ANNUAL REPORT 2011

Molecular Neuroscience Research Center

Shiga University of Medical Science

滋賀医科大学

分子神経科学研究センター

2011年報

Preface

It is our pleasure to present our annual report for 2011. The Molecular Neuroscience Research Center was founded in 1989 as the Molecular Neurobiology Research Center. In 2009, the center was renewed as the Research Promotion Organization for Intractable Neurological Disease - Molecular Neuroscience Research Center (MNRC).

The overall aim of the MNRC is to understand the molecular basis of neural functions and pathological processes of neurological diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. On the basis of our findings thus far, we have developed diagnostic agents and methods for neurological disorders. We also collaborate with the Biomedical MR Center and Center for Animal Life Science at Shiga University of Medical Science and with other laboratories outside Japan. The Research Promotion Organization for Intractable Neurological Disease was founded specifically to enhance and extend our collaborative research. .

We hope that this annual report illustrates a pathway for MNRC research as we move forward and also as a seed to develop productive international collaborations into the future.

July 2, 2011

Ikuo Tooyama, Director, Professor

Organization

The MNRC has five research units: Neurology, Neuropathology and Diagnostics, Neurobiology and Therapeutics, Animal Models of Neurological Disorders and Dementia Research. .

Neurology Unit

Staff: Masaki Nishimura, Associate Professor
Hiroshi Hasegawa, Visiting Assistant Professor

Purpose: Clarification of the molecular pathogenesis and development of disease-modifying therapies for Alzheimer's disease.

Unit for Neuropathology and Diagnostics

Staff: Ikuo Tooyama, Professor
Hiroyasu Taguchi, Special Contract Professor
Jean-Pierre Bellier, Assistant Professor
Satoshi Makino, Special Contract Assistant Professor

Purpose: Molecular morphological studies of neurological disorders to clarify higher brain functions and their disorders as well as develop novel diagnostic methods.

Unit for Neurobiology and Therapeutics

Staff: Makoto Urushitani, Associate Professor
Ryo Kitahara, Visiting Lecturer

Purpose: Development of novel therapies for amyotrophic lateral sclerosis (ALS) using animal models of disease and molecular biology techniques.

Unit for Animal Models of Neurological Disorders

Staff: Ryosuke Takahashi, Visiting Professor (Kyoto University)
Akinori Matsuo, Assistant Professor

Purpose: Production of appropriate animal models providing precise information about neurological disorders such as Alzheimer’s disease.

Unit for Dementia Research

A new professor is now in selection.

Neurology Unit

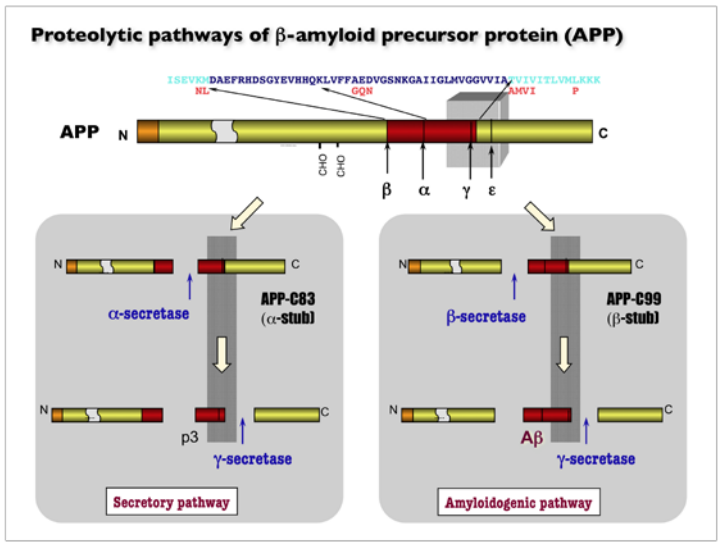
Masaki Nishimura
Associate Professor
mnishimu@belle.shiga-med.ac.jp

Hiroshi Hasegawa,
Visiting Assistant Professor
hhasgawa@belle.shiga-med.ac.jp

Lei Liu	Graduate Student
Takuya Kasami	Undergraduate Student
Makoto Tagaya	Undergraduate Student

Research projects on the pathomechanism of Alzheimer disease (AD)

Excessive accumulation of β-amyloid peptide (Aβ) in the brain is the accepted cause of AD. Excessive Aβ peptides oligomerize to cause neuronal dysfunction and degeneration in the brains of AD patients, resulting in the manifestation of severe dementia. Aβ is generated by sequential proteolysis of the amyloid precursor protein (APP). The ectodomain of APP is cleaved by β-secretase, and the transmembrane domain of the resulting C-terminal fragment (C99) is processed by γ-secretase to generate Aβ (Figure). The γ-secretase cleavage at multiple sites yields several different Aβ species including two predominant forms, Aβ40 and Aβ42. Aβ42 is more prone to aggregation and is pathogenic.



