Table of Contents

Welcome Message

Holding of the first International Symposium of Brain Protein Aging and Dementia Control

It is our great pleasure to welcome you to the first International Symposium of Brain Protein Aging and Dementia Control held in Nagoya from 9 to 10 October, 2015. This research field is funded by Scientific Research on Innovative Areas, a MEXT Grant-in-Aid Project FY2014-2018.

This current field comprised Brain protein aging and neural circuit breakdown (A01), Molecular basis of brain protein aging (A02), and Development of therapy for protein aging (A03). The study will take an interdisciplinary approach to analyze chronological changes of brain proteins and neural networks, in particular, from normal to degeneration and from various angles of molecular to individual levels. The aims of this field is as follows;

(1) Clarification of the mechanisms of initiation and pathogenicity of brain protein aging
(2) Clarification of the mechanisms of aged brain proteins' intercellular transmission and infectiveness
(3) Clarification of the mechanisms of pathogenicity acquired by aged brain proteins and its inhibition and the development of clinical markers
(4) Visualization of brain protein aging and clarification of the mechanisms of neural circuit breakdown.

In order to accelerate these purposes, the main concern of this symposium is to share the knowledge and discuss the several important topics: 1) relationship between brain protein aging and neural circuit breakdown, 2) role for brain pericytes in brain protein aging, 3) molecular bases of brain protein aging, 4) role for tau imaging in brain protein aging with outstanding domestic and overseas researchers. Furthermore, we will consider the future directions of this area.

The program consists of 18 cutting edge lectures including five invited speakers of excellence in this field from other 3 countries as well poster presentations of on going and exciting projects by our colleagues. We welcome to all participants and hope that discussion and collaboration of the relevant researches will be strongly progressed and enhanced.

Lastly, I hope that everyone will have a wonderful time in Nagoya. Nagoya is known for as a city of history and manufacturing, as well as for its' unique and distinctive food culture, which adds more to the experience of the regional culture to the scholarship. I am looking forward to seeing you all at the symposium.

Sincerely,

Gen Sobue

Project Director Gen Sobue
Nagoya University Graduate School of Medicine

Research groups

A01-1: Visualization of brain protein aging and clarification of the mechanisms of neural circuit breakdown

• Gen Sobue	Professor, Nagoya University Graduate School of Medicine
• Kengo Itoh	Chief, National Center for Geriatrics and Gerontology
• Hirohisa Watanabe	Designated Professor, Nagoya University
• Tetsuya Suhara	Team Leader, National Institute of Radiological Sciences
• Masahisa Katsuno	Professor, Nagoya University
• Naoki Atsuta	Lecturer, Nagoya University
• Hiroki Tanabe	Professor, Nagoya University

A01-2: Elucidation of mechanism for neural network disruption by protein-specific PET imaging

• Kazuhiko Yanai	Professor, Tohoku University
• Nobuyuki Okamura	Associate Professor, Tohoku University
• Shozo Furumoto	Professor, Cyclotron and Radioisotope Center, Tohoku University

A02-1: Molecular mechanism of brain protein aging

• Akihiko Takashima	Chief, National Center for Geriatrics and Gerontology
• Shinichi Hisanaga	Professor, Tokyo Metropolitan University
• Tomohiro Miyasaka	Associate Professor, Doshisha University
• Masaya Ikegawa	Professor, Doshisha University
• Shinsuke Ishigaki	Designated Assistant Professor, Nagoya University
• Akio Sumioka	Laboratory Manager, National Center for Geriatrics and Gerontology
• Hiroaki Misono	Professor, Doshisha University
• Akiko Taguchi	Chief, National Center for Geriatrics and Gerontology

A02-2: Molecular bases of pathogenic proteins and mechanisms of the propagation

• Masato Hasegawa	Head, Department of Dementia and Higher Brain Function, Tokyo Metropolitan Institute of Medical Science
• Tetsuyuki Kitamoto	Professor, Tohoku University

A02-3: Protein aging from perturbation of robustness of nucleic acid metabolism and its elimination mechanism

• Osamu Onodera	Professor, Niigata University
• Akiyoshi Kakita	Professor, Niigata University

A03-1: Establishment of brain protein aging models; human iPS cell model and non-human primate model

• Hideyuki Okano	Professor, Keio University
• Seiji Shiozawa	Assistant Professor, Keio University

A03-2: Development of imaging-based diagnostic procedures for brain protein aging

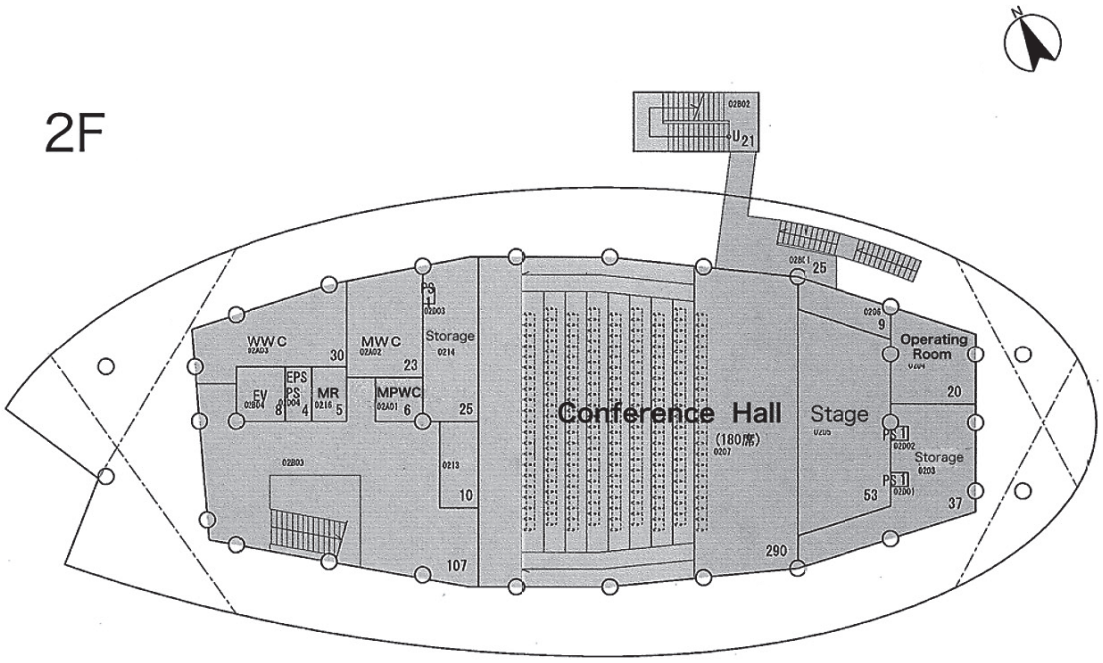
• Naruhiko Sahara	Senior Researcher, National Institute of Radiological Sciences
• Yoshiki Yamaguchi	Team Leader, RIKEN
• Makoto Higuchi	Team Leader, National Institute of Radiological Sciences
• Takafumi Minamimoto	Team Leader, National Institute of Radiological Sciences
• Ichio Aoki	Team Leader, National Institute of Radiological Sciences

Public offering members list of Project Research

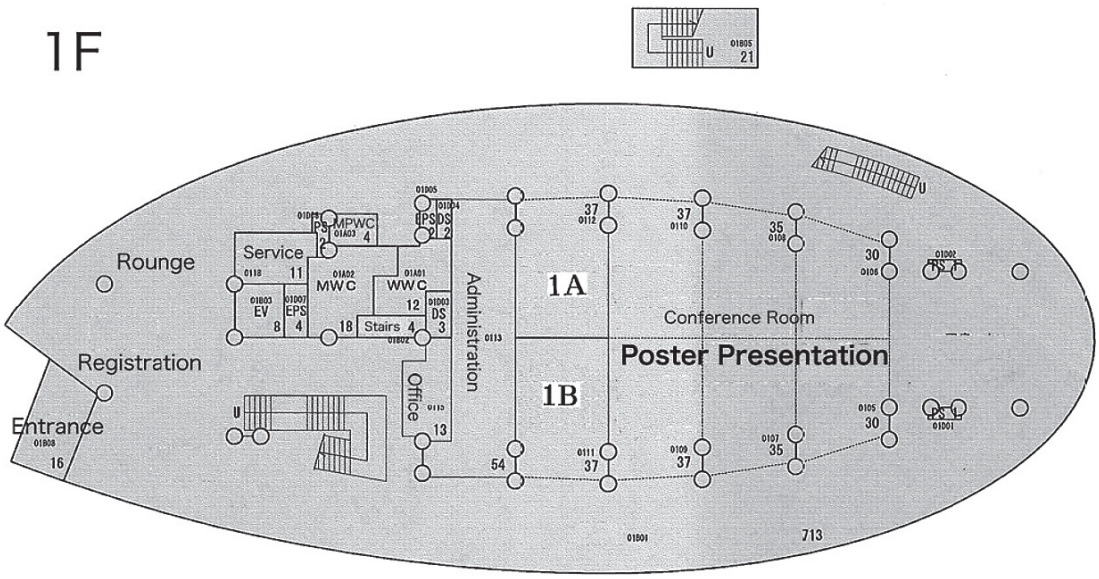
• Masahiro Ono	Associate Professor, Kyoto University
• Takenobu Murakami	Assistant Professor, Fukushima Medical University
• Kotaro Mizuta	Researcher, RIKEN
• Masashi Aoki	Professor and Chair, Tohoku University
• Motoyuki Itoh	Professor, Chiba University
• Kaoru Yamada	Assistant professor, The University of Tokyo
• Yuri Shibata	Assistant professor, The University of Tokyo
• Hiromitsu Tanaka	Assistant Professor, Kyoto University
• Mikiko Ohno	Assistant Professor, Kyoto University
• Suehiro Sakaguchi	Professor, Tokushima University
• Gen Matsumoto	Associate Professor, Nagasaki University School of Medicine
• Shingo Ito	Assistant Professor, Kumamoto University
• Kanae Ando	Associate professor, Tokyo Metropolitan University
• Etsuro Ohta	Assistant professor, Kitasato University
• Yoshiaki Furukawa	Associate Professor, Keio University
• Nobuyuki Nukina	Professor, Doshisha University
• Masaki Fukata	Professor, National Institute for Physiological Sciences
• Kozo Hamada	Research scientist, RIKEN
• Shigeomi Shimizu	Professor, Tokyo Medical and Dental University
• Hideki Mochizuki	Professor, Osaka University
• Yohei Okada	Associate Professor, Aichi Medical University

