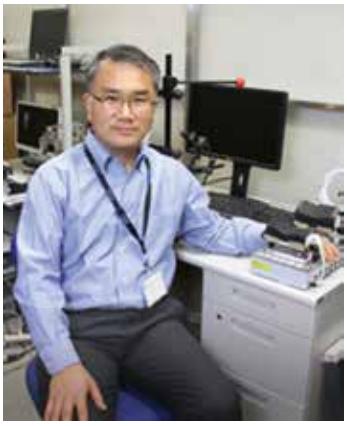

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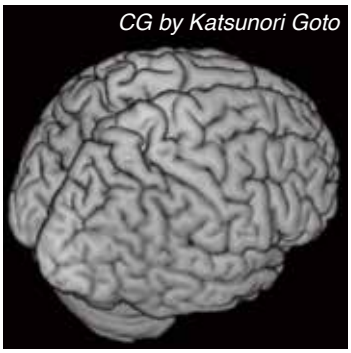
Project Leader **Shinji Kakei** Motor Disorders Project

From Neuron to Action and its Disorders

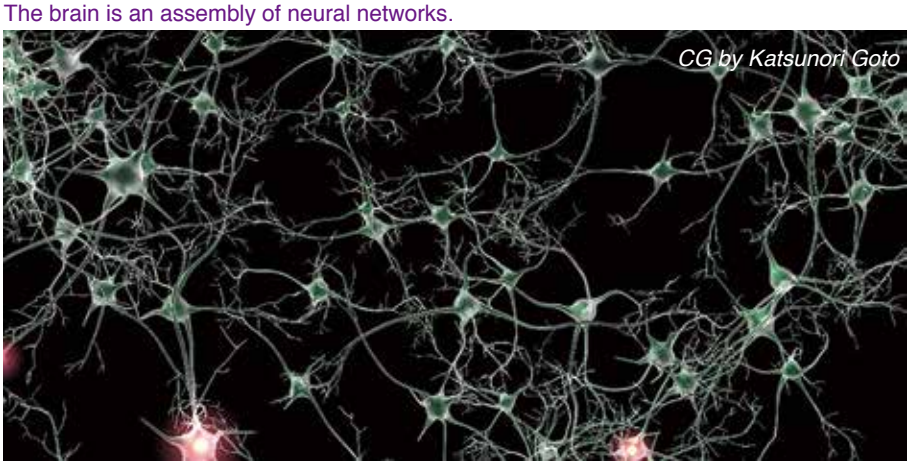
We try to understand how the brain controls our movements in the real world. We study the process of action generation at a single neuron level using animal models to understand how movements are processed in the brain. We also study actions of healthy people, as well as those with neurological disorders, such as cerebellar disorders, Parkinson's disease or strokes. We look for building-blocks of motor control with multidisciplinary approaches. Our tools include various neurophysiological recording techniques (single unit recording, electromyography (EMG) and electro-encephalography (EEG)), brain stimulation, neuroimaging, analysis of movement kinematics and a large-scale modeling. We have two long-term goals: 1) to understand the basic function of the motor structures of the brain including the cerebellum, the basal ganglia, and the motor cortex; and 2) to understand how our brain controls our movements on the basis of the findings in 1).

"Through our research, we are trying to understand the brain. The brain was first created to control movement and extended to control higher brain functions."



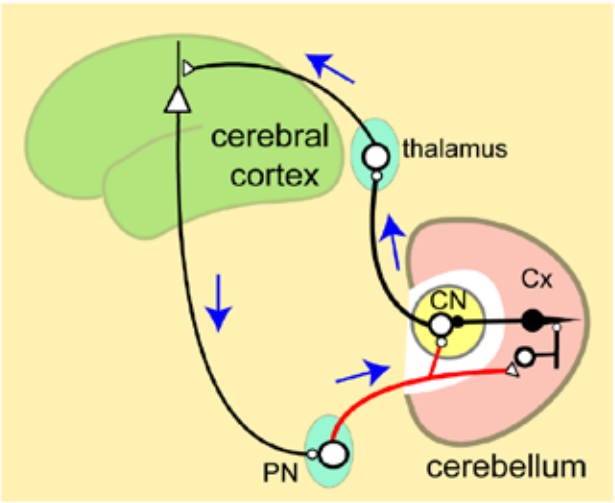
"The brain mechanism for motor control must provide a basic framework to understand higher brain functions."