(1) Molecular mechanism underlying regulation of cellular γ-secretase activity

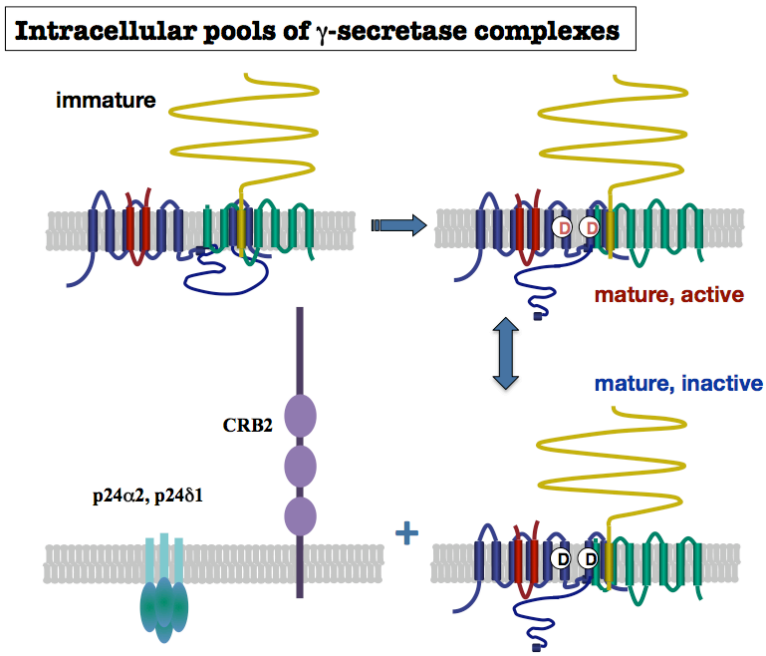
γ-Secretase is a membrane-embedded, multimeric protein complex composed of four membrane proteins: presenilin (PS), nicastrin (NCT), APH-1, and PEN-2. Presenilins (PS1 and PS2) have a catalytic center, although three other components are required for activity. Control of γ-secretase activity is considered a promising therapeutic strategy for AD. However, inhibition of γ-secretase activity has serious adverse effects in mammals, because γ-secretase plays a critical role in regulated intramembrane proteolysis of many type I membrane proteins including Notch receptors, whose proteolyzed cytoplasmic domains mediate pivotal signal transduction *in vivo*. The mechanism of intrinsic γ-secretase regulation remains to be elucidated, although some candidate regulatory proteins have recently been reported. In a screen for proteins that interact with the γ-secretase complex, we identified several proteins that could potentially reduce Aβ secretion.

<CRB2>

Drosophila Crumbs attenuates Notch signaling by inhibiting γ-secretase cleavage at the wing margins. We re-examined γ-secretase inhibition by human CRB2, which is the most abundant Crumbs ortholog in human brain. Transfected CRB2 inhibited proteolytic production of Aβ and APP intracellular domains from APP C-terminal fragments. Conversely, knockdown of endogenous CRB2 increased γ-secretase cleavage products in SH-SY5Y cells. CRB2 inhibition of γ-cleavage was also detected in cell-free assays. CRB2 interacted with the γ-secretase complex, but was not a competitive substrate for γ-cleavage. The transmembrane domain of CRB2 was indispensable for inhibiting Aβ generation, and mediated CRB2 binding with the γ-secretase complex. In addition, the cytoplasmic domain of CRB2 seemed to play a supportive role in γ-secretase inhibition. Co-overexpression of presenilin-1 or APH-1 abrogated γ-secretase inhibition probably by preventing the incorporation of CRB2 into the γ-secretase complex. Our results suggest that CRB2 functions as an inhibitory binding protein involved in forming a mature but inactive pool of the γ-secretase complex.

<p24α_2>

A member of the p24 cargo protein family, named p24δ_1 or TMP21, was identified as an activity-modulating component of the γ-secretase complex. The p24 family proteins are divided into four subfamilies (p24α, β, δ and γ). In contrast to p24δ_1, p24β_1 has reportedly no effect on γ-cleavage. We investigated whether p24α_2, p24γ_3, or p24γ_4 modulates APP processing. Knockdown of cellular p24α_2 induced a significant increase in Aβ generation, but not in AICD production in cell-based and cell-free assays, whereas p24α_2 overexpression suppressed Aβ secretion. By contrast, Aβ secretion was not altered by p24γ_3 or p24γ_4 knockdown. Endogenous p24α_2 co-immunoprecipitated with core components of the γ-secretase complex. Mutational disruption of the conserved dilysine ER-retrieval motifs of p24α_2 and p24δ_1 perturbed inhibition of γ-cleavage. Simultaneous knockdown, or overexpression, of both p24α_2 and p24δ_1 had no additive or synergistic effect on Aβ generation. Our findings suggest that dilysine ER-retrieval signal-containing p24 proteins, p24α_2 and p24δ_1, bind with γ-secretase complexes and collaborate in attenuating γ-cleavage of APP.



(2) Molecular basis of high incidence of Alzheimer disease with increasing age: analysis of functional and molecular modification of the γ-secretase complex in aged brains

Recent reports suggested that γ-secretase activity is modulated to preferentially generate Aβ42 in brains of patients with late-onset sporadic AD. On the other hand, it is well known that aging is a major risk factor for AD, and the Aβ42/Aβ40 ratio in mouse brain increases in an age-dependent manner. Hence, it is possible that the increasing vulnerability of the aged to AD reflects an increase in Aβ42 generation with aging. Recent advances in aging research implicated several signaling pathways and components in animal aging and cellular senescence. We are therefore investigating aging-associated modification of the γ-secretase complex. This study could shed light on an important aspect of AD pathogenesis, and lead to future study on development of small-molecule agents to inhibit or reverse pathological modifications of the γ-secretase complex.