Noyori Conference Hall (NCH)

2nd Floor
(Oral presentation)

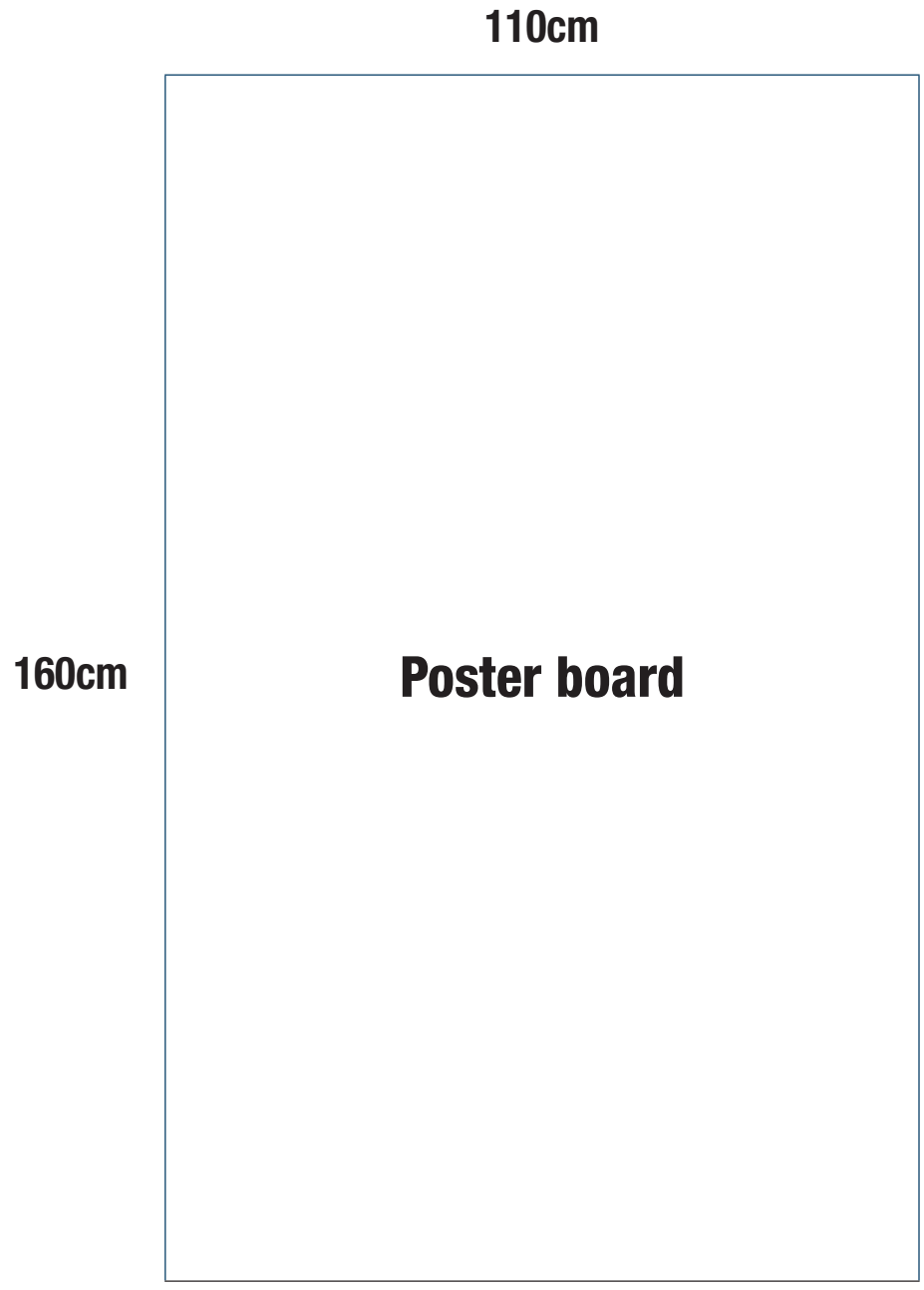


1st Floor
(Poster, Information exchange meeting, Lunch, WiFi, Space for relaxation)



Instruction for Poster Presenters

1. The secretariat prepares poster board, pins, and poster numbers.
2. There is designated mounting time, but you are asked to complete poster mounting by day 1st. Your poster is requested to be posted during the conference.
3. Posters have to be brought to the conference and not mailed as the secretariat cannot be responsible for loss or mishandling.
4. Audio-visual equipment may not be used.
5. Poster left after the removal time will be removed by the secretariat, and they will not be kept after the conference.
6. Poster presenters are required to stand by their posters.



Program

October 9 (Friday)

12:50 – 13:00 Welcome speech

Gen Sobue (Nagoya University Graduate School of Medicine)

13:00 – 14:40 Debate of a role for brain pericytes in brain protein aging

Moderator: Roy O Weller, Osamu Onodera

13:00 – 13:40 **Roy O Weller** (Clinical Neurosciences, Faculty of Medicine, University of Southampton, UK)
Failure of elimination of Amyloid β (Aβ) from the brain in the pathogenesis of Alzheimer's disease and cerebral amyloid angiopathy

13:40 – 14:10 **Osamu Onodera** (Niigata University)
How does the cerebral small vessel system contribute the brain function in aging?
– Lesson from the hereditary small vessel disease –

14:10 – 14:40 **Masafumi Ihara** (National Cerebral and Cardiovascular Center)
Impact of cerebrovascular disease and potential of neurovascular approach in dementia

14:40 – 15:00 **Coffee break & Poster viewing**

15:00 – 16:20 Molecular bases of brain protein aging (1)

Moderator: Akihiko Takashima, Tetsuyuki Kitamoto

15:00 – 15:30 **Akihiko Takashima** (National Center for Geriatrics and Gerontology)
Mechanism of neurodegeneration through tau and therapy for taupathy.

15:30 – 16:00 **Masato Hasegawa** (Tokyo Metropolitan Institute of Medical Science)
Molecular analyses of pathological tau in tauopathy brains

16:00 – 16:20 **Tetsuyuki Kitamoto** (Tohoku University)
New Phenotypes of Prion Disease provide a clue to reveal an iatrogenic transmission

16:20 – 16:30 **Coffee break & Poster viewing**

16:30 – 17:50 Keynote Lectures

Moderator: Masato Hasegawa

16:30 – 17:10 **Michel Goedert** (MRC Laboratory of Molecular Biology)
The prion concept in relation to tauopathies and synucleinopathies

Moderator: Naruhiko Sahara

17:10 – 17:50 **Dennis W. Dickson** (Department of Neuroscience, Mayo Clinic)
Clinicopathologic spectrum of neurodegenerative tauopathies

18:15 Information exchange meeting

October 10 (Saturday)

9:30 – 10:10 **Keynote lectures**

Moderator: Akihiko Takashima

9:30 – 10:10 **Khalid Iqbal** (Department of Neurochemistry, New York State Institute for Basic Research)
Why tau?

