) Research on molecular mechanisms governing the formation of neuronal layer structure in the brain

In the brain, neurons with similar morphology and function form "layers" and their structural abnormality is associated with the onset of various neuronal diseases. Reelin is a secreted protein deficient in a mutant mouse strain *reeler* as well as in some human patients of lissencephaly. Reelin is essential for neuronal layer formation, but its specific function and the molecular mechanisms involved in its regulation are not fully understood. Recently, Reelin is thought to be involved in the onset and exacerbation of schizophrenia and Alzheimer's disease, and is attracting attention as a drug discovery target. We have been conducting research to increase the function of Reelin and have identified the protase that inactivates Reelin in the brain. Inhibitors of this enzyme may be potential new drugs for neuropsychiatric and neurodegenerative diseases.

(2) Elucidation of the physiological significance of lipid molecules and their dynamics in neurons

Neuronal cell membranes have a characteristic lipid composition that differs from other cell membranes. It is also known that abnormalities in lipid composition and lipid metabolism in the brain are responsible for the development of many neuropsychiatric disorders. However, little is known about lipid metabolism and its abnormalities in neurons at the molecular level. To understand the function of lipids in neurons and their regulatory mechanisms, we are conducting research using lipid-specific probes and genome editing techniques, and in collaboration with many other researchers.

3. Publications (original articles)

1. Nakao Y, Yokawa S, Kohno T, Suzuki T, *Hattori M: Visualization of Reelin secretion from primary cultured neurons by bioluminescence imaging. ***J. Biochem.*** (in press)
2. Tsuneura Y, Sawahata M, Itoh N, Miyajima R, Mori D, Kohno T, Hattori M, Sobue A, Nagai T, Mizoguchi H, Nabeshima T, Ozaki N, *Yamada K: Analysis of Reelin signaling and neurodevelopmental trajectory in primary cultured cortical neurons with *RELN* deletion identified in schizophrenia. ***Neurochem. Int.*** 144, 104954 (2021)
3. Nagae M, Suzuki K, Yasui N, Nogi T, Kohno T, Hattori M, *Takagi J: Structural studies of reelin N-terminal region provides insights into a unique structural arrangement and functional multimerization. ***J. Biochem.*** 169, 555-564 (2021)
4. Kohno T, Ishii K, Hirota Y, Honda T, Makino M, Kawasaki T, Nakajima K, *Hattori M: Reelin-Nrp1 interaction regulates neocortical dendrite development in a context-specific manner. ***J. Neurosci.*** 43, 8248 (2020)
5. Ogino H, Nakajima T, Hirota Y, Toriuchi K, Aoyama M, Nakajima K, *Hattori, M: The secreted glycoprotein Reelin suppresses the proliferation and regulates the distribution of oligodendrocyte progenitor cells in the embryonic neocortex. ***J. Neurosci.*** 40, 7625 (2020)
6. Ibi D, Nakasai G, Sawahata M, Kohno T, Takaba R, Nagai T, Hattori M, Nabeshima T, Yamada K, *Hiramatsu, M. Reelin supplementation into the hippocampus rescues abnormal behavior in a mouse model of neurodevelopmental disorder. ***Front. Cell. Neurosci.*** 14, 285 (2020)
7. Okugawa E, Ogino H, Shigenobu T, Yamakage Y, Tsuiji H, Oishi H, Kohno T, *Hattori, M: Physiological significance of proteolytic processing of Reelin revealed by cleavage-resistant Reelin knock-in mice. ***Sci. Rep.*** 10, 4471 (2020)
8. Yamakage Y, Kato M, Hongo A, Ogino H, Ishii K, Ishizuka T, Kamei T, Tsuiji H, Miyamoto T, Oishi H, Kohno T, *Hattori, M: A disintegrin and metalloproteinase with thrombospondin motifs 2 cleaves and inactivates Reelin in the postnatal cerebral cortex and hippocampus, but not in the cerebellum. ***Mol. Cell. Neurosci.*** 100, 103401 (2019)
9. *Hatanaka Y, Kawasaki T, Abe T, Shioi G, Kohno T, Hattori M, Sakakibara A, Kawaguchi Y, Hirata, T. Interactions between neuron and radial glia mediated by Semaphorin 6A-Plexin A2/A4 signaling regulates migration termination of superficial layer neurons of the cerebral cortex. ***iScience*** 21, 359 (2019)