Unit for Neuropathology and Diagnostics

Ikuo Tooyama
Professor
kinchan@belle.shiga-med.ac.jp

Hiroyasu Taguchi
Special Contract Professor
taguti@belle.shiga-med.ac.jp

Jean-Pierre Bellier
Assistant Professor
bellier@belle.shiga-med.ac.jp

Satoshi Makino
Special Contract Assistant Professor
smakino@belle.shiga-med.ac.jp

Ken-nosuke Wada	Visiting Professor (Nagahama insitutute of Bio-science and Technology)
Tatuyuki Takada	Visiting Professor (Ritsumeikan University)
Yoshihiro Konishi	Visiting Associate Professor (Tottori Medical Center)
Yasuhiro Akatsu	Visiting Associate Professor (Choju Medical Institute, Fukushimura Hospital)
Nobuaki Shirai	Visiting Lecturer (Industrial Research Center of Shiga Prefecture)
Koichi Hirao	Visiting Assistant Professor (Industrial Research Center of Shiga Prefecture)
Atsushi Saito	Visiting Assistant Professor (Yosanoumi Hospital)
Haruhisa Sato	Visiting Lecturer (RAKUWAKAI Health Care System)
Takaomi Fukuhara	Visiting Assistant Professor (Panasonic Healthcare Co., Ltd.)
Kazuyoshi Mori	Visiting Lecturer (Panasonic Healthcare Co., Ltd.)
Masahiro Koge	Visiting Lecturer (Panasonic Healthcare Co., Ltd.)
Toshifumi Nanjoh	Visiting Lecturer (Panasonic Healthcare Co., Ltd.)
Daijiro Yanagisawa	Research Fellow of JSPS (PD)
Essam Mohamed Abdelalim	Visiting Foreign Research Fellow of JSPS
Chiaki Masuda	Graduate Student
Shigeko Takeuchi	Graduate Student
Piers Vigers	Graduate Student
Naoko Kameshima	Graduate Student
Naomi Bisem	Graduate Student (Monbukagakusho Scholarship Student)
Hougkuan Yang	Graduate Student (Foreign Student supported by SUMS)
Mingchun Yang	Graduate Student (Foreign Student)

The aim of this laboratory is to understand the molecular basis of neural functions and pathological processes of neurological diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Based on our findings, we aim to develop diagnostic agents and methods for neurological disorders. To increase our productivity, we collaborate with other units in MNRC, the Biomedical MR Center, and the Center for Animal Life Science.

Research Projects and Topics

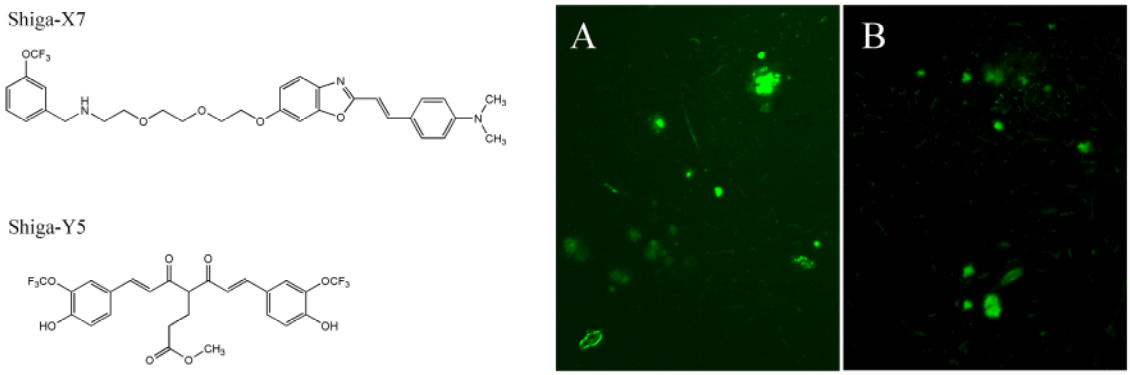


Figure 1. Structures of Shiga-X7 and Shiga-Y5, and fluorescent signals of Shiga-X7 (A) and Shiga-Y5 (B) in the brain of transgenic mouse models of Alzheimer's disease. These fluorochromes were injected into the tail vein of mice, and subsequently bound to senile plaques in the brain.

High-field MRI also allows us to image not only protons but also other nuclear elements such as ^{17}O, ^{13}C, and ^{19}F. In particular, low-abundant elements such as ^{19}F can provide better signal-to-noise ratios. We designed a novel positive contrast agent based on a peptide, poly-L-lysine-CF_3 (PLK-CF_3), labeled with FITC or Cy5 for MRI microscopy (Maki et al. ***Biomaterials*** 28: 434-440, 2007). Higuchi et al. reported the imaging of amyloid plaques using ^{19}F-MRI with (E,E)-1-fluoro-2, 5-bis- (3-hydroxycarbonyl-4-hydroxy) styrylbenzene (FSB), which allowed the detection of Aß plaques in APP transgenic mice (*Nature Neurosci* 2005). We also used TFMB-2Et and TFMB-3Et for amyloid imaging in APP transgenic mice (Amatsubo et al., ***Neurosci Res***. 63:76-81, 2009).

Curcumin, which can exist in equilibria between keto and enol tautomers, binds to Aβ fibrils/aggregates. Curcumin derivatives with keto-enol tautomerism showed high levels of binding to Aβ aggregates including Aβ oligomers and Aβ fibrils, but not to Aβ monomers (Yanagisawa et al. ***J Alzheimers Dis***. S24: 33-42, 2011). The binding activity of the keto form of curcumin derivatives to Aβ aggregates was found to be much weaker than that of the enol form. The color of a curcumin derivative with keto-enol tautomerism, which was substituted at the C-4 position, changed from yellow to orange within 30 minutes of being combined with Aβ aggregates in physiological buffer. This followed a remarkable increase in the enol form with extended conjugation of double bonds upon binding (Yanagisawa et al. ***Biomaterials***. 31: 4179-4185, 2010).

