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

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

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

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

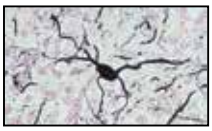
Shimonaka S, Nonaka T, Suzuki G, Hisanaga S, and Hasegawa M. (2016) "Templated Aggregation of TAR DNA-binding Protein of 43 kDa (TDP-43) by Seeding with TDP-43 Peptide Fibrils." ***J. Biol. Chem.*** 291:8896-8907.

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

Project Leader **Masato Hasegawa** Dementia Research Project

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

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



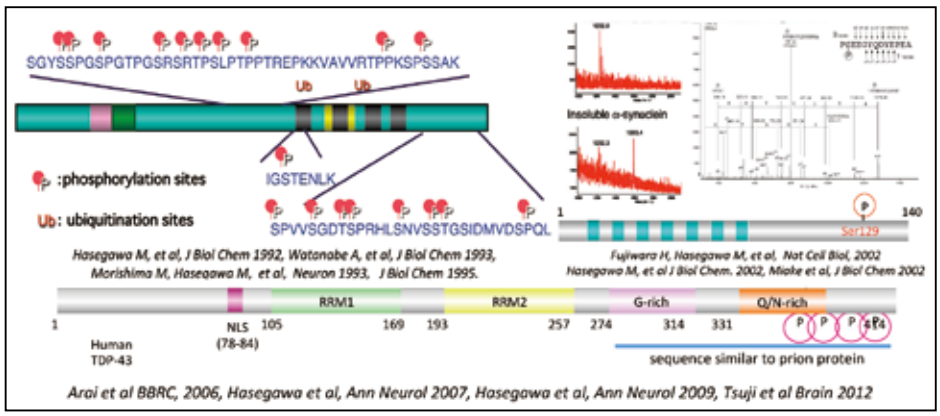
Tau in AD

TDP-43 in ALS

α-synuclein in DLB

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

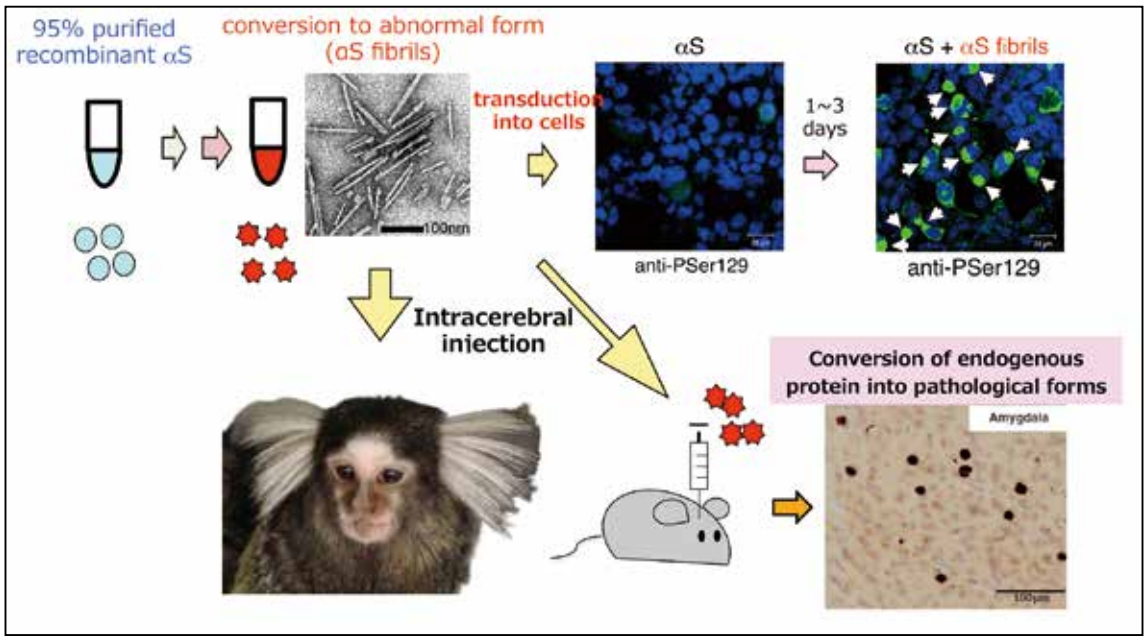
We have been investigating these intracellular abnormal proteins in brains of patients, biochemically using LC/MS/MS, immuno-histochemically with specific antibodies and ultrastructurally. And we found that all of these proteins accumulate in brains of patients as fibrous or filamentous forms in hyperphosphorylated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



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

Dementia Research

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



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

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

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

Senior Research Scientist **Takashi Nonaka**

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

I am studying molecular mechanisms of cell-to-cell propagation of aggregated proteins (tau, α-synuclein and TDP-43) in neurodegenerative diseases. I am also trying to make in vitro and in vivo models recapitulating abnormal features found in cells of brains of patients using cultured cells and mice. These models will contribute to a better understanding of the mechanisms involved in these diseases, and also to the development of novel therapeutic strategies.