4. Review Articles and Books

1. *Hattori M, Kohno, T: Regulation of Reelin function by proteolytic processing in the brain. ***J. Biochem.*** 169, 511-516 (2021)
2. Ogino H, Yamakage Y, Kohno T, *Hattori, M: Assay for Reelin-cleaving activity of ADAMTS and detection of Reelin and its fragments in brain. ***Methods Mol. Biol.*** 2043, 105 (2020)
3. Kohno T, Ogino H, *Hattori M: Expression and preparation of Reelin and ADAMTS-3 proteins. ***Methods Mol. Biol.*** 2043, 93 (2020)

Department of Molecular Biology
FY2021

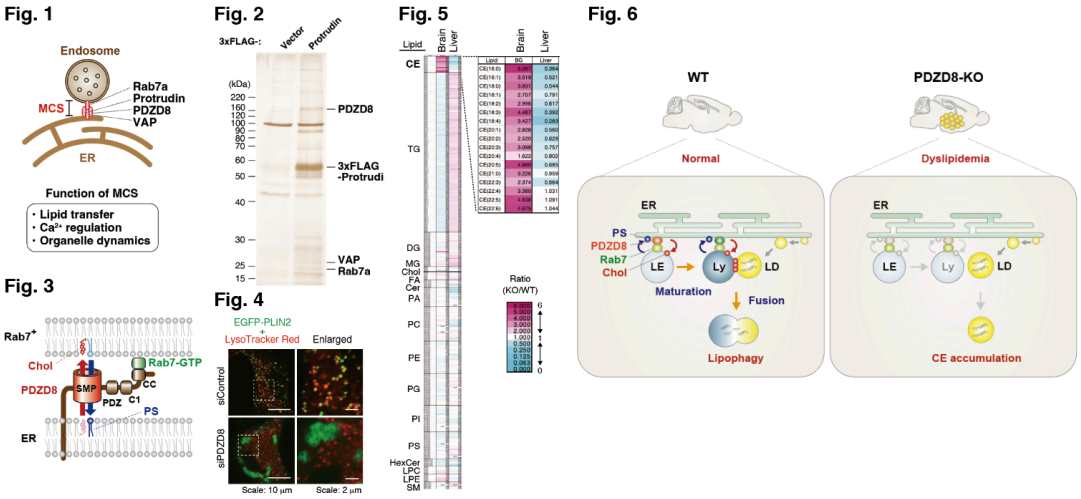
1. Laboratory members

Full-time Staff
- Michiko Shirane, (Professor)
- Hirokazu Nakatsumi (Associate Professor)
- Yuuji Kurihara (Assistant Professor)

Graduate School Students
- Keitaro Yamamoto (Master's Course)
- Hikari Kitano (Undergraduate)
- Kotone Mitsunari (Undergraduate)
- Haruki Ishimoto (Undergraduate)
- Nagi Mukae (Undergraduate)
- Yukino Ishiwata (Undergraduate)
- Wakana Okuda (Undergraduate)
- Yumi Morisugi (Undergraduate)
- Rie Watanabe (Undergraduate)
- Honoka Maki (Undergraduate)

2. Research to date

We are studying the "regulatory mechanisms of the nervous system via intracellular organelles". In particular, we focus on intracellular organelle contacts. Organelle contacts are intracellular microdomains in which different organelles are in close proximity to each other without membrane fusion, and are involved in the regulation of cell functions through intermembrane molecular exchange. We aim to elucidate the regulatory mechanism of brain functions by this organelle communication and the pathogenesis of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease caused by the disruption of organelle communication. Cholesterol abnormalities in the brain and increased inflammation mediated by microglia have been strongly implicated in these neurodegenerative diseases. Recently we have shown that organelle contacts are involved in the regulation of lipid metabolism in the brain and have also found that they are involved in the regulation of inflammation in the brain. Based on this organelle research, we are now focusing on elucidating the relevant mechanisms of neuroimmunity. We use diverse approaches, including biochemistry, cell biology, and mouse genetics, with the aim of comprehensive understanding from intracellular mechanisms to individual physiological functions.



