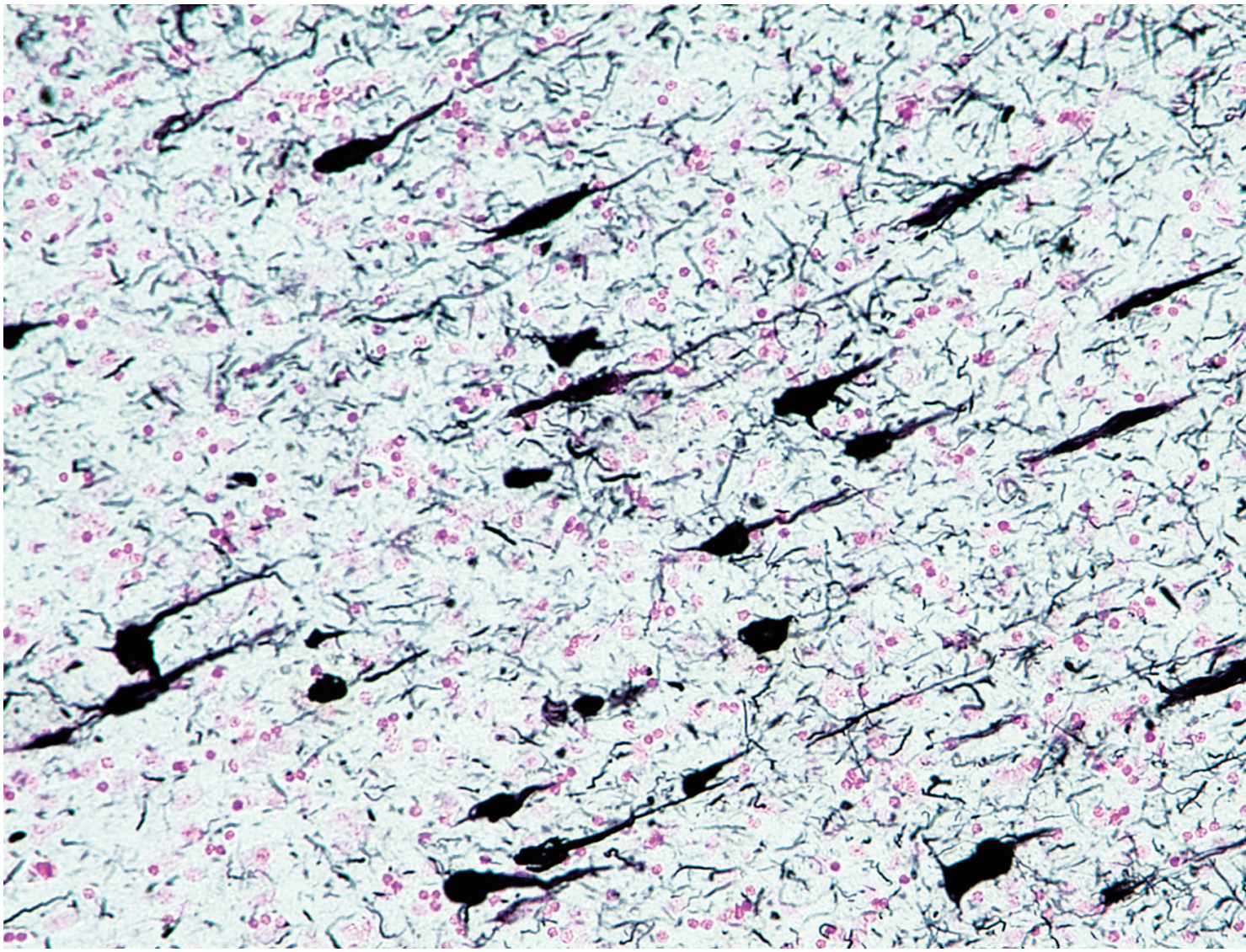
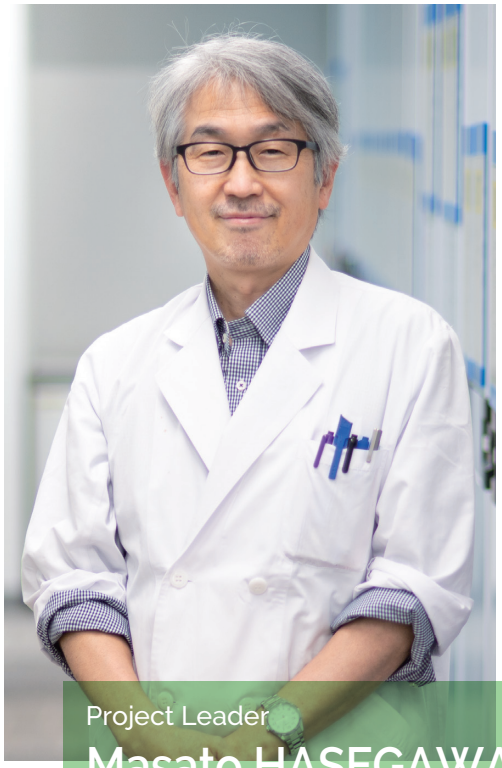