Dementia Research

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

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

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

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

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

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

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

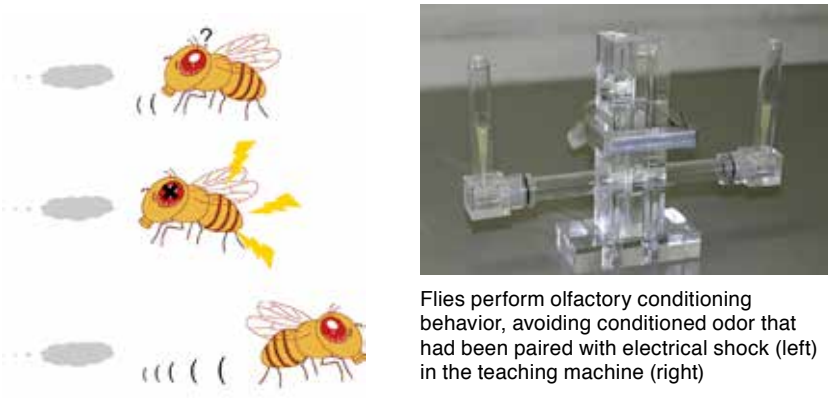
Tamura T, Chiang AS, Ito N, Liu HP, Horiuchi J, Tully T, and Saitoe M. (2003) "Aging specifically impairs amnesiac-dependent memory in Drosophila." ***Neuron*** 40: 1003-1011.

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

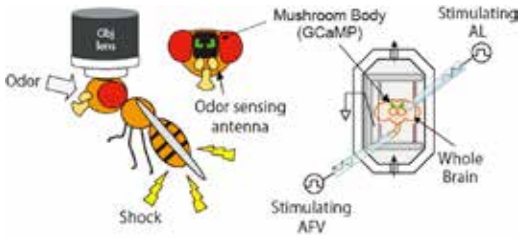
Investigating the Molecular Mechanisms that Generate Memory-encoding Neural Networks

Memories mold our personalities to make us who we are: Using powerful genetic tools, a number of genes and neural substrates underlying memory-associated behaviors have been identified in Drosophila. We have investigated when, where and how identified memory-associated gene products function to produce memory-based behavior, and how the underlying mechanism changes in response to changes in physical conditions such as aging.
In addition to behavioral genetic approaches, we employ in vivo and ex vivo imaging techniques to characterize physiological properties of memory-associated neural networks, and understand how memory-associated genes and neuromodulatory systems regulate function of these networks: how sensory information is associated, and how memory information is stored in neural substrates, and later recalled.

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



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

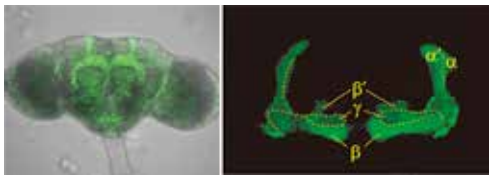


Left, schematic diagram of our in vivo imaging set-up. A living fly is fixed under a microscope and can be exposed to both odors and electrical shocks. Neuronal activity can be observed during formation, storage, and retrieval of odor-shock associative memories.Right, in our ex vivo imaging set-up, we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

Learning and Memory

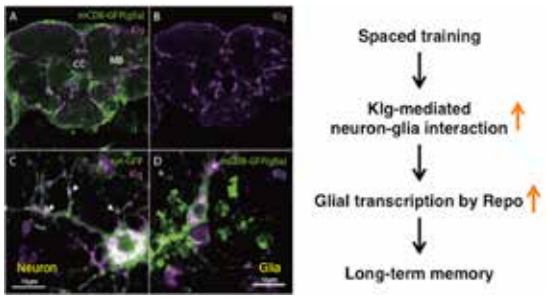
Current Research Topics

Encoding and decoding memory: In Drosophila, formation, storage, and recall of odor memories require activity in a brain region known as the mushroom bodies (MBs). There are various subsets of MB neurons including alpha/beta, alpha prime/beta prime, and gamma neurons. Similarly, there are various different phases of memory including initial learning, short-term memories, middle-term memories, anesthesia resistant memories, and long-term memories. Interestingly, different phases of memory require activity of different subsets of MB neurons. We are studying how anatomical shifting of memory phases occurs and how information is moved between different MB subtypes during different phases of memory.



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

Neuron-glia interactions: Communication between neurons and glia are important for memory formation. We have identified a cell adhesion molecule, Klingon (Klg) that is expressed in both neurons and glia and is required for memory-associated communication between these cell types. Currently we are studying how Klg signaling is required for memory formation, stabilization and retrieval. We are also studying how Klg signaling is altered upon aging.