Curcumin derivatives exist predominantly in the enol form during binding to Aβ aggregates, and that the enolization of curcumin derivatives is crucial for binding to Aβ aggregates. These findings suggest that the keto-enol tautomerism of curcumin derivatives could provide a novel target for amyloid-binding agents that could be used for therapy and for amyloid detection in Alzheimer's disease. (The study was supported by the JST Practical Application Research Program).

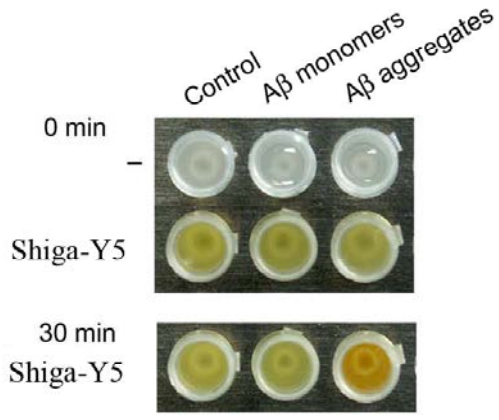


Figure 2. In the presence of Aß aggregates (right), the color of Shiga-Y5 gradually, but dramatically, changed to reddish orange during 30 min. However, Shiga-Y5 did not react with Aß monomers.

2. **Research on neurotrasnmitters and neuropeptides**

We also investigate gene functions in the nervous system. Recently, we identified a novel splice variant of choline acetyltransferase that is preferentially expressed in peripheral nervous system (pChAT). We are now investigating the structure, localization, and function of pChAT (Figure 3).

Dr. Essam M. Abdelalim is studying natriuretic peptides in the central nervous system and in embryonic stem cells. His results thus far have implicated these molecules in stem cell functions (Abdelalim EM, Tooyama I, ***PLoS ONE*** 4(4): e5341, 2009; ***Cell Death Dis.*** 10(2): e127, 2011).

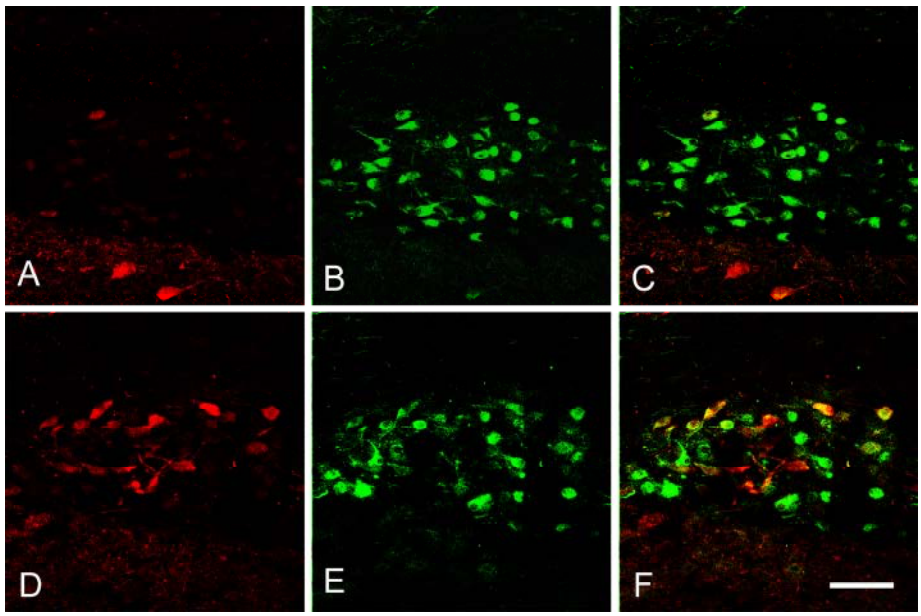


Figure 3. Double-immunostaining for cChAT (red) and pChAT (green) in the DMNV at 7 days (**A-C**) and 28 days (**D-F**) post-vagotomy. (**A, D**) cChAT-immunoreactive neurons. (**B, E**) pChAT-immunoreactive neurons. (**C**) Merged image of (**A**) and (**B**). **(F)** Merged image of (**D**) and (**E**). (**A-C**) Only a few neurons co-express cChAT and pChAT. (**D-F**) Some of the cChAT-positive and pChAT-positive neurons co-express the two markers. HN, hypoglossal nucleus. Scale bars: **A-F**, 200 μm. （Saito et al., ***J Comp Neurol*** 513:237-248, 2009）