3. Publications (original articles) (5 in total)

1. Morita, K, Wada, M, Nakatani, K, Matsumoto, Y, Hayashi, N, Yamahata, I, Mitsunari, K, Mukae, N, Takahashi, M, Izumi, Y, Bamba, T, and *Shirane, M. PDZD8-deficient mice accumulate cholesteryl esters in the brain as a result of impaired lipophagy. ***iScience***, 16;25(12):105612 (2022)
2. *Shirane, M. and Kamiguchi, H. Molecular machinery regulating organelle dynamics during axon growth and guidance. ***Semin Cell Dev Biol***, S1084-9521(22), 00058-1 (2022)
3. Arora A, Kivelä AM, Wang L, Minkeviciene R, Taskinen JH, Zhang B, Koponen A, Sun J, Shirane M, Zhou Y, Hotulainen P, Raiborg C, *Olkkonen VM. Protrudin regulates FAK activation, endothelial cell migration and angiogenesis. ***Cell Mol Life Sci***, 79(4):220 (2022)
4. *Shirane, M, Wada, M., Morita, K, Hayashi, N, Kunimatsu, R, Nakatsumi, H, Ohta, K, Tamura, Y, and Nakayama, KI. Protrudin and PDZD8 contribute to neuronal integrity by promoting lipid extraction required for endosome maturation. ***Nat Commun***, 11, 4576-4594 (2020)
5. *Shirane, M, Shoji, H, Hashimoto, Y, Katagiri, H, Kobayashi, S, Manabe, T, Miyakawa, T, and Nakayama, KI. Protrudin-deficient mice manifest depression-like behavior with abnormalities in activity, attention, and cued fear-conditioning. ***Mol Brain***, 13, 146-163 (2020)

4. Review Articles and Books (4 in total)

1. Shirane, M. *羊土社 論文図表を読む作法*, FRET, BiFC/SplitGFP (2022)
2. * Shirane, M., Interorganelle communication by protrudin complex and its neuronal function, ***Seikagaku***, 93, 4, 441-450 (2021)
3. *Shirane, M. Lipid Transfer–Dependent Endosome Maturation Mediated by Protrudin and PDZD8 in Neurons. ***Front Cell Dev Biol***, 8, 615600-615609 (2020)
4. *Shirane, M. Roles of protrudin at interorganelle membrane contact sites. ***Proc Jpn Acad Ser B***, 95, 312-320 (2019)

5. Other activities (8 in total)

1. Michiko Shirane, Mechanism of endosome maturation by lipid transport protein PDZD8. The 142nd Annual Meeting of the Pharmaceutical Society of Japan, Symposium, 2022. 3. 26 (Online)
2. Michiko Shirane, Inter-organelle membrane contact site complex and neuropsychiatric disorders. The 44th Annual Meeting of the Molecular Biology Society of Japan, Workshop, 2021.12.2 (Yokohama, Hybrid)
3. Michiko Shirane, Mechanisms of Neuronal Regulation by Endosomal Maturation via Lipid Transport. Grant-in-Aid for Scientific Research on Innovative Areas, Organell zone conference, 2022. 3. 15 (Tokyo, Hybrid)
4. Michiko Shirane, Relationship between endosomal maturation and brain function by lipid transfer protein complexes. Grant-in-Aid for Scientific Research on Innovative Areas, Organell zone conference, 2021. 6. 24 (Online)
5. Michiko Shirane, Lipid transfer-mediated endosome maturation and neurodegeneration. The

43th Annual Meeting of the Molecular Biology Society of Japan, 2020. 12. 3（Online）