The brain is an assembly of neural networks.

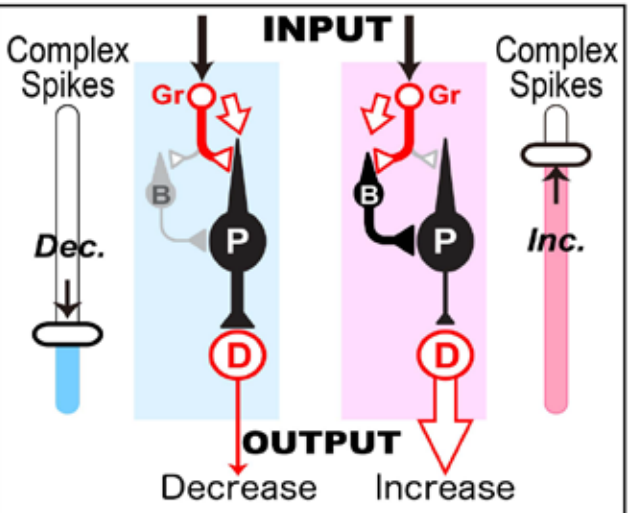


Motor Disorders

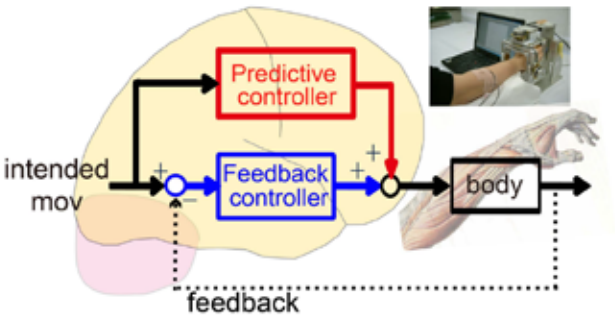
Hot Topics of Our Research



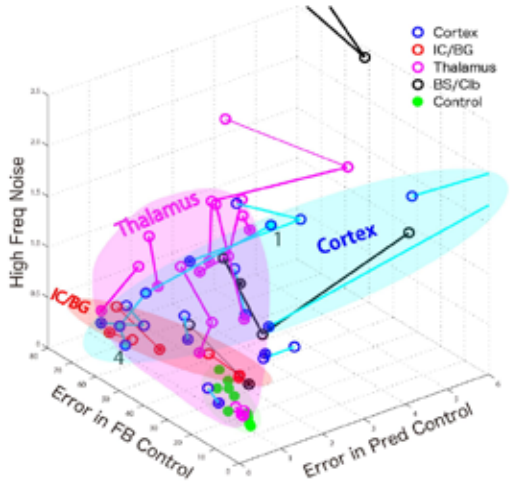
The cerebro-cerebellar communication loop plays essential roles to organize both motor control and higher brain functions such as thought and speech.



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



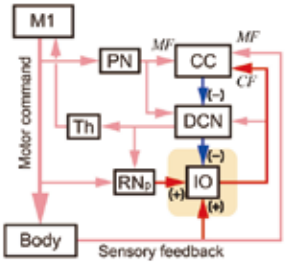
We were the first group in the world to build a system (*inset*) to dissociate predictive motor control and feedback motor control (below) in patients with neurological disorders. This system provides quantitative parameters that characterize the two controllers.



With new quantitative parameters, we were the first group to visualize different courses of recovery for stroke patients with different localization of brain lesions.

Members

Kyuengbo Min,
Jongho Lee,
Takahiro Ishikawa,
Takeru Honda



Motor Disorders

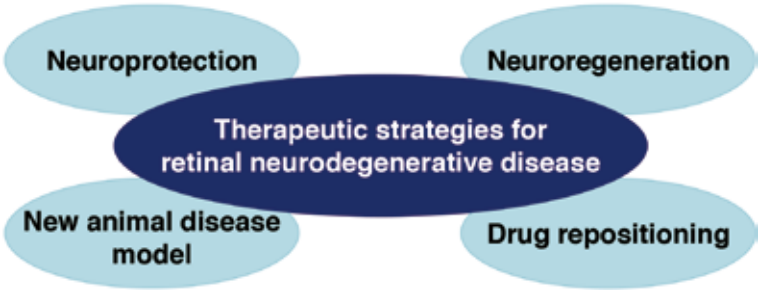
Project Leader **Takayuki Harada** Visual Research Project