10:10 – 11:10 **Future directions of this area**

Moderator: Kazuhiko Yanai

10:10 – 10:40 **Gen Sobue** (Nagoya University Graduate School of Medicine)
Brain protein aging and neurodegeneration from animal model to human:
Focusing on the underlying mechanism of tauopathies

10:40 – 11:10 **Hideyuki Okano** (Keio University)
Modeling Neurological Diseases using iPS cells and Transgenic Non-human Primates

11:10 – 13:00 **Poster discussion and Lunch**

13:00 – 14:00 **Molecular bases of brain protein aging (2)**

Moderator: Masato Hasegawa

13:00 – 13:20 **Tomoyuki Yamanaka, Nobuyuki Nukina** (Doshisha University)
NF-Y inactivation induces differential, cell type-specific neuropathology

13:20 – 13:40 **Shigeomi Shimizu** (Tokyo Medical and Dental University)
Development of small compound against polyglutamine diseases based on the regulation of alternative autophagy

13:40 – 14:00 **Takafumi Hasegawa, Masashi Aoki** (Tohoku University)
Forebrain-specific knockdown of ESCRT-0/Hrs disrupts protein quality control and promotes ER stress-mediated neuronal cell death via apoptotic and necroptotic pathway

14:00 – 14:20 **Coffee break & Poster viewing**

14:20 – 16:00 **Debate of a role for tau imaging in brain protein aging**

Moderator: Hideyuki Okano

14:20 – 15:00 **Victor L Villemagne** (Department of Nuclear Medicine & Centre for PET, Austin Health)
In vivo evaluation of the pathology of Alzheimer's disease: Ab and tau imaging

15:00 – 15:30 **Kazuhiko Yanai** (Tohoku University)
Molecular PET imaging of disease-related pathology in Alzheimer disease

15:30 – 16:00 **Naruhiko Sahara** (National Institute of Radiological Science)
Utility of tau imaging probe PBB3 in human and mouse brains

16:00 **Closing remarks**

Poster presentation

P1-1. Development of SPECT imaging probes targeting b-amyloid and tau

Name: Masahiro Ono
Institution: Department of Patho-Functional Bioanalysis, Graduate School of Pharmaceutical Sciences, Kyoto University

P1-2. Elucidation of the mechanisms of impairment of cortical plasticity in dementia and application to the new strategy for early diagnosis

Name: Takenobu Murakami
Institution: Neurology/Advanced Clinical Research Center, Faculty of Medicine, Fukushima Medical University

P1-3. Visualization of hippocampal microcircuit activity in a virtual navigation task to elucidate spatial-memory dysfunction in neural circuit breakdown process

Name: Kotaro Mizuta[1)], Masaaki Sato[1, 2)], Yukiko Sekine[1)], Masako Kawano[1)], Tanvir Isram[1)], Masamichi Ohkura[3)], Junichi Nakai[3)], Yasunori Hayashi[1, 3)]
Institution: [1)] Lab for Memory Mechanism, BSI RIKEN, Saitama, Japan, [2)] JST PRESTO, Saitama, Japan, [3)] Saitama Univ, Saitama, Japan

P1-4. Disrupted functional connectivity in Parkinson's disease patients with severe olfactory dysfunction

Name: Hirohisa Watanabe[1, 2)], Bagarinao Epifanio[2)], Noritaka Yoneyama[2)], Kazuhiro Hara[2)], Kazuya Kawabata[2)], Kazunori Imai[2)], Masaaki Hirayama[2)], Takashi Tsuboi[2)], Masahisa Katsuno[2)], Gen Sobue[1, 3)]
Institution: [1)] Brain and Mind Research Center, Nagoya University, Japan, [2)] Department of Neurology, Nagoya University Graduate School of Medicine, Japan , [3)] Nagoya University Graduate School of Medicine, Japan

P1-5. Involvement of striatal projection system in TAR DNA-binding protein 43kDa-related frontotemporal lobar degeneration

Name: Yuichi Riku[1)], Hirohisa Watanabe[1)], Mari Yoshida[2)], and Gen sobue[3)]
Institution: [1)] Department of Neurology, Nagoya University, [2)] Institute for Medical Science of Aging, [3)] Aichi Medical University, and Graduate School of Nagoya University

P1-6. Involvement of the caudate nucleus head and its networks in sporadic amyotrophic lateral sclerosis

Name: Michihito Masuda
Institution: Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan

P2-1. Altered tau isoform ratio caused by loss of FUS and SFPQ function leads to FTLD phenotypes, aberrant adult neurogenesis, and tau pathology.

Name: Shinsuke Ishigaki, Yusuke Fujioka, Yuichi Riku, Daiyu Honda, Satoshi Yokoi, , Hirohisa Watanabe, Masahisa Katsuno, Gen Sobue
Institution: Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan

P2-2. CADASIL Notch3 protein is not transendocytosed and degraded in lysosome.

Name: Satoshi Hiura[1)], Koki Hamada[1)], Toshiki Mizuno[2)], Motoyuki Itoh[1)]
Institution: [1)] Department of Biochemistry, Graduate School of Pharmaceutical Sciences, Chiba university, Japan. [2)] Department of Neurology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Japan

P2-3. Analysis of synaptic activity dependent release of tau protein from neuron.

Name: Kaoru Yamada
Institution: The University of Tokyo

P2-4. Analysis of ubiquitin linkage types in VCP mutation-induced neurodegeneration

Name: Yuri Shibata, Jun-ichiro Inoue
Institution: The Institute of Medical Science, The University of Tokyo

P2-5. Pathological effects of amyloid beta oligomers on synaptic plasticity

Name: Hiromitsu Tanaka, Daiki Sakaguchi, Tomoo Hirano
Institution: Department of Biophysics, Graduate School of Science, Kyoto University

P2-6. Nardilysin prevents amyloid plaque formation by enhancing a-secretase activity in an Alzheimer's disease mouse model

Name: Mikiko Ohno[1)], Yoshinori Hiraoka[2)], Stefan F. Lichtenthaler[3, 4, 5)], Kiyoto Nishi[1)], Sayaka Saijo[1)], Hidekazu Tomimoto[6)], Wataru Araki[7)], Ryosuke Takahashi[8)], Toru Kita[9)], Takeshi Kimura[1)], and Eiichiro Nishi[1)]

Institution: [1)] Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [2)] Department of Pharmaceutical Sciences, Kobe Gakuin University, Kobe, Japan, [3)] German Center for Neurodegenerative Diseases (DZNE), site Munich, Germany, [4)] Neuroproteomics, Klinikum rechts der Isar, Technische Universität München, 81675 Munich, Germany, [5)] Munich Cluster for Systems Neurology (SyNergy), Munich, Germany, [6)] Department of Neurology, Graduate School of Medicine, Mie University, Mie, Japan,, [7)] National Institute of Neuroscience, NCNP, Tokyo, Japan, [8)] Department of Neurology, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [9)] Kobe Medical Center General Hospital, Kobe, Japan

P2-7. The role of sortilin in the pathogenesis of prion disease

Name: Suehiro Sakaguchi, Keiji Uchiyama
Institution: Division of Molecular Neurobiology, The Institute for Enzyme Research, Tokushima University

P2-8. p62-mediated selective autophagy in neurons

Name: Gen Matsumoto
Institution: Nagasaki University School of Medicine, Department of Anatomy and Neurobiology

P2-9. Relative contributions of degradation in the brain and elimination across the blood-brain barrier to cerebral clearance of human amyloid-β peptide(1-40) monomer in the mouse brain

Name: Shingo Ito[1)], Sumio Ohtsuki[1)], Kohta Matsumiya[2)], Sho Murata[2)], Yuki Katsukura[2)], Junichi Kamiie[3)], Tetsuya Terasaki[2)]

Institution: [1)] Department of Pharmaceutical Microbiology, Faculty of Life Sciences, Kumamoto University, Japan, [2)] Division of Membrane Transport and Drug Targeting, Graduate School of Pharmaceutical Sciences, Tohoku University, Japan, [3)] Laboratory of Veterinary Pathology, School of Veterinary Medicine, Azabu University, Japan

P2-10. Pathological stabilization of tau through phosphorylation at Ser262/356 by Par-1/MARK contributes to abnormal metabolism and toxicity of tau caused by Aβ42

Name: Kanae Ando[1, 2)], Akiko Maruko-Otake[2)], Yosuke Ohtake[2)], Motoki Hayashishita[1)], Michiko Sekiya[3)] and Koichi M. Iijima[3)]

Institution: [1)] Department of Biological Sciences, Graduate School of Science and Engineering, Tokyo Metropolitan University, [2)] Department of Neuroscience, Thomas Jefferson University, Philadelphia, PA, USA, [3)] Department of Alzheimer's Disease Research, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan

P2-11. I2020T LRRK2 iPSC-derived neurons exhibit increased Tau phosphorylation

Name: Ohta Etsuro[1)], Nihira Tomoko[3)], Uchino Akiko[4, 5)], Imaizumi Yoichi[6)], Okada Yohei[6, 7)], Akamatsu Wado[6)], Nagai Makiko[4)], Ohyama Manabu[8)], Ryo Masafuchi[4)], Ogino Mieko[9)], Murayama Shigeo[5)], Takashima Akihiko[10)], Nishiyama Kazutoshi[4)], Mizuno Yoshikuni[3)], Mochizuki Hideki[11)], Obata Fumiya[1, 2)], Okano Hideyuki[6)]