6. Michiko Shirane, Endosome maturation via lipid transport in neural homeostasis. The 93th Annual Meeting of the Japanese Biochemical Society, 2020. 9. 14（Online）
7. Michiko Shirane, Mechanism of lipid transport-mediated endosome maturation and neural homeostasis. Grant-in-Aid for Scientific Research on Innovative Areas, Organell zone conference, 2020. 12. 23（Online）
8. Michiko Shirane, Formation of organelle zone by regulating membrane structure and its association with neuroaxonal degeneration. Grant-in-Aid for Scientific Research on Innovative Areas, Organell zone conference, 2020. 8. 26（Online）

Laboratory of Neural Circuit Function, Graduate School of Science
FY2021

1. Laboratory members

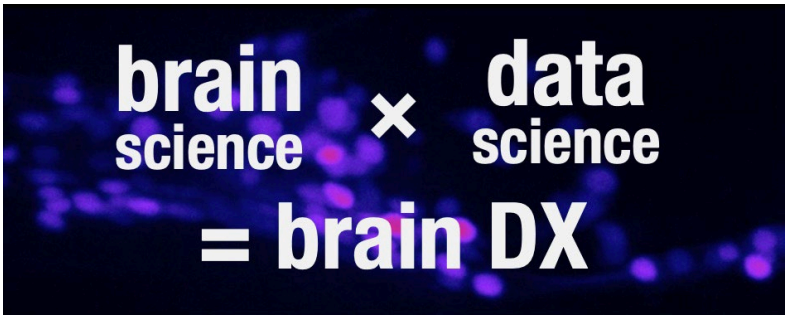
Full-time Staff
Kotaro Kimura (Professor)

Part-time Staff
Chentao Wen (Postdoc)
Miyu Miyachi (Technical Staff)

Graduate School Students
Yosuke Ikejiri (Doctor Course; Osaka Univ.)
Yuto Endo (Doctor Course; Osaka Univ.
Ling Fei Tee (Doctor Course)

2. Research to date

How do "brain functions"—such as perception, memory, emotion, and decision-making—arise from a network of nerve cells? To address this question, it is critical to rigorously quantify sensory stimuli, behavioral responses triggered by the stimuli, and neural activities in between, and to reveal the relationships among them. We study brain functions of roundworm *Caenorhabditis elegans* through measuring and analyzing multiple aspects of its sensory behavior with robot and machine learning technologies in collaborations with researchers in the fields. As a result of these studies, we have revealed "dopamine signaling for learning" and "mathematical differentiation and integration for decision making" in *C. elegans*. In 2021, we reported 3DeeCellTracker, the first deep learning technology to track 100-1000 cells in time-series 3D images (Wen et al., eLife), and an AI technology to extract characteristic behavioral features shared between dopamin-deficient humans and *C. elegans* (Maekawa et al., Nat Commun). In addition, our research activities have been recognized by Nature Index (a database of high-quality research and collaboration) and NHK-BS TV program"Humanience".



3. Publications (original articles) (5 in total)

1. Wen C, Kimura KD. Tracking moving cells in 3D time lapse images using 3DeeCellTracker. (2022) ***Bio-Protocol*** 12: e4319.
2. Maekawa T, Higashide D, Hara T, Matsumura K. Ide K, Miyatake T, Kimura KD, Takahashi T. Cross-species behavior analysis with attention-based domain-adversarial deep neural networks. (2021) ***Nature Communications*** 12: 5519.
3. Wen C, Miura T, Voleti V, Yamaguchi K, Tsutsumi M, Yamamoto K, Otomo K, Fujie Y, Teramoto T, Ishihara T, Aoki K, Nemoto T, Hillman E.M.C, Kimura KD. 3DeeCellTracker, a deep learning-based pipeline for segmenting and tracking cells in 3D time lapse images. (2021) ***eLife*** 10: e59187.
4. Tanimoto Y, Kimura KD. Calcium Imaging of Neuronal Activity under Gradually Changing Odor Stimulation in Caenorhabditis elegans. (2021) ***Bio-protocol*** 11: e3866.
5. Maekawa T, Ohara K, Zhang Y, Fukutomi M, Matsumoto S, Matsumura K, Shidara H, Yamazaki SJ, Fujisawa R, Ide K, Nagaya N, Yamazaki K, Koike S, Miyatake T, Kimura KD, Ogawa H, Takawashi S, Yoda K. Deep learning-assisted comparative analysis of animal trajectories with DeepHL. (2020) ***Nature Communications*** 11: 743-15.