Neurofibrillary changes in Alzheimer's disease brain.
Black, tau aggregates stained by Gallyas-Braak staining; pink, nuclei.

Brain & Neurosciences



Project Leader
Masato HASEGAWA

Masato Hasegawa, the Head of Department of Brain and Neurosciences, studies the molecular pathogenesis and progression of neurodegenerative diseases. He started working on Alzheimer's disease at Yasuo Ihara's lab in 1988 where he identified phosphorylation and ubiquitination sites in tau. In 1995, he joined Michel Goedert's lab at MRC LMB where he and others demonstrated that alpha-synuclein is the major component of filamentous inclusions in Parkinson's disease and dementia with Lewy bodies. He next joined Takeshi Iwatsubo's group in 1999 where he identified phosphorylation and ubiquitination of alpha-synuclein. In 2006, while at the Tokyo Metropolitan Institute of Psychiatry, he collaborated with Tetsuaki Arai and found that phosphorylated TDP-43 accumulates in frontotemporal dementias and amyotrophic lateral sclerosis. More recently, he has been studying the prion-like spread of neurodegenerative disease-associated proteins.

Dementia Research

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

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Sei IMURA
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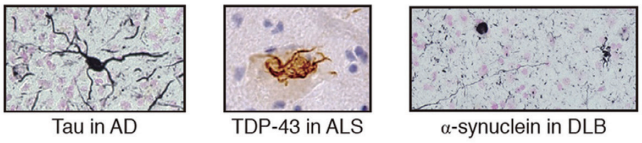
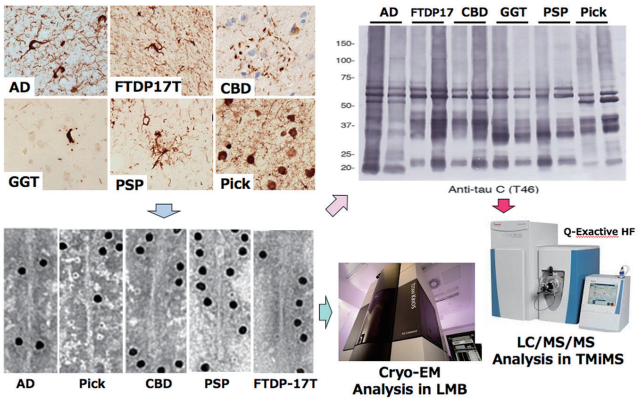
Mina TAKASE

Research Summary

Many neurodegenerative diseases are associated with intracellular amyloid-like protein pathologies, such as tau in Alzheimer's disease (AD), α-synuclein in dementia with Lewy bodies (DLB) and TDP-43 in amyotrophic lateral sclerosis (ALS) and frontotemporal dementias (FTD). Importantly, the distribution and spread of these proteins closely correlates with clinical presentation and disease progression.