Institution: [1)] Dept Immunol, Kitasato Univ of Allied Health Sci, [2)] R & D Center for Cell Design, Institute for Regenerative Medicine and Cell Design, Kitasato Univ, [3)] Dept Neuro-Regenerative Medicine, Kitasato Univ, [4)] Dept Neurology, Kitasato Univ Sch of Med, [5)] Dept Brain Bank for Aging Research, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, [6)] Dept Physiol, Keio Univ Sch of Med, [7)] Dept Neurology, Aichi Medical Univ Sch of Med, [8)] Dept Dermatol, Kyorin Univ Sch of Med, [9)] Div Integrated Care and Whole Person Care, Dept Comprehensive Medicine, Research and Development Center for New Medical Frontier, [10)] Dept Neurobiology, National Center for Geriatrics and Gerontology, [11)] Dept Neurol, Osaka Univ

P2-12. Misregulation of thiol-disulfide status in Cu,Zn-superoxide dismutase with mutations causing amyotrophic lateral sclerosis

Name: Yoshiaki Furukawa, Itsuki Anzai, Mariko Ogawa, and Eiichi Tokuda

Institution: Department of Chemistry, Keio University

P2-13. Aberrant calcium signaling in endoplasmic reticulum

Name: Kozo Hamada

Institution: RIKEN, Brain Science Institution

P2-14. Transcription factors HSF1, HSF2 and NFATc2 suppress Huntington's disease progression

Name: Naoki Hayashida

Institution: Department of Biochemistry, Yamaguchi University School of Medicine

P2-15. Quantitative analysis of GSK3Beta activity in cells.

Name: Ambika Krishnankutty[1)], Taeko Kimura[1)], Ryo Yonezawa[1)], Koichi Ishiguro[2)], Akiko Asada[1)], Taro Saito[1)] and Shin-ichi Hisanaga[1)]

Institution: [1)] Department of Biological Sciences, Tokyo Metropolitan University, Tokyo.
[2)] Juntendo University, Tokyo.

P2-16. Gain-of-function Profilin 1 mutations linked to familial amyotrophic lateral sclerosis cause seed-dependent intracellular TDP-43 aggregation

Name: Yoshinori Tanaka, Takashi Nonaka, Genjiro Suzuki, Fuyuki Kametani, Masato Hasegawa

Institution: Dementia Research Project, Tokyo Metropolitan Institute of Medical Science

P2-17. New insights in quantitative analysis of phosphorylation of Tau in AD model mouse and Tauopathy brains by Phos-tag SDS-PAGE

Name: Taeko Kimura[1)], Hiroyuki Hatsuta[2)], Masami Masuda-Suzukake[3)], Masato Hosokawa[3)], Koichi Ishiguro[4)], Haruhiko Akiyama[3)], Shigeo Murayama[2)], Masato Hasegawa[3)], and Shin-ichi Hisanaga[1)]

Institution: [1)] Department of Biological Sciences, Tokyo Metropolitan University, Tokyo, Japan
[2)] Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan neuropathology
[3)] Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan4Juntendo University, Tokyo, Japan

P2-18. The loss of FUS leads to brain atrophy accompanied with neuronal loss.

Name: Yusuke Fujioka[1)], Shinsuke Ishigaki[1)], Misato Yoshikawa[2)], Satoshi Yokoi[1)], Daiyu Honda[1)], Hirohisa Watanabe[1)], Masahisa Katsuno[1)], Akihiko Takashima[2)], Gen Sobue[1)]

Institution: [1)] Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan, [2)] Natl. Ctr. for Geriatrics and Gerontology, Aichi, Japan

P2-19. Silencing of FUS induces the morphologic abnormities of dendritic spines

Name: Satoshi Yokoi, Shinsuke Ishigaki, Yusuke Fujioka, Daiyu Honda, Masahisa Katsuno, Gen Sobue

Institution: Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan

P2-20. FUS regulates AMPA receptor function and FTLD/ALS-associated behavior via GluA1 mRNA stabilization

Name: Daiyu Honda[1)], Tsuyoshi Udagawa[1)], Yusuke Fujioka[1)], Motoki Tanaka[2)], Satoshi Yokoi[1)], Hirohisa Watanabe[1)], Masahisa Katsuno[1)], Masahiro Sokabe[2)], Shinsuke Ishigaki[1)], and Gen Sobue[1)]

Institution: [1)] Department of Neurology, Nagoya University Graduate School of Medicine, [2)] Mechanobiology Laboratory, Nagoya University Graduate School of Medicine

P3-1. Identification of propagation system using α-syn in PARK4 iPS cells

Name: Yonehiro Kanemura

Institution: [1)] Division of Regenerative Medicine, Institute for Clinical Research, Osaka National Hospital, National Hospital Organization, Osaka, Japan, [2)] Department of Neurosurgery, Osaka National Hospital, National Hospital Organization, Osaka, Japan

P3-2. Pathophysiological analysis of neurodegenerative disorders using disease specific iPSCs

Name: Yohei Okada[1, 2, 3)], Kazunari Onodera[1, 3)], Daisuke Shimojo[1, 2)], Manabu Doyu[1)], Masahisa Katsuno[3)], Gen Sobue[4)], Hideyuki Okano[2)]

Institution: [1)] Department of Neurology, School of Medicine, Aichi Medical University, [2)] Department of Physiology, School of Medicine, Keio University, [3)] Department of Neurology, Graduate School of Medicine, Nagoya University, [4)] Graduate School of Medicine, Nagoya University

P3-3. *In vivo* PET imaging of mitochondrial abnormalities in a mouse model of tauopathy

Name: Anna M. Barron[1)], Bin Ji[1)], Masayuki Fujinaga[1)], Ming-Rong Zhang[1)], Tetsuya Suhara[1)], Naruhiko Sahara[1)], Hideo Tsukada[2)], Makoto Higuchi[1)]

Institution: [1)] Molecular Imaging Center, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan. [2)] Central Research Laboratory, Hamamatsu Photonics K.K., Hamamatsu, Shizuoka, Japan.

First day

Debate of a role for brain pericytes in brain protein aging

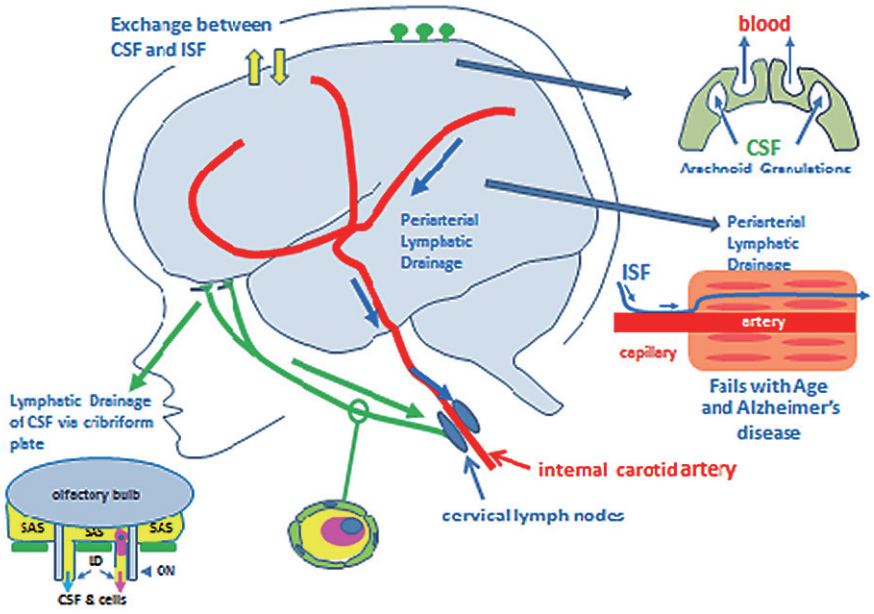
Roy O Weller

Clinical Neurosciences, Faculty of Medicine, University of Southampton, UK

Title

Failure of elimination of Amyloid β (Aβ) from the brain in the pathogenesis of Alzheimer's disease and cerebral amyloid angiopathy

Accumulation of soluble and insoluble amyloid β (Aβ) in the brain in Alzheimer's disease indicates an age-related failure of elimination of Aβ. A variety of mechanisms for elimination of Aβ have been identified that includes microglial and enzymatic degradation, receptor-mediated absorption of Aβ into the blood and lymphatic drainage of Aβ along walls of cerebral arteries. These mechanisms fail with age; cerebral amyloid angiopathy (CAA) reflects the failure of periarterial lymphatic drainage of Aβ. There are no conventional lymphatics in the brain that is one of the only organs in which there is age-related extracellular accumulation of Aβ. However, there is a very efficient lymphatic drainage of interstitial fluid and solutes, including Aβ, from the brain parenchyma to cervical lymph nodes in young individuals that is separate from lymphatic drainage of CSF. When fluorescent Aβ is injected into cerebral grey matter, it initially diffuses through the extracellular spaces but rapidly enters 100 nm-thick basement membranes in the walls of cerebral capillaries and arteries to drain out of the brain to cervical lymph nodes. Periarterial lymphatic drainage is impaired with age (Protein-Elimination-Failure Angiopathy: PEFA) and in the presence of ApoE ε4, both of which are major risk factors for Alzheimer's disease. The motive force for periarterial lymphatic drainage appears to be derived from arterial pulsations that diminish with age and arteriosclerosis. It seems that ageing of cerebral blood vessels results in failure of lymphatic drainage of Aβ and other soluble metabolites from the brain leading to loss of homoeostasis of the neuronal environment. In turn this may act as a trigger for the amyloid cascade that drives the generation of amyloid plaques in the brain and also promotes propagation of tau pathology in Alzheimer's disease. Age-related failure of periarterial elimination of Aβ (PEFA) has major implications for immunotherapy in Alzheimer's disease.