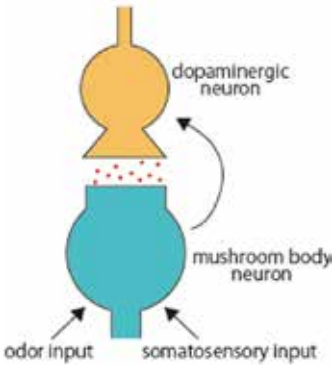


Klingon mediates neuron-glia interaction for LTM formation. A, B) Expression of Klingon (Klg) in the fly brain. C) Expression of Klg in neurons. D) Expression of Klg in glial cells.
Spaced training increases Klg-mediated neuron-glia interaction, thereby induces Repo-dependent glial transcription required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

Senior Research Scientist **Kohei Ueno**

Exploring Physiological Systems Underlying Learning and Memory

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



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

Learning and Memory

Kato K, Sasada S, and Nishimura Y. (2016) "Flexible adaptation to an artificial recurrent connection from muscle to peripheral nerve in man." ***J. Neurophysiol.*** 115(2):978-991.

Sawada M, Kato K, Kunieda T, Mikuni N, Miyamoto S, Onoe H, Isa T, and Nishimura Y (2015) "Function of the nucleus accumbens in motor control during recovery after spinal cord injury." ***Science.*** 350(6256):98-101.

Sasada S, Kato K, Kadowaki S, Groiss SJ, Ugawa Y, Komiyama T, and Nishimura Y. (2014) "Volitional walking via upper limb muscle-controlled stimulation of the lumbar locomotor center in man." ***J. Neurosci.*** 34(33):11131-11142.

Nishimura Y, Perlmutter SI, Eaton RW, and Fetz EE. (2013) "Spike-timing-dependent plasticity in primate corticospinal connections induced during free behavior." ***Neuron.*** 80(5):1301-1309.

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

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

Nishimura Y, Onoe H, Morichika Y, Perfiliev S, Tsukada H, and Isa T. (2007) "Time-dependent central compensatory mechanisms of finger dexterity after spinal cord injury." ***Science.*** 318(5853):1150-1155.

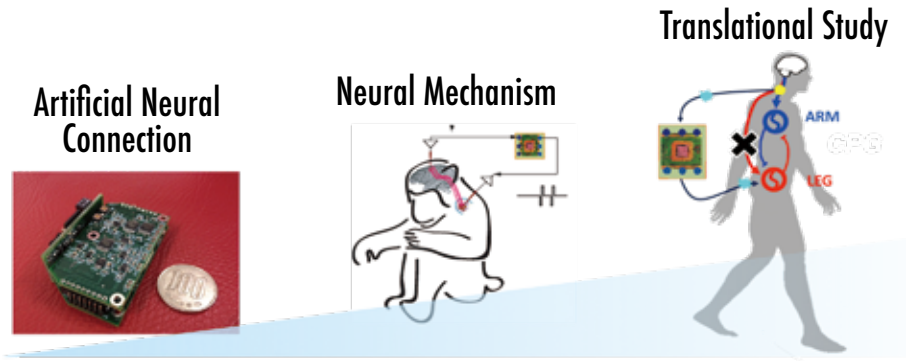
Project Leader **Yukio Nishimura** Neural Prosthesis Project

Restoring Lost Function After Neural Damage

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

"Bridging Damaged Neural Pathways using a Neural Interface."

Regaining the function of an impaired limb is necessary for individuals experiencing paralysis. Functional loss of limb control in individuals with spinal cord injury or stroke is often caused by transection of descending and ascending pathways connecting cortical to spinal networks, with neural circuits located above and below the impaired site remaining functional.



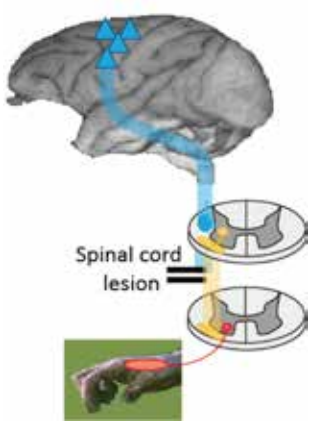
Neuron 2013 | Frontiers 2013 | J Neurosci 2014

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

Neural Prosthesis

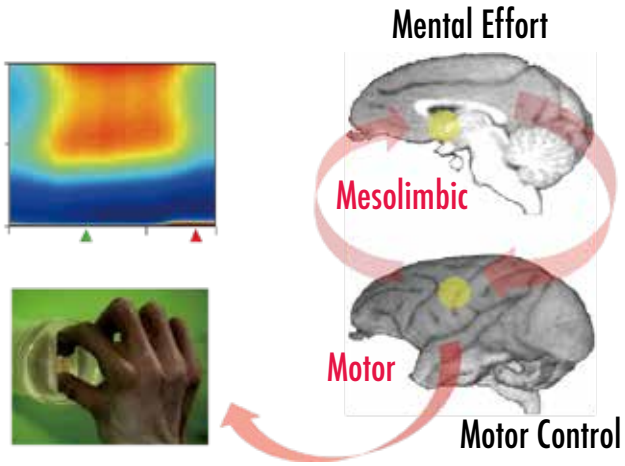
Neural Mechanisms of Functional Recovery