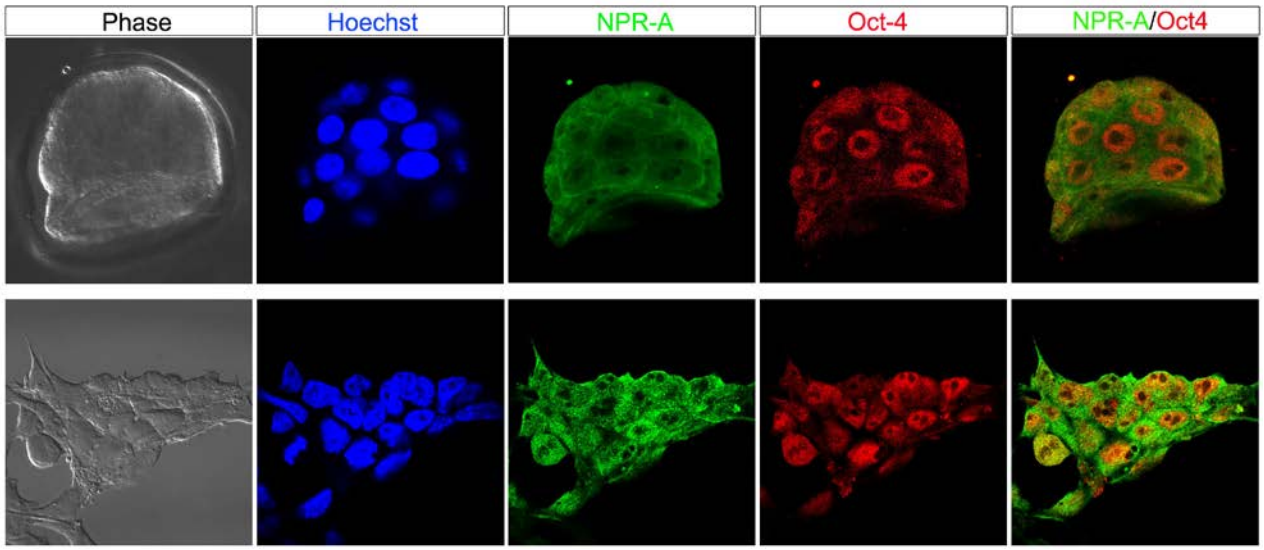


Figure 4. Natriuretic peptide receptor-A (NPR-A) is expressed in pre-implantation embryos and pluripotent embryonic stem (ES) cells. *Upper panels*, double-immunofluorescence images of 3.5-day-old blastocysts stained with antibodies against NPR-A and Oct4 (a pluripotency marker), and counterstained with Hoechst reagent. *Lower panels*, double-immunofluorescence images of undifferentiated murine ES cells stained as in *upper panels*. (Abdelalim EM, Tooyama I, ***PLoS ONE*** 4(4): e5341, 2009)

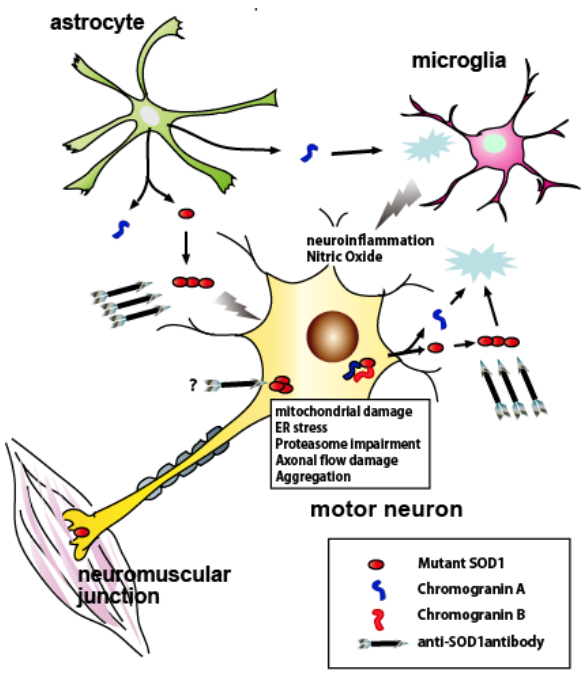
Unit for Neurobiology and Therapeutics

Makoto Urushitani
Associate Professor
uru@belle.shiga-med.ac.jp

Akemi Ido	Researcher (Non-Full-time)
Miki Oono	Special Research Student
Ryo Kitahara	Visiting Associate Professor (Ritsumeikan University)
Masatoshi Inden	Visiting Assistant Professor (Ritsumeikan University)

The Unit for Neurobiology and Therapeutics (Neurotherapy Group) is a new laboratory at the MNRC that was launched in June in 2009. Our mission is to develop innovative therapies for amyotrophic lateral sclerosis (ALS), a fatal neurodegenerative disease characterized by progressive muscle wasting and atrophy. There are no effective therapies for ALS, although recent advances in life science technology have yielded significant clues to understanding ALS, including genetic mutations in superoxide dismutase 1 (SOD1) in familial ALS and the abnormal deposition of TAR DNA-binding protein 43 (TDP-43) in sporadic ALS cases. By using ALS model mice (mutant SOD1 transgenic mice) and various in vivo and in vitro techniques, we aim to clarify the pathomechanisms of ALS and to develop effective and practical treatments for ALS patients.

Projects



The ultimate goal of our research is to develop innovative therapies against ALS. To this end, we are currently taking multiple approaches using cultured cells, cell-free systems, and ALS model mice. Expertise in our lab encompasses cell biology, protein chemistry, genetics, immunohistochemistry, and animal surgery.

ALS involves multiple pathological pathways, thus combination therapy is accepted as the most practical way to block as many pathways as possible. One of the most important concepts in understanding the pathogenesis of ALS (especially mutant SOD1-linked ALS) is "non-cell-autonomous motor neuron death". According to this theory, the toxicity of motor neuron death is determined by surrounding cells, but not by the motor neurons themselves (1). Various mechanisms have been proposed to explain this phenomenon including neuroinflammation, reactive oxygen species, and excess glutamate. The group of Prof. Jean-Pierre Julien, in which I pursued postdoctoral training, found that mutant SOD1 is secreted together with a neurosecretory protein chromogranin, to generate a proinflammatory effect (2). We also showed the beneficial effect of vaccination and antibody therapy targeting the extracellular SOD1 mutant (3). We are working together with the lab of Prof. Jean-Pierre Julien to develop more effective immunotherapy regimes for ALS.