Drainage of CSF and Interstitial Fluid (ISF) from the Human Brain

Roy O Weller BSc, MD, PhD, FRC Path.

Emeritus Professor of Neuropathology, Faculty of Medicine, University of Southampton, UK.

row@soton.ac.uk

Roy Weller qualified at Guy's Hospital Medical School in London, and then worked in New York and London. In Southampton, As Professor of Neuropathology, he was responsible for the diagnostic neuropathology clinical service, for teaching neuropathology and for organising research in neuropathology. His early research interests were in the pathology of peripheral neuropathies, atherosclerosis, brain tumours and hydrocephalus. More recent research has been directed at the role of lymphatic drainage of the brain in the pathogenesis of Multiple Sclerosis and Alzheimer's disease. He has published some 200 papers and written or edited 6 major text books on Neuropathology. He was series editor for books on Neurodegeneration (2011) and on Muscle Disease (2013) published by the International Society of Neuropathology. For 10 years, he was editor of Neuropathology and Applied Neurobiology and has been a member of the editorial boards for a number of journals, including Acta Neuropathologica and Neuropathology. He has had close links with the charity Alzheimer's Research UK since its foundation and is currently chairman of the Grants Advisory Board for the Alzheimer's Society, UK. Roy Weller has had long-standing links with Japan and has hosted Japanese research fellows in his laboratory in Southampton.

Selected Papers

Kida S, Pantazis A, Weller RO (1993) CSF drains directly from the subarachnoid space into nasal lymphatics in the rat. Anatomy, histology and immunological significance. Neuropathology and Applied Neurobiology 19: 480-488

Phillips MJ, Needham M, Weller RO (1997) Role of cervical lymph nodes in autoimmune encephalomyelitis in the Lewis rat. Journal of Pathology 457-464

Weller RO, Massey A, Newman TA, Hutchings M, Kuo YM, Roher AE (1998) Cerebral amyloid angiopathy: amyloid beta accumulates in putative interstitial fluid drainage pathways in Alzheimer's disease. The American Journal of Pathology 153: 725-733

Carare RO, Bernardes-Silva M, Newman TA, Page AM, Nicoll JAR, Perry VH, Weller RO (2008) Solutes, but not cells, drain from the brain parenchyma along basement membranes of capillaries and arteries. Significance for cerebral amyloid angiopathy and neuroimmunology. Neuropathology and Applied Neurobiology 34: 131-144

Weller RO, Hawkes CA, Carare RO, Hardy J (2015) Does the difference between PART and Alzheimer's disease lie in the age-related changes in cerebral arteries that trigger the accumulation of Abeta and propagation of tau? Acta Neuropathologica 129: 763-766

Osamu Onodera

Department of Molecular Neuroscience, Resource Branch for Brain Disease Research, Brain Research Institute, Niigata University, Niigata 951-8585, Japan.

Title

How does the cerebral small vessel system contribute the brain function in aging? – Lesson from the hereditary small vessel disease –

The cerebral small vessel system plays a fundamental role in maintaining higher brain function. Advances in neuroradiological examination extend our knowledge of small vessel disease to white matter lesions, microbleeds, and cortical microinfarction. Accumulating evidence indicates that the risk factors and the therapeutic strategies are quite different for large vessel disease and small vessel disease. Moreover, the recent discoveries regarding monogenic disorders, which mainly affect small vessels, clearly indicate that the human cerebral small vessels have distinct molecular characteristics, which is different from cerebral large vessels. 1However, little is known about the molecular pathogenesis of small vessel disease and how it is different from that of large vessel disease. The investigation of hereditary small vessel disease is necessary to clarify the molecular pathogenesis of cerebral small vessel disease.

Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is a rare form of inherited cerebral small vessel disease. The clinical triad for CARASIL is leukoencephalopathy, alopecia, and lumbago. The identification of the causative gene for CARASIL, high temperature requirement (HTRA)1, allows a new understanding of the molecular pathogenesis of cerebral small vessel disease.

Studies have shown that HTRA protein decreases transforming growth factor-β (TGF-β) family signaling. Loss of HTRA1 activity leads to an increase in TGF-β signaling. Thus, the increased TGF-β signaling plays a pivotal role in the pathogenesis of cerebral small vessel disease in CARASIL. Acceleration of TGF-β signaling might affect the vascular smooth muscle cells. In my lecture, I would like to present our recent data for the molecular alteration of cerebral small vessel system in model mice. Moreover, we would like to focus on how the alteration of small vessel system contributes the aging of the brain.

Masafumi Ihara

Department of Stroke and Cerebrovascular Diseases
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Title

Impact of cerebrovascular disease and potential of neurovascular approach in dementia

With the demographic shift in age in advanced countries inexorably set to progress in the 21st century, dementia will become one of the most important health problems worldwide. The discouraging results of a lot of clinical trials for Alzheimer's disease (AD) have shifted scientific attention from the mechanism underlying β amyloid (Aβ) synthesis toward clearance, including a perivascular drainage pathway for Aβ. Theoretical models indicate that arterial pulsations may be the motive force for the drainage of interstitial fluid and solutes. As arteries stiffen with age or with other co-morbid factors, the amplitude of pulsations is reduced, perivascular drainage of Aβ becomes less efficient, and insoluble Aβ is deposited in the drainage pathways as cerebral amyloid angiopathy (CAA). CAA induces cerebral infarcts or hemorrhage of varying size and type, attributing to further cognitive impairment. Sporadic AD and CAA has been suggested to be the consequence of Aβ elimination failure, mainly caused by disturbance of the perivascular drainage system. Since severe CAA is an independent risk factor for dementia, facilitation of Aβ clearance has been suggested as a potential treatment of AD and mild cognitive impairment (MCI). We previously showed that cerebral hypoperfusion accelerates CAA and promotes cortical microinfarcts in an observational study using postmortem human brains and in an experimental study using a CAA mouse model. In addition, we have found that an antiplatelet and vasodilating drug cilostazol protects against the disruption of the neurovascular unit and facilitates the arterial pulsation-driven perivascular drainage of Aβ in a CAA mouse model. Based on a retrospective clinical data that patients with MCI receiving cilostazol exhibit significantly reduced cognitive decline, we have started an investigator-led, prospective, randomized, placebo-controlled, double-blind, multicenter trial using cilostazol for patients with MCI. Recently, many epidemiological studies have shown that vascular risk factors increase incidence of MCI and its progression to AD. Consistent with these results, control of such factors has been shown to reduce risk of conversion to AD and ameliorate cognitive impairment in AD patients. Neurovascular approaches may therefore hold promise for the treatment of neurodegenerative dementia in an era of preventive neurology.

Akihiko Takashima

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Title

Mechanism of neurodegeneration through tau and therapy for taupathy.

In Alzheimer's disease (AD), distribution of neurofibrilary tangles (NFTs) diffuse from entorhinal cortex to neocortex followed by neuronal and synapse loss while this NFTs propagation fits to the clinical progression of AD symptomatology. Therefore, blocking the formation and propagation of NFTs is thought to halt the progression of AD dementia offering a promising therapeutic intervention against the disease.

Our temporal in vitro analysis of Tau fibril formation showed that there are different and distinct forms of tau aggregates that precede Tau fibril formation. Specifically, monomeric Tau binds together and form soluble tau oligomers while granular shaped precipitates (granular Tau oligomer) after forming β-pleated sheet structure. Further in vivo support was based on Braak stage I human prefrontal cortex where an increase of the number of granular tau oligomers was observed suggesting granular tau oligomer formation occur far before NFT formation.

Moreover, analysis of our P301L-Tau Tg mouse model revealed that neuronal loss and insoluble tau formation was detected without forming pathological relevant NFTs. As P301L-Tau mice do not form tau fibrils but still exhibit neuronal loss, we suggest that toxicity of Tau aggregates could be attributed to granular tau. For further testing of this notion, we aimed to reduce formation of granular tau oligomer by screening the chemical compound X1, which associates with tau inhibiting granular tau formation. Interestingly, X1 oral administration in our P301L-Tau mice resulted in reduced neuronal loss accompanying with inhibition of sarcosyl insoluble tau level compare with vehicle control. Altogether, our studies offer novel insights about Tau aggregation pathology strongly suggesting that granular tau oligomer represents a toxic tau aggregate while X1 seems a promising compound for blocking AD progression.