We have been investigating these intracellular pathological proteins prepared in these diseases, immuno-histochemically, ultrastructurally, and biochemically using liquid chromatography with tandem mass spectrometry (LC/MS/MS).



In collaboration with Michel Goedert and Sjors Scheres in LMB and the Japan brain bank network (JBBN), we determined the structures of pathological tau and alpha-synuclein filaments from brains of patients with corticobasal degeneration (CBD) and multiple system atrophy. We further identified numerous post-translational modifications in these filamentous assemblies. We demonstrated that injection of aggregate recombinant tau filaments into wild-type mice seeded the aggregation of endogenous murine tau, leading to the spread of aggregates into distinct brain areas. In addition, we generated two different types of alpha--synuclein fibrils from identical wild-type alpha--synuclein monomers under different conditions and showed that these fibrils have different prion-like ablilities to convert endogenous soluble alpha--synuclein monomers into amyloid-like fibrils.

Selected Publications

Zhang W, et al. Novel tau filament fold in corticobasal degeneration. ***Nature*** 2020 Apr;580(7802):283-287.

Masuda-Suzukake M, et al. Dextran sulphate-induced tau assemblies cause endogenous tau aggregation and propagation in wild-type mice. ***Brain Communications*** 2020 Jul 8;2(2):fcaa091.

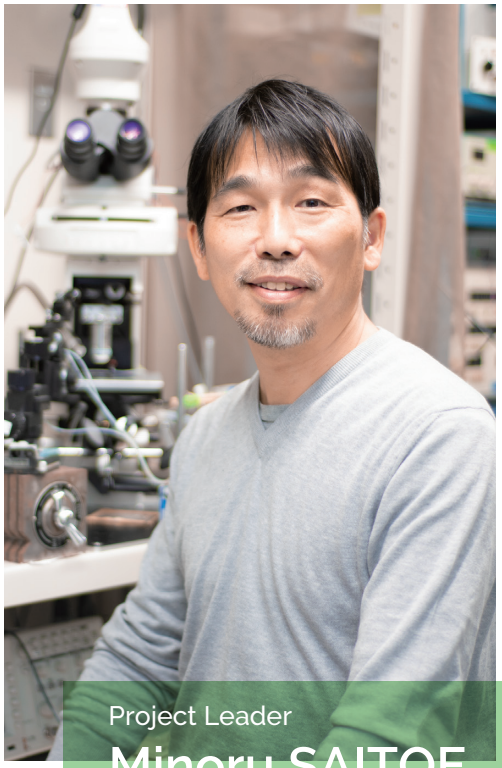
Suzuki G, et al. α-Synuclein strains that cause distinct pathologies differentially inhibit proteasome. ***eLife.*** 2020 Jul 22;9:e56825.

Schweighauser M, et al. Structures of α-synuclein filaments from multiple system atrophy. ***Nature*** 2020 Sep; 585(7825):464-469 .

Watanabe R, et al. Intracellular dynamics of Ataxin-2 in the human brains with normal and frontotemporal lobar degeneration with TDP-43 inclusions. ***Acta Neuropathol Commun*** 2020 Oct 28;8(1):176.

Kametani F, et al. Comparison of common and disease-specific post-translational modifications of pathological tau associated with a wide range of tauopathies. ***Front Neurosci 2020,*** 581936.

Hasegawa M. Experimental models of prion-like protein propagation. ***Neuropathology.*** 2020 Jun 1.



Project Leader
Minoru SAITOE

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

Learning and Memory

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

Staff

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Tomoyuki MIYASHITA
Motomi MATSUNO
Shintaro NAGANOS
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Postdoctoral fellows
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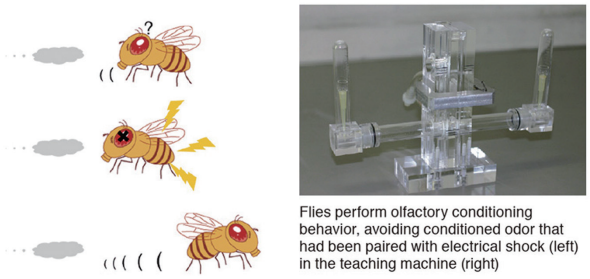
Saki KOMIYA
Tomoko TAKAMISAWA