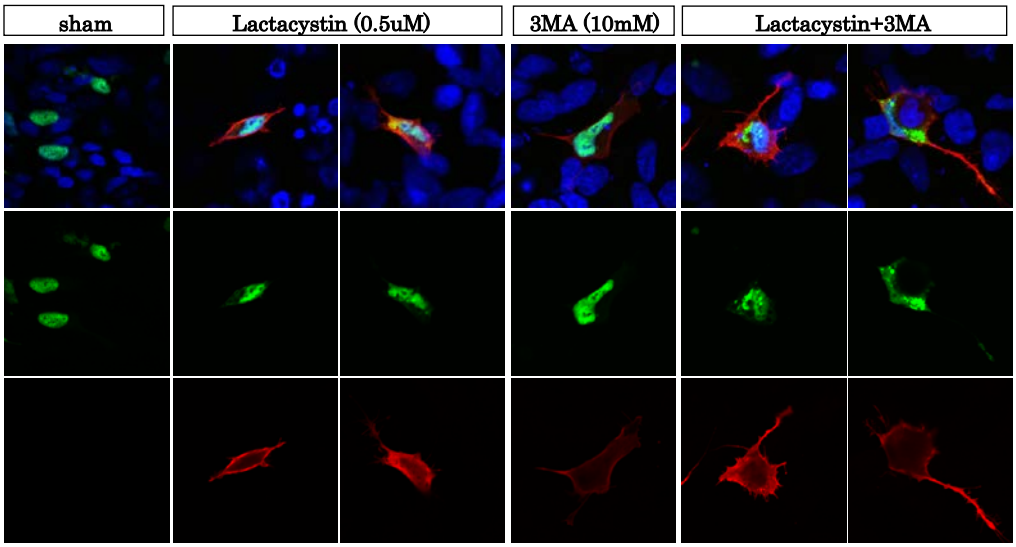
Current projects are as follows:

1. Development of novel immunotherapies for ALS

2. Identification of ALS-specific inhibitors of axonal repair

3. Clarification of the role of TDP-43 mislocalization and ubiquitination in the pathogenesis of sporadic ALS

4. Structural analysis of ALS-linked proteins using sophisticated NMR techniques.



Unit for Animal Models of Neurological Disorders

Ryosuke Takahashi
Visiting Professor
ryosuket@kuhp.kyoto-u.ac.jp

Akinori Matsuo
Senior Assistant Professor
akimatsu@belle.shiga-med.ac.jp

Projects

Our unit's aim is to produce appropriate animal models for generating more precise and translatable information about neurological disorders, such as Alzheimer's disease. Shiga University has one of Japan's largest colonies of Macaca fascicularis. Taking advantage of these valuable resources, we hope to establish non-human primate disease models.

Reliable etiologies or therapies for the majority of neurodegenerative diseases, psychiatric disorders, and developmental disorders remain to be elucidated, and appropriate animal models are an important part of addressing this knowledge gap. Many rodent-based animal models exist and have provided a lot of useful information. However, extrapolating the data from such models to understand human pathophysiology is not always precise enough due to the significant species differences between rodents and human. Non-human primate animal models are therefore needed to bridge the gap despite the associated technical challenges and ethical issues.

As a start, we are currently establishing stable monkey embryonic stem cells expressing disease-specific genes, and developing a lentiviral vector system for gene transfer into fertilized eggs of monkeys.

Publication List (2008-2011)

Original research papers and review papers (English)

1. Sako W, Morigaki R, Kaji R, Tooyama I, Okita S, Kitazato K, Nagahiro S, Graybiel AM, Goto S: Identification and localization of a neuron-specific isoform of TAF1 in rat brain: implications for neuropathology of DYT3 dystonia. ***Neuroscience***, 2011, in press.

2. Abdelalim EM, Tooyama I: Mapping of NPR-B immunoreactivity in the brain stem of Macaca fascicularis. ***Brain Struct Funct***, 2011, in press.

3. Morimoto K, Horio J, Sato H, Sue L, Beach T, Arita S, Tooyama I, Konishi Y: Expression profiles of cytokines in the brains from Alzheimer's disease (AD) patients, compared to the brains from normal control subjects and non-demented patients with increasing AD pathology. ***J Alzheimers Dis*** , 2011, in press.

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5. Hata S, Fujishige S, Araki Y, Taniguchi M, Urakami K, Peskind E, Akatsu H, Araseki M, Yamamoto K, Martins RN, Maeda M, Nishimura M, Levey A, Chung KA, Montine T, Leverenz J, Fagan A, Goate A, Bateman R, Holtzman DM, Yamamoto T, Nakaya N, Gandy S, Suzuki T. Alternative processing of γ-secretase substrates in common forms of mild cognitive impairment and Alzheimer's disease: Evidence for γ-secretase dysfunction. ***Ann Neurol***, 2011 in press.

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10. Abdelalim EM, Tooyama I: NPR-A regulates self-renewal and pluripotency of embryonic stem cells. ***Cell Death Dis*** 10; 2; e127, 2011

11. Yanagisawa D, Taguchi H, Yamamoto A, Shirai N, Hirao K, Tooyama I: Curcuminoids bind to Amyloid ß (1-42) oligomer and fibril. ***J Alzheimer Dis*** 24 (supple 2): 33-42, 2011.

12. Matsuo A, Bellier JP, Nishimura M, Yasuhara O, Saito N, Kimura H. Nuclear choline acetyltransferase activates transcription of a high-affinity choline transporter. ***J Biol Chem***. 2011;286:5836-45.