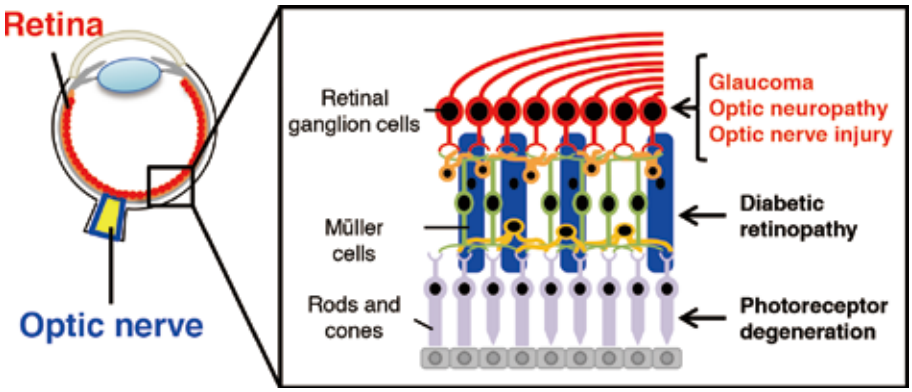
Elucidation of Pathology and Development of Therapeutic Strategies for Retinal Neurodegenerative Diseases

More than 1.6 million people in Japan are visually impaired, representing economic social losses estimated at more than 8 trillion yen. In the particular context of the increased penetration of Western lifestyles and an aging society, the increase in the number of patients with conditions such as glaucoma and diabetic retinopathy, which could be called “adult eye diseases,” has become a major social issue.
To achieve improved quality of life (QOL) for the visually impaired in an increasingly aging population, we seek to elucidate detailed pathogenic mechanisms and develop new therapies through the development of a model of intractable eye disease.

Our objectives

“We are focusing on elucidating the molecular mechanisms of neuroprotection and neuroregeneration, and our final goal is the prevention or treatment of blindness in retinal neurodegenerative disorders such as glaucoma and traumatic injury.”





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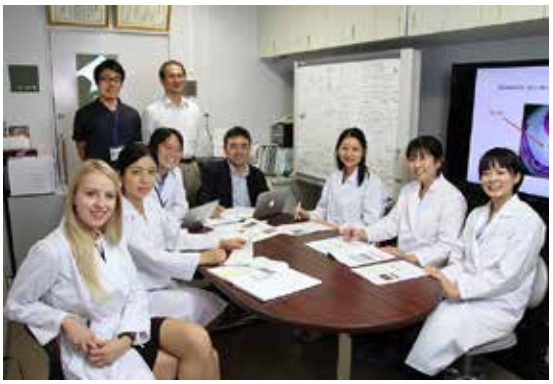
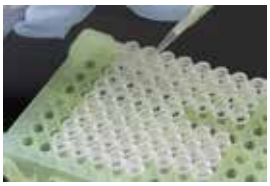
Visual Research

Our major aim

- **To develop a neuroprotective retinal therapy using animal disease models**
- **To elucidate the mechanisms involved in the onset of optic neuritis**
- **To establish a method to promote regeneration of the optic nerve**



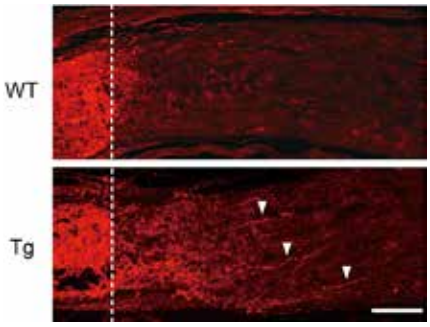




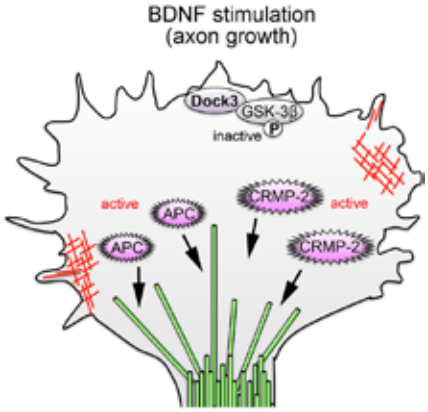
Senior Research Scientist **Kazuhiko Namekata**