Masato Hasegawa

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Title

Molecular analyses of pathological tau in tauopathy brains.

Intracellular filamentous tau pathology is the defining feature of tauopathies, which form a subset of neurodegenerative diseases. We have analysed pathological tau in Alzheimer's disease (AD), and in frontotemporal lobar degeneration associated with tauopathy (FTLD-tau) to include cases with Pick bodies (PiD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and ones due to intronic mutations in *MAPT*. We found that the C-terminal band pattern of the pathological tau species is distinct for each disease. Immunoblot analysis of trypsin-resistant tau indicated that the different band patterns of the 7~18 kDa fragments in these diseases reflect different conformations of tau molecular species. Protein sequence and mass spectrometric analyses revealed the carboxyl-terminal region (residues 243~406) of tau comprises the protease resistant core units of the tau aggregates, and the sequence lengths and precise regions involved are different among the diseases. Immunoelectron microscopy of the Sarkosyl-insoluble fractions from these tauopathy brains revealed a relationship between the trypsin-resistant cores and the morphology of the tau fibrils. These results suggest that the C-terminal band pattern of the pathological tau and the protease-resistant bands may be related to the fibril structures, especially the diameter and periodicity of the fibrils. We propose a biochemical classification of tauopathies in terms of deposition of 3R and/or 4R tau isoforms, the banding patterns of C-terminal fragments, and the protease-resistant domains.

Tetsuyuki Kitamoto

Department of Neurological Science, Tohoku University School of Medicine

Title

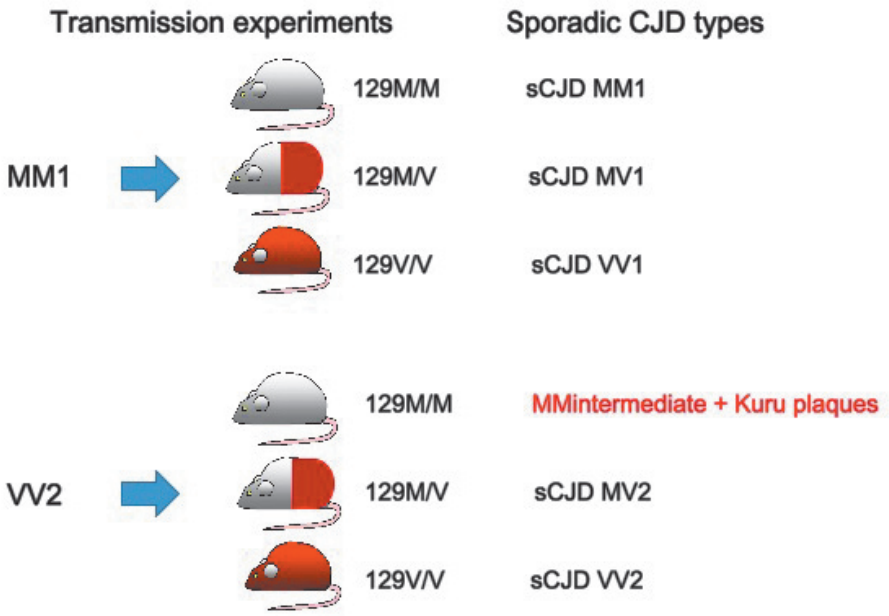
New Phenotypes of Prion Disease provide a clue to reveal an iatrogenic transmission.

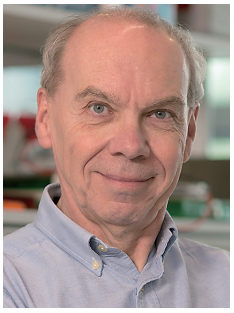
Dura grafting or human growth hormone (hGH) therapy have been reported as a risk factor of the iatrogenic Creuzfeldt-Jakob disease (CJD), because we have many, almost 200, CJD cases after the dura grafting or hGH therapy. However, it is very difficult to evaluate scientifically whether individual case is from iatrogenic origin or from sporadic origin. We cannot differentiate iatrogenic CJD from sporadic CJD (sCJD) because of the clinical and pathological similarity.

Transmission experiment of human prions with humanized knock-in mouse revealed that VV2 infections in Ki-129Met/Met make a new prion never seen in sCJD with codon 129 Met/Met genotype. This new prion shows many amyloid plaques in the brain, and shows intermediate size of PrPres between type 1 and type 2. Using this unique phenotype, we found about 30% of dura-CJD cases showed MMiK (codon 129Met/Met, intermediate PrPres, kuru plaques) prions, and 70% showed MM1 prions. This ratio correlated very well with the percentage of V2 prions and M1 prions in European sCJD.

We examined the cases with MMiK phenotype that have been reported as sCJD. We found 2 reported cases with kuru plaques and codon 129Met/Met genotype. The transmission experiment confirm the infectivity of V2 prions in these cases. One case had neurosurgical operation in the past history, and the another case was a neurosurgeon in his occupation history.

It is very important to find out the unique phenotypes never seen in sCJD, because these phenotypes provide a clue to reveal the human to human or the animal to human transmission.





Michel Goedert

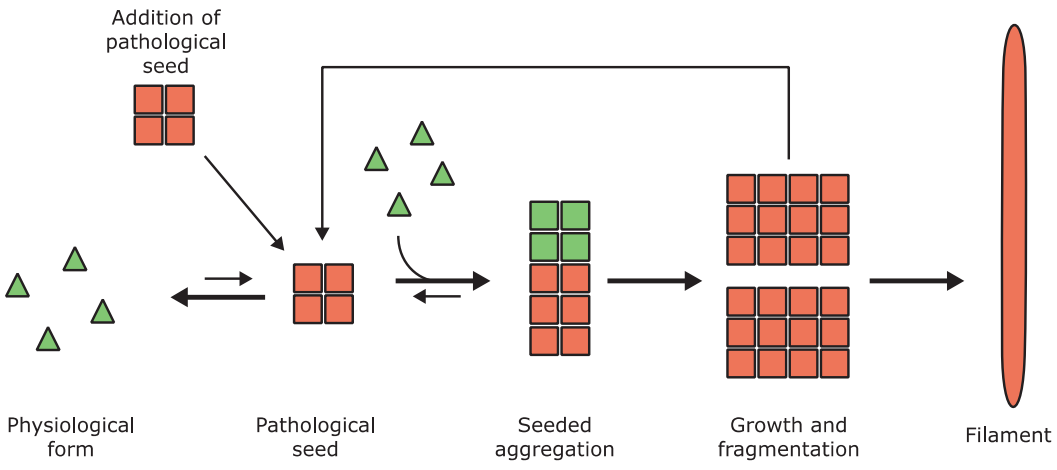
MRC Laboratory of Molecular Biology, UK

Title

The prion concept in relation to tauopathies and synucleinopathies

Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common human neurodegenerative diseases. Like most neurodegenerative diseases, AD and PD are caused by the aggregation of a small number of known proteins, with filament assemblies constituting the end-point of protein aggregation. AD is characterized by the presence of abundant extracellular plaques made of amyloid assemblies of Abeta peptides and intraneuronal inclusions made of assembled tau protein. Tau inclusions, in the absence of Abeta deposits, are characteristic of a number of neurodegenerative diseases, the so-called tauopathies, which include progressive supranuclear palsy, corticobasal degeneration, argyrophilic grain disease and Pick's disease. Unlike AD, in which two distinct amyloid assemblies are present, PD is characterized by intracellular deposits, Lewy bodies and neurites, both composed of the protein alpha-synuclein. More than 95% of those diagnosed with PD have Lewy pathology. Dementia with Lewy bodies, multiple system atrophy and primary autonomic failure are also synucleinopathies. For many years, the mechanisms underlying tauopathies and synucleinopathies were believed to be cell autonomous. This implies that the same molecular events, such as the formation of tau and alpha-synuclein assemblies, occur independently in a large number of cells in an otherwise healthy brain. Recent findings have suggested instead that non-cell autonomous processes play an important part. Inclusions are thought to form in a small number of cells and – given enough time and, perhaps, a genetic predisposition – spread in a deterministic manner to distant brain regions. The formation of the first inclusions is probably stochastic, with most seeds being degraded. Distinct molecular conformers of aggregated proteins (or strains) may underlie clinically different diseases. I will review our ongoing experimental work on the prion-like properties of aggregated tau and alpha-synuclein.