13. Nakahara H, Konishi Y, Beach TG, Yamada N, Makino S, Tooyama I: Infiltration of T-lymphocytes and expression of ICAM-1 in the hippocampus of patients with hippocampal sclerosis. ***Acta Histochem Cytochem*** 43: 157-162, 2010.

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Grant (2011)

A. Grant-in-Aid for Scientific Research (Ministry of Education, Culture, Sports, Science and Technology)

2011 (TOTAL)

(1) Grant-in-Aid for Scientific Research (B): 2010-2013 (Tooyama) “Development of amyloid imaging based on 19F-MRI”

¥3,400,000 (¥14,730,000)

(2) Challenging Exploratory Research: 2011-2012 (Tooyama) “Development of a novel serodiagnostic test for Alzheimer's disease using curcumin derivatives”

¥1,700,000 (¥2,900,000)

(3) Grant-in-Aid for Scientific Research (B): 2011-2013 (Urushitani) “Identification of pathogenic intramolecular domains of TDP-43 and its application for new antibody therapy against ALS ”

¥5,500,000 (¥15,400,000)

(4) Grant-in-Aid for Scientific Research (C): 2011-2013 (Nishimura) “Development of therapeutic strategy for Alzheimer disease by targeting APP-C99”

¥1,500,000 (¥5,1000,000)

(5) Grant-in-Aid for Scientific Research (C): 2011-2013 (Hasegawa) “Analysis of a novel regulator for amyloid-β generation”

¥1,700,000 (¥5,330,000)

(6) Challenging Exploratory Research: 2010-2011 (Urushitani) “Exploration of the novel pathomechanism of ALS through the investigation of structural instability of TDP-43”

¥1,300,000 (¥2,800,000)

(7) Grant-in-Aid for Young Scientists (B): 2010-2011 (J.P. Bellier) “Mechanism of analgesia by GCH1 inhibitor”

¥1,200,000 (¥3,280,000)

(8) Grant-in-Aid for Young Scientists (B): 2010-2011 (Makino) “Functional analysis of N-TAF1, the disease causative gene of X-linked recessive dystonia-parkinsonism”

¥1,400,000 (¥3,480,000)

(9) Grant-in-Aid for JSPS Fellows: 2009-2011 (Abdelam, Tooyama) “Elucidation of the role of natriuretic peptides in ES cells”

¥600,000 (¥1,500,000)

(10) Grant-in-Aid for JSPS Fellows: 2011-2013 (Yanagisawa, Tooyama) “Utilization of keto-enol tautomerism of curcuminoid for diagnosing and treating Alzheimer's disease”

¥800,000 (¥2,400,000)

(11) Grant-in-Aid for Scientific Research (B):2011-2014 (Matsuo) “Development of a monkey model of sporadic Alzheimer’s disease by overexpression of human APP mutant, and formation of senile plaques”

￥400,000 (￥1,600,000)

(12) Grant-in-Aid for Scientific Research (B):2011-2014 (Nishimura) “Development of a monkey model of sporadic Alzheimer’s disease by overexpression of human APP mutant, and formation of senile plaques”

￥400,000 (￥1,600,000)

(13) Grant-in-Aid for Scientific Research (C):2010-2012 (Matsuo) “Analysis for projection al pattern of septo-hippocampal system and progression of neurodegeneration”

￥150,000 (￥500,000)

B. Ministry of Health, Labour and Welfare

(1) 2011-2013 (Urushitani) “Grant for Research on Neurodegenerative diseases”

￥1,400,000 (￥4,200,000)

C. National Center of Neurology and Psychiatry

(1) 2010-2012 (Urushitani) “Development of diagnostic techniques and treatments for intractableneuropathy”

￥600,000 (￥2,000,000)

International Symposium

Since 2000, we have held annual international symposia aiming at contributing to the development in neuroscience research by further international collaborations.

(1) The 1st MNRC international symposium: *scheduled on* Oct 2, 2000
Title: "Molecular Biology of Neurodegenerative Diseases"
Guest speakers: Dr. P. H. St George-Hyslop (University of Toronto, Canada)
Dr. S. Tsuji (Niigata University, Japan)
Dr. R. Takahashi (RIKEN Brain Science Institute, Japan)
Host speaker: I. Tooyama (MNRC)

(2) The 2nd MNRC international symposium: *scheduled on* Nov 21, 2000
Title: "Recent Advances in Neuroscience"
Guest speakers: Dr. H. W. M. Steinbusch (University of Maastricht, Netherlands)
Dr. S. Mori (National Institute of Physiological Sciences, Japan)
Dr. J. I. Nagy (University of Manitoba, Canada)
Host speaker: H. Kimura (MNRC)

(3) The 3rd MNRC international symposium: *scheduled on* Oct 9, 2001
Title: "Alzheimer's disease: towards the elucidation of the pathological process"
Guest speakers: Dr. K. Tanaka (Kyoto Pharmaceutical University, Japan)
Dr. T. Kawamata (Kobe University, Japan)
Dr. K. Duff (New York University, U.S.A.)
Host speaker: O. Yasuhara (MNRC)

(4) The 4th MNRC international symposium: *scheduled on* Mar 4, 2002
Title: "Cholinergic Mechanisms in the Enteric Nervous System"
Guest speakers: Dr. J. B Furness (University of Melbourne, Australia)
Dr. Y. Tache (University of California, U.S.A.)
Dr. A. Brehmer (University of Erlangen-Nürnberg, Germany)
Dr. T. Powley (Purdue University, U.S.A)
Dr. R. Phillips (Purdue University, U.S.A)