4. Review Articles and Books (1 in total)

1. Wen C, Kimura KD. How do we know how the brain works?—Analyzing whole brain activities with classic mathematical and machine learning methods. (2020) ***Japanese Journal of Applied Physics***, 59:030501.

5. Presentations at Conferences, etc.（1 in total）

1. Wen C, Kimura K. 3DeeCellTracker: a deep learning-based method for tracking cells in 3D time lapse images. **The 15th IEEE International Conference on Nano/Molecular Medicine & Engineering (IEEE-NANOMED 2021)** (Oral presentation, Invited), online meeting, 2021 年 11 月 15 日

6. Other activities (2 in total)

1. **Nature Index**: "The challenge of leading interdisciplinary research projects" (https://www.natureindex.com/news-blog/challenge-of-leading-interdisciplinary-research-projects) (2021)
2. **Nature Index**: "Tracking cells with AI" (https://www. natureindex.com/article/10.7554/elife.59187#highlight) (2021)

Visual Information Processing Laboratory FY2021

1. Laboratory members

Full-time Staff
Sei-ichi Tsujimura (Professor)

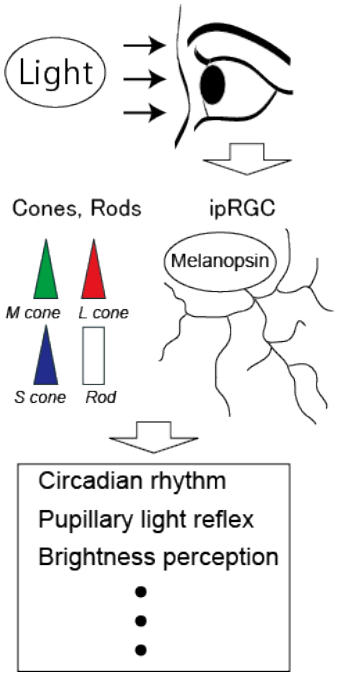
Part-time Staff
Chiho Onoue (Research asssitant)

Graduate School Students
Tomoe Ito (Master's Course)
Aoi Takasu (Master's Course)

2. Research to date

We are concerned with the relationship between sensory information processes such as color and brightness perception, and higher level of brain functions. Especially we focus on a function of intrinsically photosensitive retinal ganglion cell, (ipRGCs) which play an important role in encoding of ambient light in the brain. Our goal is to answer the question of how these functions work, how signals from the retina are integrated and how it is represented in the brain. We employ psychophysical and neurological methods in our research.

There are two types of photoreceptors (i.e. cones and rods) in the retina of our eye. These two photoreceptors were assumed to be the only photoreeptors in human. However, a third photoreceptor, the intrinsically photosensitive retinal ganglion cell (melanopsin cell) which includes melanopsin photopigment, has been discovered. The discovery of melanopsin cells has led to a fundamental review of non-image-forming pathways such as pupillary light reflecx and photoentrainment of circadian rhythm, and image-forming pathway associated with vision. Melanopsin cells are assumed to play an important role in encoding ambient light in the brain. Signals from melanopsin cells stimulated by ambient light, together with signals from the classical photoreceptor cells, contribute to the function of non-imaging and imaging pathways in the brain.