Figure



Michel Goedert

Michel Goedert's research focuses on the aetiology and pathogenesis of common human neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. In 1988, he showed that tau protein is an integral component of the paired helical and straight filaments of Alzheimer's disease. The following year he identified tau isoforms with four repeats and described the six tau isoforms that are expressed in adult human brain. He went on to show that the tau filaments of Alzheimer's disease are made of all six tau isoforms, each full-length and hyperphosphorylated. In 1996, Goedert and colleagues described a method using heparin for assembling full-length recombinant tau into Alzheimer-like filaments. In June 1998, he was part of one of three groups describing causative mutations in MAPT, the tau gene, in families with frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17T). This work proved that dysfunction of tau protein is sufficient to cause neurodegeneration and dementia. In 1997, in collaboration with Maria Grazia Spillantini, Goedert and colleagues showed that the protein alpha-synuclein is the major component of Lewy inclusions, the defining neuropathological characteristics of Parkinson's disease and dementia with Lewy bodies. A year later, several groups, including Goedert and colleagues, showed that alpha-synuclein is also the major component of the filamentous inclusions of multiple system atrophy. In more recent work, in collaboration with Florence Clavaguera and Markus Tolnay, Goedert discovered that assembled human tau protein exhibits prion-like properties. Much of his current work aims to understand the mechanisms underlying the propagation of tau and alpha-synuclein assemblies.

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Dennis W. Dickson

Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA.

Title

Clinicopathologic spectrum of neurodegenerative tauopathies

The most common of the sporadic and familial frontotemporal lobar degenerations (FTLDs) fall into one of two categories – FTLD-TDP and FTLD-tau. FTLD-tau includes familial tauopathies due to mutations in the tau gene (MAPT) on chromosome 17 and sporadic tauopathies. MAPT mutations recapitulate almost all of the sporadic tauopathies, including Pick's disease (PiD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), globular glial tauopathy (GGT), and neurofibrillary tangle predominant dementia (TPD). Some MAPT mutations have distinctive features so far not described in sporadic tauopathies. Tauopathies can be subdivided according to the predominant species of pathologic tau that accumulates in neurons and glia, specifically, with respect to tau species generated by alternative splicing of exon 10. Exon 10 encodes one of the four 31-32 amino acid repeats in the microtubule binding domain; alternative splicing of exon 10 generates 3 repeat (3R) or 4 repeat (4R) tau. FTLD-tau with predominant 3R tau is seen in PiD, while predominant 4R tau is characteristic of CBD and PSP. PSP and CBD have extensive clinical and pathologic overlap, with no distinctive clinical syndrome or biomarker that permits their differentiation. Diagnosis rests upon postmortem examination of the brain. The anatomical distribution of tau pathology, which determines the clinical phenotype, differs in typical PSP and CBD, but there is overlap in atypical cases. Low molecular weight cleavage fragments of tau differ between PSP and CBD, but no biomarkers based upon this difference currently exist. A nearly equal mixture of 3R and 4R tau is found in TPD (and in Alzheimer's disease, which is considered a "secondary tauopathy"). A sporadic tauopathy of increasing interest is that observed in brains of individuals with a history of repeated head injury – chronic traumatic encephalopathy (CTE). Tau in CTE is similar to TPD. In addition to tauopathies that are associated with neurological disorders (i.e. frontotemporal or Parkinsonian clinical syndromes), tau abnormalities of neurons ("primary age-related tauopathy") and astrocytes ("age-related astroglial tauopathy") are frequent in the aged brain. The significance of age-related neuronal and astrocytic tau pathologies on diagnostic biomarkers for neurodegenerative tauopathies, such as tau PET imaging and CSF tau analyses, is an area of active investigation.

Dennis W. Dickson, M.D.

Dr. Dickson's professional career has been devoted to the neuropathology of degenerative disorders, particularly those that produce dementia and Parkinsonism. He is the neuropathologist for the Mayo Clinic Alzheimer Disease Research Center and the Director of the Udall Center for Excellence in Parkinson's Disease Research. He runs the brain bank for the State of Florida Alzheimer Disease Initiative and the Society for Progressive Supranuclear Palsy. He received his B.S. (Biochemistry) and M.D. degrees from the University of Iowa. He was awarded the Metropolitan Life Award in 2001 and the Potamkin Prize from the American Academy of Neurology in 2011. He is past president of the American Association of Neuropathologists and editor of a monograph sponsored by the International Society of Neuropathology, now in its second edition, entitled "Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders."

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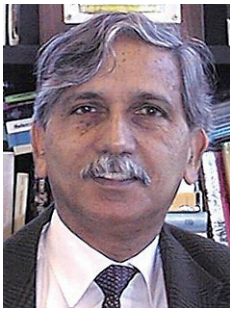
Keynote Lectures



Khalid Iqbal

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Title

Why Tau?

Neurofibrillary pathology of abnormally hyperphosphorylated tau is the key lesion of Alzheimer's disease (AD) and other tauopathies. In AD brain tau pathology is seen as intraneuronal neurofibrillary tangles, neuropil threads, and dystrophic neurites surrounding the Aβ core in neuritic (senile) plaques. The density of neurofibrillary tangles directly correlates with the degree of dementia in these patients. Without exception, neurofibrillary pathology is made up of hyperphosphorylated tau in tauopathies. Tau can be both a primary and a secondary cause of neurodegeneration. Certain tau mutations are inherited in autosomal dominant fashion and cause frontolobar dementias. In AD tau is abnormally hyperphosphorylated in the absence of any tau mutations due to a protein phosphorylation/dephosphorylation imbalance, leading to neurofibrillary degeneration and dementia. AD is a multifactorial disorder. Brain acidosis following ischemia and hypoxia, especially after hyperglycemia in diabetics, can lead to inhibition of protein phosphatase-2A (PP2A), the major tau phosphatase, through activation of asparaginyl endopeptidase and cleavage and translocation of inhibitor-2 of PP2A, I2PP2A, from the neuronal nucleus to the cytoplasm. Biomagnification of β-N-methylamino-N-alanine (BMAA) in the brain by cyanobacterial infection, such as in Guam ALS-PD complex and a subgroup of AD cases, can lead to inhibition of PP2A through activation of metabotropic glutamate receptor mGluR5 and consequent dissociation from it of PP2A catalytic subunit PP2Ac and its inhibitory phosphorylation by Src kinase at Tyr307. The hyperphosphorylated tau sequesters and templates normal tau. Thus, inhibition of the hyperphosphorylation of tau and/or its clearance are potentially promising therapeutic approaches for AD and related tauopathies.

Khalid Iqbal

Khalid Iqbal, Professor and Chairman, Department of Neurochemistry at the New York State Institute for Basic Research in Developmental Disabilities, Staten Island, New York, received his Ph.D. in Biochemistry in 1969 from the University of Edinburgh, UK. Dr. Iqbal was the first to describe in 1974 the bulk isolation and protein composition of neurofibrillary tangles/paired helical filaments (PHF) from Alzheimer disease brains. In 1986 he, along with Dr. Inge Grundke-Iqbal, discovered that the PHF protein and the microtubule-associated protein tau are the same and that tau in PHF is hyperphosphorylated.

Dr. Iqbal is the recipient of many prestigious honors and awards, including the Potamkin Prize for Alzheimer Disease Research from the American Academy of Neurology, and the Zenith Award from Alzheimer's Association, USA. He founded and chaired the biennial International Conference on Alzheimer's Disease from 1988 to 2008. In 2008 Alzheimer's Association, USA established a Khalid Iqbal Lifetime Achievement Award for Alzheimer's Disease Research, which is given out annually at the Alzheimer's Conference to a senior established researcher. Dr. Iqbal has authored over 300 scientific papers and edited seven books on research advances in Alzheimer disease and related neurodegenerative disorders. He currently serves on the editorial boards of several journals.

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Gen Sobue

Nagoya University Graduate School of Medicine

Title

Brain protein aging and neurodegeneration from animal model to human: Focusing on the underlying mechanism of tauopathies

Visualization of brain protein aging and clarification of the mechanisms of neural circuit breakdown from micro to macro perspective are important for very early diagnosis of dementia and disease-modifying therapy.

Recently, we established hippocampal-specific mouse model of tauopathy by injecting AAV encoding shRNA for FUS and SFPQ. It revealed that FUS and SFPG interaction plays a role in regulating alternative splicing of the Mapt gene at exon 10, which generates two isoforms of Tau, 4-repeat Tau (4R-T) and 3-repeat Tau (3R-T). Silencing of FUS or SFPQ resulted in an increased ratio of 4R-T / 3R-T. Mice with hippocampus-specific FUS-knockdown or SFPQ knockdown both exhibited abnormal behaviors mimicking FTLD-like behavioral impairments, neurodegeneration, phosphorylated tau deposition, and impaired adult neurogenesis. These aberrant phenotypic expression and neurodegeneration with tau pathology were well rescued by co-silencing 4R-T. These results suggest a novel pathophysiological link between FUS and SFPQ interaction and tauopathy through the regulation of 4R-T/3R-T isoform ratio.