Dock family proteins

The dedicator of cytokinesis (Dock) family is composed of atypical guanine exchange factors (GEFs) that induce actin polymerization. To date, 11 Dock family members have been identified. Dock3 is predominantly expressed in the central nervous system. In the growth cone, Dock3 induces actin polymerization by activating WASP family verprolin-homologous protein (WAVE) and modulates microtubule dynamics through inactivation of GSK-3β, leading to axon elongation. In addition, Dock3 plays a role in protecting retinal ganglion cells from neurotoxicity and oxidative stress. Dock3 may be a therapeutic target for optic neuropathy including glaucoma.



Axonal regeneration was enhanced in Dock3 overexpressing mouse (Tg) (Arrow heads indicate regenerating axons)



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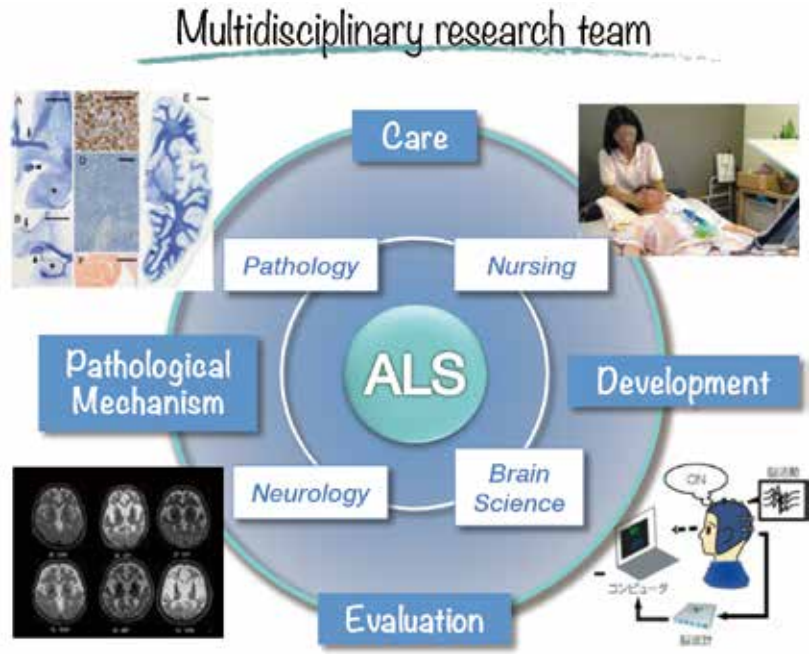
Visual Research

Project Leader **Yuki Nakayama** ALS Nursing Care Project

Improving the Quality Of Life of Patients with Amyotrophic Lateral Sclerosis

"Our mission is to establish the best practices for respiratory and communication management for ALS patients in a community-based setting . We have established a multidisciplinary research team to develop a Brain Machine Interface for ALS patients."



Nakayama Y, Shimizu T, Matsuda C, Haraguchi M, Hayashi K, Bokuda K, Nagao M, Kawata A, Ishikawa-Takata K, Isozaki E. (2019) "Body weight variation predicts disease progression after invasive ventilation in amyotrophic lateral sclerosis." ***Scientific Reports*** volume 9, Article number: 12262

Shimizu T, Nakayama Y, Matsuda C, Haraguchi M, Bokuda K, Ishikawa-Takata K, Kawata A, Isozaki E. 2019 "Prognostic significance of body weight variation after diagnosis in ALS: a single-centre prospective cohort study." ***Journal of Neurology*** .266(6), 1412–1420