Our research group was the first in the world to discover that melanopsin cells contribute to the perception of brightness perception. Apart from entrainment of circadian rhythms, pupillary light reflex, and brightness perception, there may still be other functions of melanopsin cells. For example, they may also contribute to working memory, attention, mood and migraine pain. We are exploring these unknown functions

3. Publications (original articles) (2 in total) ※

1. Sung-En Chien, Yi-Chuan Chen, Akiko Matsumoto, Wakayo Yamashita, Kuaug-Tsu Shi, Sei-ichi Tsujimura, *Su-Ling Yeh, "The modulation of background color on perceiving audiovisual simultaneity" ***Vision Res.*** 172, 1-10 (2020).
2. DeLawyer, T., Tsujimura, S., and *Shinomori, K. "Relative contributions of melanopsin to brightness discrimination when hue and luminance also vary," ***J. Opt. Soc. Am. A*** 37, A81-A88 2020.

4. Review Articles and Books (1 in total)

1. Tsujimura, S., & Takahashi, Y. (2020). Melanopsin Contributions to Human Brightness Perception. In R. Shamey (Ed.), *Encyclopedia of Color Science and Technology* (pp. 1-8). Berlin, Heidelberg: Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-642-27851-8_422-1

5. Presentations at Conferences, etc. (5 in total)

1. S Tsujimura, "Contribution of melanopsin cells to brightness perception" "Friday Lunch Seminar", **CiNet**, 21Jan2022 Oral presentation, Invited
2. A. Takasu, S. Tsujimura, Achromatic contrast sensitivity varies depending on melanopsin stimulation of the background, 43rd **ECVP (European Conference on Visual Perception)**, online, 22-27Aug2021, 26Aug2021 Poster
3. T. Ito, S. Tsujimura, The effect of photoreceptor stimulations on steady-state pupil diameter, 43rd **ECVP (European Conference on Visual Perception)**, online, 22-27Aug2021, 26Aug2021 Poster
4. S.Tsujimura & K. Okajima, A weak melanopsin contribution to color perception, **the Asia Color Association Conference** 2019, Nagoya Oral presentation
5. S. Tsujimura, "Intrinsic phase delays between cone and melanopsin-mediated signals in the pupillary pathway" The Scientific Committee of the 33rd **International Pupil Colloquium**, Murcia, Spain, 02-04 October, 2019. 02Oct2019 Oral presentation

6. Other activities (0 in total)

Department of Neurocognitive Psychology
FY2021

1. Laboratory members and titles of thesis。

Full-time Staff

Atsuko Nakagawa (Professor)

Graduate School Students

Ayato Iida (Doctor's Course)

Mikiko Tachi (Master's Course): Conflicts between parents and children with foreign roots caused by children's adaptation of Japanese culture

Yuki Hikichi (Master's Course): Intervention for emotional regulation using breathing techniques for pre-school children

Undergraduate School Students

Rokuta Kuze: Examination of the psychological effects of remotely monitoring writing tasks

Kiho Futamura: A study of the information searching process in Japanese indecisiveness (yujufudan) through eye movement measurement

Marino Miwa: Effects of wearing sanitary masks on perceptions of eye size

Fumiya Nakamura: Examining the effects of diary writing on anticipated regret and risk-taking behavior

Kana Nakatogawa: Gaze holding in detection tests of deception: Focusing on lying skills and the sense of unwanted transparency

Kyoka Sato: Effects of physical movement in writing a character on evaluation of impression on that character

Taira Watanabe: Effects of imagining past and future episodic scenes on facial recognition

2. Research to date

In our laboratory, we conduct psychological experiments using behavioral measurements such as physiological indicators and reaction times to explore the mechanisms of the human mind in relation to brain functions. In this fiscal year, some themes selected for bachelor theses were affected by the Coronavirus crisis, such as whether the eyes look larger because the face is perceived as smaller as a result of wearing a sanitary mask, and how the monitoring of work conducted in remote mode affects work efficiency.

A longitudinal study of attention in infancy and toddler led by the Head Professor was conducted to explore how the development of attentional neural networks interact with functions such as cognition, motion, and emotion. Using questionnaires and tracking eye movements, we follow individual differences in attentional functions within the framework of temperament as observed in newborn babies. In this fiscal year, we summarized a longitudinal study from 6 months to 24 months of age and replicated the finding that the orienting attentional network (or the localization function for sensory events) plays a key role in emotional regulation during infancy. Our results also suggest that infants who find it difficult to disengage to the left visual field are less likely to be soothed.