Students
Nozomi UEMURA

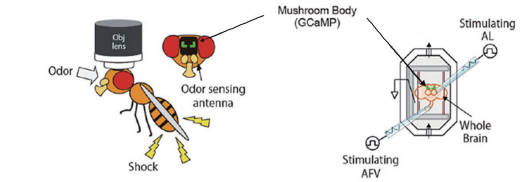
Research Summary

Memories define us and mold our personalities. Using genetic tools, we have identified genes and neural substrates required for memory-associated behaviors in Drosophila. We investigate when, where and how memory-associated gene products function to produce memory-based behaviors and how memory mechanisms are affected by physiological changes such as aging.

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



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



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

Selected Publications

Ueno K et al. (2020). Carbon monoxide, a retrograde messenger generated in post-synaptic mushroom body neurons evokes non-canonical dopamine release. ***J Neurosci.*** 40, 3533-3548.

Ueno K, et al. (2017) Coincident postsynaptic activity gates presynaptic dopamine release to induce plasticity in Drosophila mushroom bodies. ***eLife,*** 6: e21076.

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

Matsuno M, et al. (2015) "Long-term memory formation in Drosophila requires training-dependent glial transcription." ***J. Neurosci.*** 35: 5557-5565.

Yamazaki D, et al. (2014) "Glial dysfunction causes age-related memory impairment in Drosophila." ***Neuron*** 84: 753-763.

Hirano Y, et al. (2013) "Fasting Launches CRTC to Facilitate Long-term Memory Formation in Drosophila." ***Science*** 339: 443-446.

Miyashita T, et al. (2012) "Mg2+ block of Drosophila NMDA receptors is required for long-term memory formation and CREB-dependent gene expression." ***Neuron*** 74: 887-898.

Project Leader
Yukio NISHIMURA

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

Neural Prosthetics

Laboratory HP: https://www.igakuken.or.jp/english/project/detail/neuroprosth1.html
https://www.igakuken.or.jp/neuroprosth/

Staff

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Tomomi GOTO

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Kei OBARA
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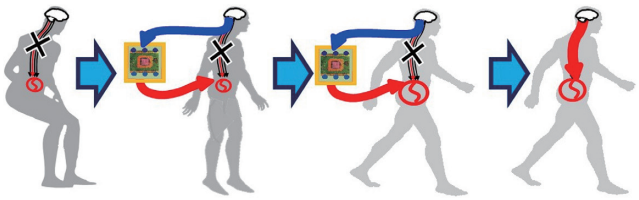
Kouichi UAMARU

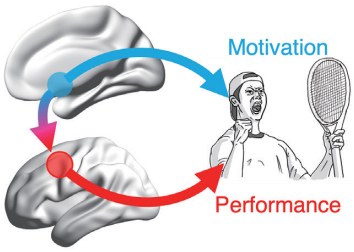
Research Summary

Our goal is to conceive of innovative ideas for neuro-rehabilitation of lost functions after nervous system damage, and to translate these ideas into clinical applications capable of improving the quality of life for individuals with neural damage.

Specifically, we are developing a neural interface known as an "artificial neuronal connection (ANC)". This ANC bridges spinal lesions by connecting supra-spinal systems with spinal networks distal to the lesion to restore lost functions. We are conducting clinical trials to assess the effectiveness of ANCs in restoring motor function in paralyzed patients. We are also investigating neural changes that occur during recovery.

Depression impedes, and motivation enhances, functional recovery after neuronal damage. Although higher motivation seems to boost motor performance and recovery, neural substrates underlying this psychological effect remains unknown. We are identifying these neuronal substrates using humans and animal models.





Selected Publications

Kato K, et al. (2019) "Bypassing stroke-damaged neural pathways via a neural interface induces targeted cortical adaptation." ***Nature Communications.*** 10(1):4699.