(5) The 5th MNRC international symposium: *scheduled on Oct* 7, 2002
Title: "Mechanism of neuron survival and death"
Guest speakers: Dr. K. Nishi (Shiga University of Medical Science)
Dr. M. Yasuhara (Kyoto Prefectural University of Medicine)
Dr. W. Staines (University of Ottawa, Canada)
Dr. N. von Wurmb-Schwark (Kiel University, Germany)
Dr. M. Oehmichen (Lübeck University, Germany)
Host speaker: Petra Minnash (MNRC)

(6) The 6th MNRC international symposium: *scheduled on* Nov 15, 2002
Title: "Developments in MR-Guided Minimally Invasive Surgery"
Guest speakers: Dr. Y. Kurumi (Shiga University of Medical Science)
Dr. E. Kumamoto (Kobe University, Japan)
Dr. N. Hata (Tokyo University, Japan)
Dr. F.A. Jolesz (Harvard Medical School, USA)
Host speaker: S. Morikawa (MNRC)

(7) The 7th MNRC international symposium: *scheduled on* Feb 21, 2002
Title: Prospect of MR Research in Biomedicine –New Dimensions of Clinical Tools"
Guest speakers: Dr. R.E. Lenkinski (Harvard School of Medicine, USA)
Dr. S. Cerdan (Instituto de Investigaciones Biomedicas, Spain)
Dr. S.G. Hushek (Norton Hospital, USA)
Dr. J. Murashita (Shiga University of Medical Science)
Dr. M. Suzuki (Shiga University of Medical Science)
Dr. Y. Nishida (Shiga University of Medical Science)
Dr. Y. Kurumi (Shiga University of Medical Science)
Dr. M. Seto (Shiga University of Medical Science)
Host speakers: T. Inubushi (MNRC)
S. Morikawa (MNRC)

(8) The 8th MNRC international symposium: *scheduled on* Sep 14, 2003
Title: Peptide and Protein Sciences in the Postgenomic Era"
Guest speakers: Dr. PL. McGeer (University of British Columbia, Canada)
Dr. M. Kunimatsu (Nagoya University, Japan)
Host speaker: A. Matsuo (MNRC)

(9) The 9th MNRC international symposium: *scheduled on* Aug 24, 2004
Title: "Neural Structure and Function"
"In Celebration of the 30th Anniversary of SUMS"
Guest speakers: Shinichi Nakagawa (RIKEN Kobe Institute, Japan)
Dr. Kathleen Rockland (RIKEN Wako Institute, Japan)
Dr. Uel J McMahan (Stanford University, USA)
Dr. John Furness (University of Melbourne, Australia)
Host speakers: Naoaki Saito (MNRC/Kobe University, Japan)
A. Matsuo (MNRC)
Mohamed Elnasharty (MNRC, Japan/Egypt)

(10) The 10th MNRC international symposium: *scheduled on* Dec 18, 2006
Title: "Acetylcholine in the peripheral nervous system"
Guest speaker: Dr. Gabriella Augusti-Tocco (University of Rome La Sapienza, Italy)
Host speaker: H. Kimura (MNRC)

(11) The 11th MNRC international symposium: *scheduled on* Feb 20, 2009
Title: "Neurodegenerative Disorders"
Guest speakers: Dr. Gordon W Arbuthnott (Okinawa Institute of Science and Technology)
Dr. Kheira Jolin-Dahel (University of Ottawa, Canada)
Dr. Sarah Schock (University of Ottawa, Canada)
Host speaker: M. Urushitani (MNRC)

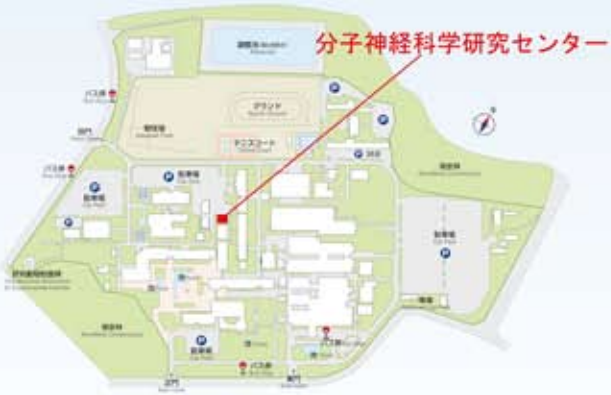
(12) The 12th MNRC international symposium: *scheduled on* Jun 24, 2009
Title: "Functional Analysis of Neural Network - from cell to the Brain"
Guest speaker: Dr. William Staines (University of Ottawa, Canada)
Host speaker: H. Kimura (MNRC)

(13) The 13th MNRC international symposium: *scheduled on* Sep 10, 2010
Title: "How to direct therapeutic strategies in ALS"
Guest speakers: Albrecht Clement (University of Mainz, Germany)
Ryo Kitahara (Ritsumeikan University)
Janice Robertson (University of Toronto, Canada)
Koji Yamanaka (RIKEN Brain Science Institute)
Host speaker: Makoto Urushitani (MNRC)

国立大学法人　　神経難病研究推進機構

滋賀医科大学　　分子神経科学研究センター

Molecular Neuroscience Research Center
Shiga University of Medical Science



〒520-2192 滋賀県大津市瀬田月輪町
TEL 077-548-2330 FAX 077-548-2331

Seta-tsukiwa-Cho, Otsu, Japan, 520-2192
http://ben.shiga-med.ac.jp/~hqmnran/