Using large scale multichannel recordings, pharmacological interventions, neuroanatomy, viral tools, computation, and whole brain imaging, we seek to uncover the neural mechanisms underlying voluntary limb movement in intact animals, as well as the processes in which motor functions are reestablished after neural damage such as spinal cord injury and stroke. We are also performing clinical studies to test the efficacy of ANCs in human patients.



Science. 2007, Brain 2009

Psychological Effects on Motor Control



PLoS ONE 2011, Science. 2015

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

Members

Yukio Nishimura
Toshiki Tazoe
Osamu Yokoyama
Nobuya Sano
Noboru Usuda
Kei Obara
Yu Shimada
Yoshihisa Nakayama
Hiroaki Ishida
Michiaki Suzuki
Miki Kaneshige
Ryoutaro Numata
Naoya Kabe

Neural Prosthesis

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

Protection from neurodegenerative diseases

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

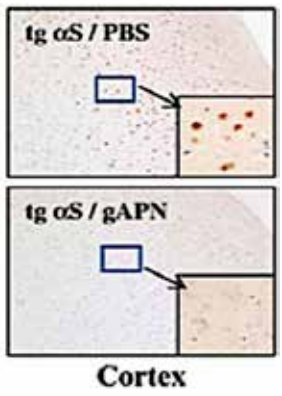


Fig. 1
Effect of adiponectin on neurodegeneration in tg mice

In our laboratory, we seek to exploit a mechanism-based disease-modifying strategy for α-synucleinopathies, such as PD and dementia with Lewy bodies. In this context, we have a particular interest in the suppressive effect of adiponectin on neurodegeneration (Fig.1). We are also identifying new molecules that could be useful for the prevention of neurodegenerative diseases. For this purpose, we currently perform Drosophila molecular genetics (Fig.2) in addition to cell biological and transgenic mice studies. Our results should be applicable to diseases, such as AD and Huntington's disease.

Members

Yoshiki Takamatsu
Masaaki Waragai
Hiromu Sugino
Ryoko Wada

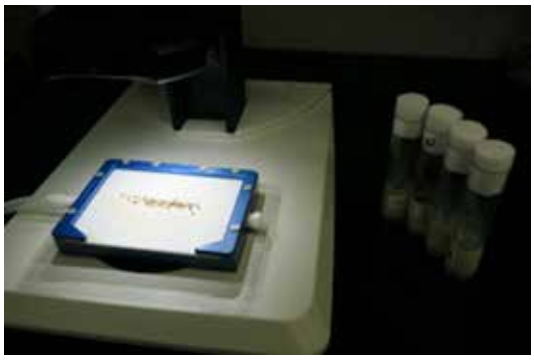


Fig. 2 Drosophila molecular genetics

Hashimoto M, Ho G, Takamatsu Y, Wada R, Sugama S, Takenouchi T, Waragai M, Masliah E. (2019) "Possible Role of Amyloid Cross-Seeding in Evolvability and Neurodegenerative Disease."***J Parkinsons Dis.*** in press.

Takamatsu Y, Ho G, Waragai M, Wada R, Sugama S, Takenouchi T, Masliah E, Hashimoto M. (2019) "Transgenerational Interaction of Alzheimer's Disease with Schizophrenia through Amyloid Evolvability." ***J. Alzheimers Dis.*** 68(2):473-481.

Hashimoto M, Ho G, Takamatsu Y, Shimizu Y, Sugama S, Takenouchi T, Waragai M, and Masliah E. (2018) "Evolvability and Neurodegenerative Disease: Antagonistic Pleiotropy Phenomena Derived from Amyloid Aggregates." ***J. Parkinsons Dis.*** 8(3):405-408.

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

Waragai M, Ho G, Takamatsu Y, Sekiyama K, Sugama S, Takenouchi T, Masliah E, and Hashimoto M. (2017) "Importance of adiponectin activity in the Pathogenesis of Alzheimer's Disease." ***Ann. Clin. Transl. Neurol.*** 4:591-600.

Takamatsu Y, Ho G, Koike W, Sugama S, Takenouchi T, Waragai M, Wei J, Sekiyama K, and Hashimoto M. (2017) "Combined immunotherapy with "anti-insulin resistance" therapy as a novel therapeutic strategy against neurodegenerative diseases." ***NPJ Parkinson's Disease*** 3: 4.

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

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

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