Umeda, et al., (2019) "The somatosensory cortex receives information about motor output." ***Science Advances***., 5(7):eaaw5388.

Sawada M, et al. (2015) "Function of the nucleus accumbens in motor control during recovery after spinal cord injury." ***Science*** 350(6256):98-101.

Nishimura Y, et al. (2013) "Spike-timing-dependent plasticity in primate corticospinal connections induced during free behavior." ***Neuron*** 80(5):1301-1309.

Nishimura Y, et al. (2009) "A subcortical oscillatory network contributes to recovery of hand dexterity after spinal cord injury." ***Brain*** 132(Pt 3):709-721

Nishimura Y, et al. (2007) "Time-dependent central compensatory mechanisms of finger dexterity after spinal cord injury." ***Science***. 318(5853):1150-1155

Project Leader
Hiroshi SAKUMA

Hiroshi Sakuma has been the leader of the Child Brain Project since 2015. He obtained his MD (1993) and PhD (2005) degrees from Tokyo Medical and Dental University and trained in pediatric neurology at the National Center of Neurology and Psychiatry. He then studied neuroimmunology at the National Institute of Neuroscience with Prof. Sachiko Miyake in 2010, and has been involved in Health Labour Sciences Research on virus-associated acute encephalopathy since 2010. He has been working at the Tokyo Metropolitan Institute of Medical Science since 2012. His current interests include 1) mechanisms of virus-associated acute encephalopathies including febrile infection-related epilepsy syndrome, 2) biomarkers for pediatric immune-mediated neurological diseases, and 3) generating an international consensus on pediatric autoimmune neurological diseases.

Child Brain

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

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Naoyuki TANUMA
Masaharu HAYASHI

Research Assistants
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Students
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Hiroya NISHIDA
Kengo MORIYAMA
Motoshi FUJITA
Rie NAKAI
Takayuki MORI

Research Summary

Our research focuses on childhood autoimmune and inflammatory neurological diseases (AINDs). These diseases are a significant social burden because of poor prognosis and high mortality. We have created a multicenter registry of patients and sample repository for AINDs, based on nationwide collaborations, which we are using for cohort studies. We perform multi-omics analyses of biomarkers including inflammatory mediators, microRNAs, and metabolites. This multifaceted approach using high-throughput methods enables us to explore novel molecular targets associated with AINDs.
Recent studies have highlighted the importance of glial cells in the pathogenesis of AINDs. We have developed transgenic animal models to determine how glial cells contribute to pathomechanisms of AINDs by regulating brain metabolism and inflammation. These studies will help us develop novel therapeutic strategies.

Our main research areas include:
1. Pathomechanisms of virus-associated acute encephalopathies
2. The role of inflammation in febrile infection-related epilepsy syndrome
3. Autoimmune encephalitis and acquired demyelinating syndromes
4. Autoantibodies associated with neurological diseases
5. New biomarkers for pediatric immune-mediated neurological diseases

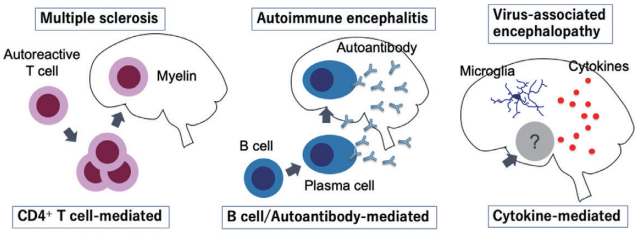


Figure Pathomechanisms of inflammatory and autoimmune neurological diseases
Multiple sclerosis has been regarded as a CD4 T-cell mediated disease in which autoreactive T cells are activated, proliferate, migrate to the brain, and cause myelin damage. Autoimmune encephalitis is caused by autoantibodies against neuronal surface antigens, produced by plasma cells in both the periphery and the central nervous system. Although the pathogenesis of virus-associated encephalopathy has not been fully elucidated, pro-inflammatory cytokines and chemokines are highly increased in biofluids, suggesting cytokine-mediated mechanisms.

