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 the movement is 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. We employ both invasive and non-invasive approaches to achieve the deepest understanding of our brain. Our tools include various neurophysiological recording techniques (single unit recording, electromyography (EMG) and electroencephalography (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.
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
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.

“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.”

Our objectives

- Neuroprotection
- Neuroregeneration
- Drug repositioning
- New animal disease model

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


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.

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
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.


ALS Nursing Care Project  Ground design

Administration of Community-Based Nursing
How many visiting nurse stations are there in the 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.

Patients with Intractable Diseases
Analyze their physical and psycho-social Data
Yumi Itagaki, M.S.

Multivariate analysis for the occurrence of exacerbation by logistic regression

Table 1 Characteristics of patient and comparison between 2000 and 2012

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>2000</th>
<th>2012</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>23%</td>
<td>27%</td>
<td>.225</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57</td>
<td>53</td>
<td>.003</td>
</tr>
<tr>
<td>Disability</td>
<td>80%</td>
<td>85%</td>
<td>.021</td>
</tr>
<tr>
<td>Duration from symptom to diagnosis (weeks)</td>
<td>32±14</td>
<td>30±13</td>
<td>.005</td>
</tr>
<tr>
<td>Duration from symptom to the beginning of the year</td>
<td>17±4</td>
<td>16±2</td>
<td>.001</td>
</tr>
<tr>
<td>RV (L)</td>
<td>2.7</td>
<td>2.3</td>
<td>.006</td>
</tr>
<tr>
<td>O2 saturation in %</td>
<td>84±5</td>
<td>89±7</td>
<td>.001</td>
</tr>
<tr>
<td>Duration of FVC change (%)</td>
<td>50±20</td>
<td>30±15</td>
<td>.001</td>
</tr>
<tr>
<td>Duration of FVC change (%)</td>
<td>10±20</td>
<td>5±10</td>
<td>.001</td>
</tr>
</tbody>
</table>

ALS Nursing Care
Peripheral neuropathy is one of the most common complications of Diabetes Mellitus, and its irritating symptoms such as pain and numbness can be the cause of insomnia and depression, and when allowed to progress to more advanced disease stages 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.

**Pathogenesis-based Therapeutic Approaches to Diabetic Neuropathy**

"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 link between metabolic dysfunction and neurodegenerative diseases.
Project 1: 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.

![Diagram of Glucose, Glycation, AGEs, Nerve damage, Polyol Pathway, Sorbitol, Fructose, GSH, Nitric oxide, Nerve ischemia, Galectin-3, Pyruvate, Rho kinase inhibitors]

Project 2: 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 Drosophila model, we aim to understand the molecular mechanism by which metabolic condition influences misfolding protein-induced neurodegeneration.

![Drosophila models of neurodegenerative diseases]

- Alzheimer’s
- Parkinson’s
- Polyglutamine
- ALS etc.

![High-nutrient diet, Nutrient-restricted diet, Protein aggregation (brain)]