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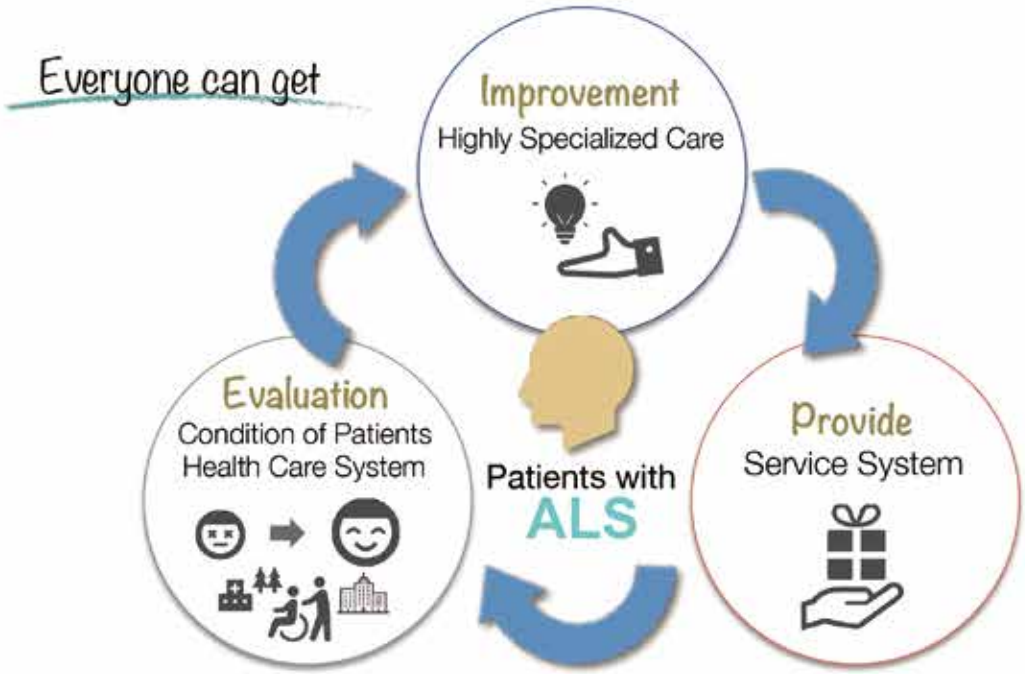
ALS Nursing Care

ALS Nursing Care Project Ground design



Administration of Community-Based Nursing

How many visiting nurse stations are there in this community?

" Do Patients live well? "

Akiko Ogura, Ph.D.

Quality Assurance of Home Care

Collaboration between visiting Nurse and care workers.
Risk management on Home Mechanical Ventilation, and Construction of information system for Medical Near-miss/adverse event.
Needs of Nursing Support in Outpatient Department on Patients with ALS.

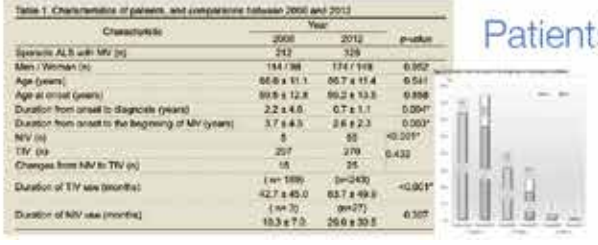
Michiko Haraguchi, Ph.D.

Establishing specialized Oral Nursing care system for advanced amyotrophic lateral sclerosis patient

Chiharu Matsuda, Ph.D.

Multivariate analysis for the occurrence of macroglossia by logistic regression

Variables	Odds ratio	95% CI	P-value
Age at beginning of TIV use, years	0.937	0.845–1.041	0.225
Duration of TIV use, months	1.022	1.000–1.044	0.050
ALSFRS-R score	0.822	0.314–2.146	0.314
Body mass index, kg/m²	1.653	1.150–2.370	0.007
Energy intake, kcal/d	1.001	0.995–1.006	0.784
Stages of communication impairments (I, II–IV, V)	3.771	1.150–12.370	0.029



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

Yumi Itagaki, M.S.

ALS Nursing Care

Nakamura S*, Oba M*, Suzuki M, Takahashi A, Yamamuro T, Fujiwara M, Ikenaka K, Minami S, Tabata N, Yamamoto K, Kubo S, Tokumura A, Akamatsu K, Miyazaki Y, Kawabata T, Hamasaki M, Fukui K, Sango K, Watanabe Y, Takabatake Y, Kitajima TS, Okada Y, Mochizuki H, Isaka Y, Antebi A, and Yoshimori T. (2019) "Suppression of autophagic activity by Rubicon is a signature of aging." ***Nat. Commun.*** 10:847 (*First authors)

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

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

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

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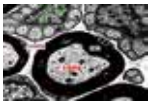
Project Leader **Kazunori Sango** Diabetic Neuropathy Project

Pathogenesis-based Therapeutic Approaches to Diabetic Neuropathy

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

"We are trying to improve QOL for diabetics and help them to live longer lives by elucidating the pathogenesis of neurological disorders and establishing effective treatments."