Selected Publications

Horino A, et al. (2021) "Intrathecal dexamethasone therapy for febrile infection-related epilepsy syndrome." ***Ann. Clin. Transl. Neurol.*** In press.

Mizuguchi M, et al. (2020) "Guidelines for the diagnosis and treatment of acute encephalopathy in childhood." ***Brain Dev***. In press.

Suzuki T, et al. (2020) "Extracellular ADP augments microglial inflammasome and NF-κB activation via the P2Y12 receptor." ***Eur. J. Immunol.*** 50:205-219.

Igarashi A, "et al. (2018) "Cytokine-induced differentiation of hematopoietic cells into microglia-like cells in vitro." ***Clin. Exp. Neuroimmunol.*** 9:139-149.

Saika R, et al. (2017) "MicroRNA-101a regulates microglial morphology and inflammation." ***J. Neuroinflammation*** 14:109

Nakahara E, et al. (2015) "A diagnostic approach for identifying anti-neuronal antibodies in children with suspected autoimmune encephalitis." ***J. Neuroimmunol.*** 285:150-155.

Sakuma H, et al. (2015) "Intrathecal overproduction of proinflammatory cytokines and chemokines in febrile infection-related refractory status epilepticus." ***J. Neurol. Neurosurg. Psychiatr***. 86:820-822

Project Leader
Takashi SHICHITA

Takashi SHICHITA has been the project leader of the Stroke Renaissance Project since 2017. After graduating from the Faculty of Medicine, Kyushu University in 2004, he practiced internal medicine and was affiliated with the Cerebrovascular Center, Kyushu Medical Center. He conducted research at Kyushu University and Keio University and received a Ph.D in 2010 from Kyushu University for clarifying molecular and cellular mechanisms underlying inflammation after ischemic stroke. His current interest is to clarify the precise molecular mechanisms for the neural repair in brains damaged by stroke and dementia. His group will develop therapeutic methods which sustain the reconstruction of neural circuits for accelerated recovery from stroke and dementia.

Stroke Renaissance

Laboratory HP: https://www.igakuken.or.jp/stroke-renaiss/

Staff

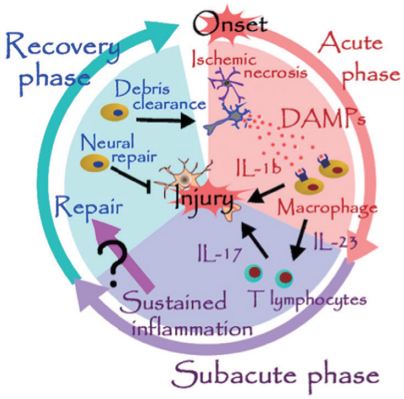
Researchers	Research Assistants	Students
Seiichiro SAKAI	Yoshiko YOGIASHI	Koutaro NAKAMURA
Jun TSUYAMA	Kumiko KURABAYASHI	Akari NAKAMURA
		Kento OTANI

Research Summary

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

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

Sterile Inflammation After Ischemic Stroke



"What triggers neural repair after stroke?"

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

Selected Publications

Tsuyama J, et al. (2018) "Pivotal role of innate myeloid cells in cerebral post-ischemic sterile inflammation." ***Semin. Immunopathol.*** 40(6): 523-538.

Shichita T, et al. (2017) "Mafb prevents excess inflammation after ischemic stroke by accelerating clearance of danger signals through MSR1." ***Nat. Med.*** 23(6): 723-732.

Shichita T, et al. (2012) "Peroxiredoxin family proteins are key initiators of post-ischemic inflammation in the brain." ***Nat. Med.*** 18(6): 911-917.

Shichita T, et al. (2009) "Pivotal role of cerebral interleukin-17-producing gammadelta T cells in the delayed phase of ischemic brain injury." ***Nat. Med.*** 15(8):946-950.