In addition, we published "Mindfulness for Adult ADHD" translated by graduate students. Mindfulness consists of training for awareness in the moment and is also used for the treatment of depression and anxiety. Through this training, which aims to improve attentional function, the brain is altered and attention improves. There are also reports of improved control of emotions. In our laboratory, with the cooperation of infants and their families, we continue to study the typical development of attention. We believe that mindfulness, a clinical technique for gaining

metacognitive awareness, can be supported by the attentional function nurtured from infancy.

3. Publications (original articles) (2 in total)

1. *Ishikawa-Omori, Y., Nishimura, T., Nakagawa, A., Okumura, A., Harada, T., Nakayasu, C., Iwabuchi, T., Amma, Y., Suzuki, H., Rahman, M. S., Nakahara, R., Takahashi, N., Nomura, Y., & Tsuchiya, K. J. (2022). Early temperament as a predictor of language skills at 40 months. ***BMC pediatrics*****,** *22*(1), 56.
2. *Ogasawara,K., & Nakagawa, A. (2021) The effect of rejection avoidance need on cognitive failure during speech: Focusing on psychological tension and heart rate during failure recognition. ***Japanese Journal of Research on Emotions*** 28, 67─72

4. Book of Transration (1 in total)

1. LidiaZylowska, *the Mindfulness Prescription for Adult ADHD: An Eight-Step Program for strengthening Attention,Managing Emotions, and Achiving Your Goals* (translated by Ohno, Y., Nakano, Y, Nakagawa, A., Kongo Shuppan, December, 2021)

5. Presentations at Conferences, etc.（7 in total）

1. Miyachi, T., Nakagawa, A., Matuski, T., Nakai, A. Temperament of Developmental Cooedination Disorder **The 19th Tokai Hokuriku Regional Meeting of the Japanese Society of Psychosomatic Pediatrics Japan**
2. Nakagawa, A Symposium organizer and topic provision "Emotions surrounding babies; Be babies soothable " **The 10th Japan Emotionology Society**, December,2021
3. *Nakagawa, A., Sukigara, M., Kimura, K. Emotion regulation and Attentional Asymmetry: **The 45th Japan Society for Higher Brain Dysfunction**, November, 2021
4. *Nakagawa, A., Sukigara, M, Yamamoto, H. The effect of the phasic alertness during attentional disengagement in infancy **The 85th Annual Convention of the Japanese Psychological Association** September, 2021
5. Iida,A., Nakagawa, A. The effects of Attentiom ytaining on Mindwondering and metacognition **The 85th Annual Convention of the Japanese Psychological Association** September, 2021
6. Yamanaka, R., Kubota, K., Amaya, Y., Ito, A., Ogawa, S., Tsuboi, H., Nakagawa, A., Yamamoto, T. Research for fostering intercultural receptive attitudes in graduate students to be human service providers **The 85th Annual Convention of the Japanese Psychological Association** September, 2021
7. *Nakagawa,A.,Miyachi,T., Matsuki, T., Tomida, M. Temperament and its relationship to motor development: A 6-42-month longitudinal study **SRCD 2021Biennial Meeting**, 2021 年 4 月

V. Other activity reports

・Opening ceremony of IBS

To commemorate the opening of the Institute of Brain Science, a commemorative lecture titled "Toward the Next 30 Years" - New Challenges - was held on July 17, 2019. The Mayor of Nagoya City, the Chancellor of Nagoya City University, and other executive advisors were present and gave congratulatory speeches.

・The 1st IBS Retreat

The first IBS Retreat was held on March 31, 2022. Due to the corona disaster, we avoided holding the retreat in an external training center, etc., and held it in a space on campus with ventilation and other corona countermeasures. All faculty, students, and technical staffs gave their poster presentations, including the achievements since the IBS was established in 2019. Presentations were also given by collaborative laboratories, leading to a very lively discussion. It was an great opportunity to satisfy the spirit of intellectual inquiry that had been suppressed by the Corona Disaster and to begin new collaborative research.