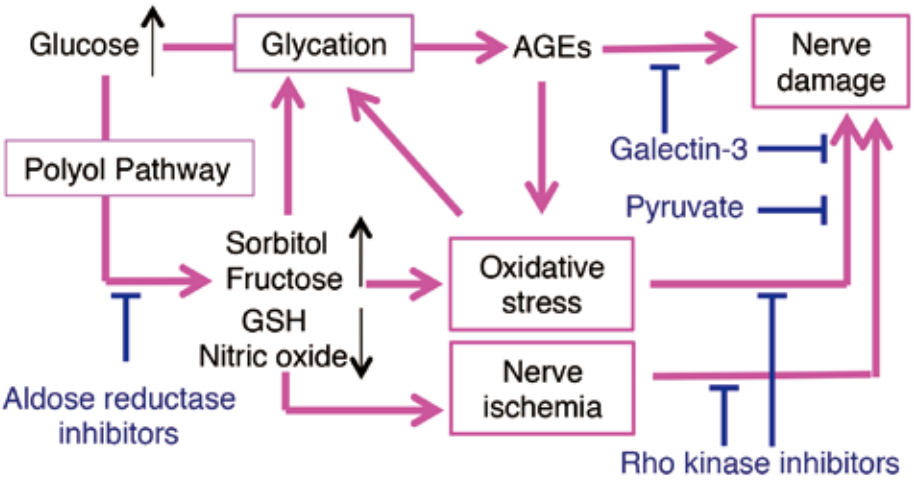
The goals of our project are as follows:

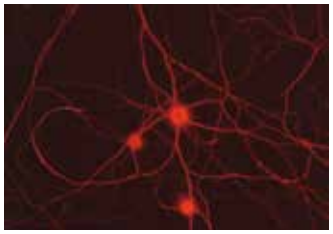
1) Establishing effective pathogenesis-based treatments for diabetic peripheral neuropathy.
2) Elucidating mechanistic links between metabolic dysfunction and neurodegenerative diseases.

Diabetic Neuropathy

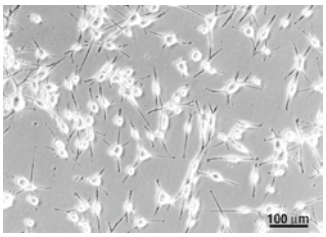
Project1: Therapeutic Approaches to Diabetic *Peripheral Neuropathy* [Sango, Yako, Niimi, Takaku, Akamine]

Metabolic disorders and vascular abnormalities caused by hyperglycemia appear to be closely related to the development and progression of diabetic peripheral neuropathy.
Using diabetic model animals and culture systems of adult rodent **dorsal root ganglion (DRG) neurons** and **immortalized Schwann cells,** we seek to establish effective pathogenesis-based treatments for peripheral neuropathy.





Adult rat DRG neurons



Immortalized mouse Schwann cells IMS32

Project2: Mechanistic link between *Metabolic dysfunction* and *Neurodegenerative* Diseases [Suzuki, Oba]

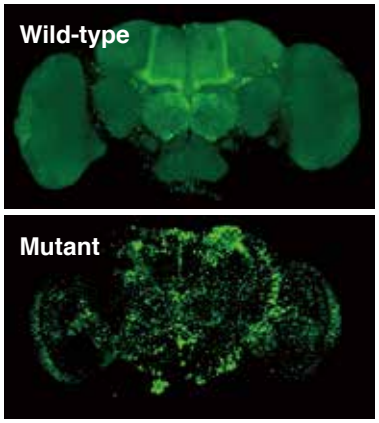
Neurodegenerative diseases are considered to share a common molecular pathogenesis involving protein misfolding and aggregation. Recently, increasing evidence suggests a relationship between metabolic syndrome and Alzheimer's disease. By using a **Drosophila model,** we aim to understand the molecular mechanism by which metabolic conditions influence misfolding protein-induced neurodegeneration.

High-nutrient diet

Nutrient-restricted diet

Drosophila models of neurodegenerative diseases

- Alzheimer's
- Parkinson's
- Polyglutamine
- ALS *etc*…



Protein aggregation (brain)

Diabetic Neuropathy