Project Leader
Chiaki Ohtaka-MARUYAMA

Chiaki Ohtaka-Maruyama obtained her Ph.D. in Biology from the University of Tokyo. After postdoctoral training at NEI, NIH (Bethesda, MD, USA) and RIKEN (Wako), she became a Research Scientist at the Tokyo Metropolitan Institute for Neuroscience in 2006. She studies neural development and has been the project leader of the Developmental Neuroscience Project since 2019. Her research focuses on understanding the molecular and cellular mechanisms of cortical development and evolution. In particular, she is interested in how the mammalian six-layer cortical structure developed during evolution. Using time-lapse imaging and functional analyses, she found novel functions of subplate neurons in regulating radial neuronal migration.

Developmental Neuroscience

Laboratory HP: https://www.igakuken.or.jp/stroke-renaiss/

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Yoshiko TAKAHSAHI
Kaori MIURA

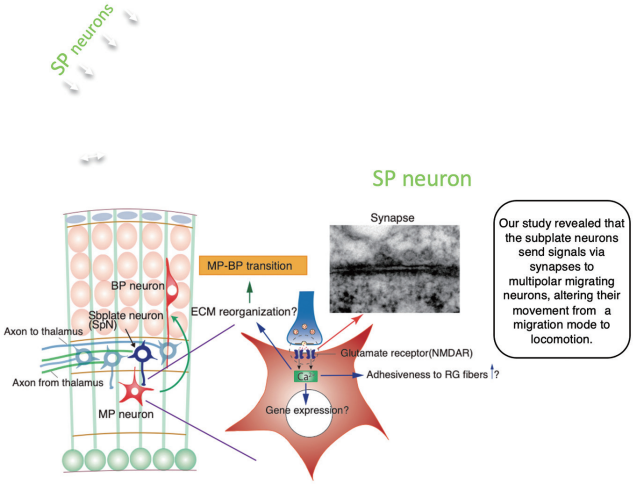
Students
Hitomi ACHIWA
Kyosuke WADA
Xiang SONG
Saki ONODERA
Mayu OZAKI

Research Summary

Mechanisms of Neural Network Formation: Neocortical development and synapse formation

How does the mammalian neocortex acquire the unique six-layered structure that is thought to be the structural basis for the remarkable evolution of complex neural circuits? We focus on subplate (SP) neurons that develop extremely early during cortical development and disappear postnatally. Recently, we found that SP neurons interact directly with young migrating neurons and play an essential role in radial neuronal migration. Moreover, the SP layer is surrounded by a rich extracellular matrix (ECM), suggesting that it may be an important signaling center for mammalian corticogenesis. Functional studies of the SP layer should lead to a better understanding of brain development during evolution.

"We are interested in the roles of the subplate layer in the development of the cerebral cortex. Subplate neurons are a transient cell population that plays a crucial role as a "control tower" during neocortical formation and also exerts effects on adult cortical function."



Selected Publications

Ohtaka-Maruyama C (2020) "Subplate neurons as an organizer of mammalian neocortical development. "***Front. Neuroanat.*** 14, 8.

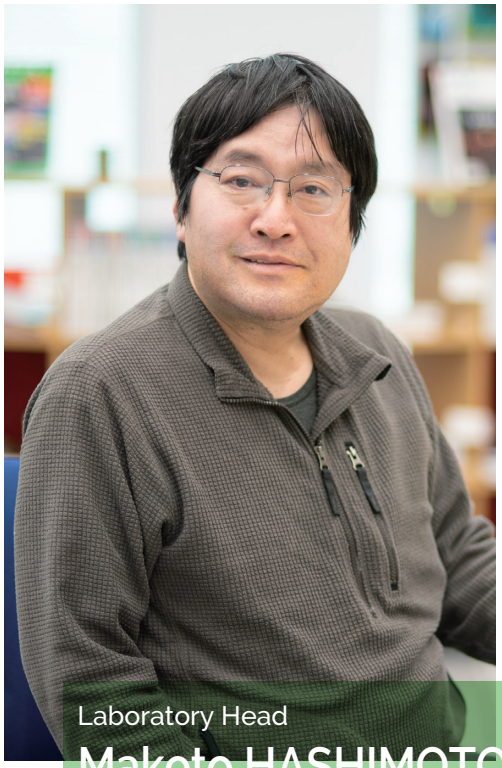
Nomura T, et al. (2020) "Changes in Wnt-dependent neuronal morphology underlie the anatomical diversification of neocortical homologs in amniotes." ***Cell Reports, 31***,107592.

Kamimura K et al. (2019) "The HSPG Glypican Regulates Experience-Dependent Synaptic and Behavioral Plasticity by Modulating the Non-Canonical BMP Pathway." ***Cell Reports, 28***, 3144-3156.

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

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

Kamimura, K, et al. (2013) "Perlecan regulates bidirectional Wnt signaling at the Drosophila neuromuscular junction." ***J Cell Biol.*** 200, 219-233.



Laboratory Head

Makoto HASHIMOTO

Makoto Hashimoto has been the head of the Laboratory of Parkinson's Disease since 2011. He obtained his MD from the University of Tokyo School of Medicine in 1986, after which he worked at the University of Tokyo Hospital until 1988. In 1992 he graduated from the Graduate School of Medicine at the University of Tokyo with a PhD in Biochemistry. He then worked as a research associate at the Salk Institute from 1992 to 1995 and as a postdoctoral fellow in the Dept of Neurosciences at the University of California, San Diego from 1995 to 2000. From 2004 to 2011 he worked as a deputy councilor researcher at the Tokyo Metropolitan Institute for Neuroscience before joining the staff at TMIMS.

Parkinson's Disease

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

Staff

Researchers
Yoshiki TAKAMATSU

Research Assistants
Ryoko WADA

Research Summary

Our goal is to develop effective disease-modifying therapies for age-associated neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD).

1. Despite extensive investigation, the physiological functions of amyloidogenic proteins (APs) associated with neurodegenerative diseases, including amyloid β for AD and α-synuclein for PD, are currently unclear. We recently proposed that APs may protect the brain from multiple stressors through a heritable proteinaceous adaptation mechanism we call evolvability (Fig.1) (Hashimoto M, et al. J. Alzheimers Dis. 2018, J. Parkinsons Dis. 2018). Further studies of evolvability should contribute to the development of novel therapy strategies for neurodegenerative diseases.

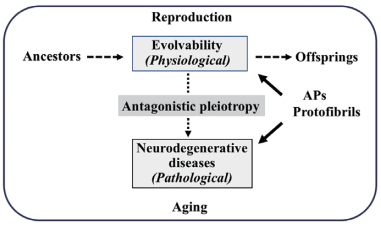


Fig 1. Evolvability and neurodegenerative disease: antagonistic pleiotropy of AP protofibrils

2. We are also identifying small molecules that could be useful for the prevention of neurodegenerative diseases using *Drosophila* molecular genetics (Fig. 2), cell biology, and transgenic mice studies. Molecules identified in our study may also be applicable to other diseases, including AD and Huntington's disease.

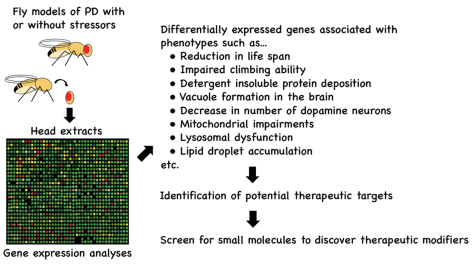


Fig. 2 *Drosophila* molecular genetics

Selected Publications

Takamatsu Y, et al. (2020) "Adiponectin Paradox as a therapeutic target of the cancer evolvability in aging. " ***Neoplasia.*** in press

Hashimoto M, et al. (2020) "Understanding Creutzfeldt-Jacob Disease from a Viewpoint of Evolvability". ***Prion.*** 14(1):1-8.

Ho G, et al. (2020) "Connecting Alzheimer's Disease with Diabetes Mellitus through Amyloidogenic Evolvability ***Front Aging Neurosci.***12:576192.

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