As for visualization of macro brain network, we have investigated the change of brain network in 1,000 healthy control aging subjects using MRI and MEG. Based on preliminary analysis, brain atrophy was observed in mainly limbic and premotor area with aging and DTI showed anatomical network disruption surrounding the lateral ventricle. However, resting connectivity across multiple cortical areas were more frequently enhanced than the decrease of those. These types of enhanced connectivities were also observed in Parkinson's disease and early Alzheimaer's disease. Interestingly, a number of these networks were originated from specific anatomical lesions. Thus, collapse of these "hub" lesions which may play an important role for maintaining the cognitive function will be closely associated with the development of dementia. We also introduced new tau PET tracers PBB3 and THK-5351. We now promote the association analysis between protein deposit and brain network to clarify the mechanism of relationship between brain protein aging and neural circuit breakdown.

Hideyuki Okano

Dean, Keio University Graduate School of Medicine, Japan
Professor, Dept of Physiology

Title

Modeling Neurological Diseases using iPS cells and Transgenic Non-human Primates.

What makes the investigation of human psychiatric/psychiatric disorders so difficult? This could be attributed to the following reasons 1) Diseases model mice do not always recapitulate the pathophysiology of human diseases, 2) It is extremely difficult to investigate what is taking place in vivo at the onset of the disease due to the low accessibility to the pathological foci in the brain, and 3) The responsible neuronal circuits for the phenotype are not identified. In order to overcome these difficulties, we took advantage of iPS cell technologies and transgenic non-human primates for modeling human psychiatric/psychiatric disorders. So far, we have established iPS cells from the patients of about 40 human psychiatric/psychiatric disorders and characterized their pathophysiology. For example, in collaboration with the group of Dr. Etsuro Ohta at Kitasato University, we established iPS cells from the familial Parkinson Disease (PARK8) patients with I2020T LRRK2 in the Sagamihara family (Ohta et al., 2015). Interestingly, we found that I2020T mutant LRRK2 iPSC-derived neurons released less dopamine than control-iPSC-derived neurons and that patient iPSC-derived neurons had a lower phospho-AKT level than control-iPSC-derived neurons, and that the former showed an increased incidence of apoptosis relative to the controls. Interestingly, patient iPSC-derived neurons exhibited activation of glycogen synthase kinase-3β (GSK-3β) and high Tau phosphorylation.

Furthermore, for faithfully modeling the human psychiatric/psychiatric disorders *in vivo*, we developed transgenic non-human primates (common marmosets) with germline transmission (Sasaki et al., Nature, 2009). In the present talk, we also wish to mention our recent data of generation of common marmoset transgenic models of neurodegenrerative diseases, including Parkinson disease, Alzheimer disease and ALS. Furthermore, we could generate knock-out technologies of common marmoset using genome editing technologies for the generation of transgenic marmoset model of autism and psychiatric disorders.

Tomoyuki Yamanaka, Asako Tosaki, Haruko Miyazaki, Masaru Kurosawa, Masato Koike, Yasuo Uchiyama, Sankar N. Maity, Hidemi Misawa, Nobutaka Hattori and Nobuyuki Nukina

Doshisha Univ. Brain Sci, Kyoto, Japan, Juntendo Univ. Med., Tokyo, Japan, RIKEN BSI, Saitama, Japan, Univ. Texas MDACC, Texas, USA, Keio Univ. Pharm, Tokyo, Japan

Title

NF-Y inactivation induces differential, cell type-specific neuropathology.

NF-Y transcription factor, composed of NF-YA, NF-YB and NF-YC subunits, regulates expression of various genes including molecular chaperones. The observations of NF-YA sequestration by mutant huntingtin and other polyglutamine proteins suggest its potential significance in neurodegeneration. We have recently found that NF-YA knockout in mouse cerebral pyramidal neurons induces progressive neurodegeneration. Notably, the degeneration accompanies accumulation of ubiquitin, p62 and several membrane proteins on disorganized ER. Downregulation of an ER chaperone Grp94 and other ER-related genes suggests implication of deregulated ER homeostasis in pyramidal cell degeneration.

To explore the physiological significance of NF-Y in central nervous system, we inactivate NF-Y in other types of neurons. In striatal medium spiny neurons and cerebellar Purkinje neurons, AAV-mediated knockdown of NF-Y induces accumulation of ubiquitin, p62 and several membrane proteins and selective loss of Grp94 expression. These are similar to the pathologies observed in pyramidal neurons described above. On the contrary, NF-YA knockout in motor neurons by VAchT-cre induces neuronal loss with no accumulation of ubiquitin and p62. Detailed analysis revealed downregulation of another ER chaperone Grp78 (Bip) in addition to Gpr94, suggesting that loss of two major ER chaperones may contribute to the neurodegeneration. Indeed, knockdown of both ER chaperones recapitulates the pathology observed in the NF-YA knockout neurons. These data suggest that inactivation of NF-Y, a common target of several polyglutamine proteins, induces differential transcriptional dysregulation to mediate neuronal type-specific degeneration.

Shigeomi Shimizu

Pathological Cell Biology, Medical Research Institute, Tokyo Medical and Dental University

Title

Development of small compound against polyglutamine diseases based on the induction of alternative autophagy

Autophagy is the process of bulk degradation of cellular constituents that plays an integral role in various physiological events. Atg5 and Atg7 have been considered as essential molecules for induction of autophagy. Recently, however, we discovered that in mouse cells lacking both Atg5 and Atg7 autophagy still occurs. Therefore, mammalian autophagy can occur via at least two different pathways, which are an Atg5/Atg7-dependent conventional pathway and an Atg5/Atg7-independent alternative pathway.

Given that autophagy degrades unfavourable proteins, polyglutamine proteins are good candidate substrates of autophagy. Thus, we tried to develop molecularly targeted agents that degrade polyglutamine proteins through mediating alternative autophagy. To pursue this objective, we first established a high-throughput assay system that can monitor degradation of polyglutamine via alternative autophagy. We used this system to screen 24,000 low–molecular weight compounds. From this screen, we identified 3 compounds. Then we administered these 3 compounds to polyglutamine disease model mice, and found that one compound (TMD-B03) has strong anti-polyglutamine disease activity. This compound did not cause significant side-effect in mice. We will further improve the compounds based on structure-activity relationships.

We have also extended our study to analyze molecular mechanism of the alternative autophagy, and identified several crucial molecules. Thus, in this meeting, by describing some of these data together with more recent data, I will discuss physiological and pathological roles of alternative autophagy.

Takafumi Hasegawa[1)], Ryuji Oshima[1, 2)], Nobuyuki Tanaka[2)], Masashi Aoki[1)]

[1)] Division of Neurology, Department of Neuroscience & Sensory Organs, Tohoku University Graduate School of Medicine, Sendai, Japan; [2)] Division of Cancer Biology and Therapeutics, Miyagi Cancer Center Research Institute, Natori, Japan

Title

Forebrain-specific knockdown of ESCRT-0/Hrs disrupts protein quality control and promotes ER stress-mediated neuronal cell death via apoptotic and necroptotic pathway

Selective neuronal loss accompanied by misfolded, noxious protein aggregates is the characteristic neuropathological hallmark of neurodegenerative diseases. In order to fight against these continuous threat, cells have evolved ingenious defense mechanisms which act either to facilitate refolding of misfolded proteins by molecular chaperones or to remove them by proteolytic degradation machinery including the ubiquitin-proteasome system and autophagy-lysosome pathway. The endosomal sorting required for transport (ESCRT) complexes orchestrate endo-lysosomal soring of ubiquitinated protein, multivesicular body formation and autophagic protein degradation. Defects in the ESCRT pathway have been implicated in a variety of neurodegenerative diseases, but the underlying molecular events linking neurodegeneration still remain unknown. To elucidate the mechanisms by which ESCRT dysfunction leads to cellular toxicity and subsequent neurodegeneration, here we specifically deleted the key ESCRT-0 component, hepatocyte growth factor-regulated tyrosine kinase substrate (Hrs), in neurons of the forebrain by crossing *loxP*-flanked *Hrs* mice with transgenic mice expressing the *CaMKIIα-cre*. The $Hrs^{flox/flox}$; *CaMKIIα-cre* mice showed postnatal growth retardation and progressive locomotor decline with shortened lifespan. Histologically, $Hrs^{flox/flox}$; *CaMKIIα-cre* mice revealed marked hippocampal neuron loss accompanied by the accumulation of ubiquitinated protein including α-synuclein, TDP-43 and huntingtin together with autophagic substrate SQSTM1/p62. Consistent with this, RNAi-mediated silencing of *Hrs* in cultured neurons not only led to α-synuclein accumulation together with impaired autophagic flux, but also impaired cell viability through the induction of ER stress followed by the activation of SAPK/JNK signaling and receptor-interacting serine/threonine kinase (RIPK)1, a key regulator of necroptosis. Moreover, necrostatin-1, a specific inhibitor of RIPK1, as well as pan-caspase inhibitor partially restored neurotoxicity in Hrs-silenced cells. Altogether, these findings suggest that the disruption of ESCRT in the nervous system compromises autophagic/lysosomal degradation of aggregate-prone proteins, which would thereby trigger ER stress-mediated apoptotic and necroptotic cell death.

Debate of a role for tau imaging in brain protein aging

Victor L Villemagne

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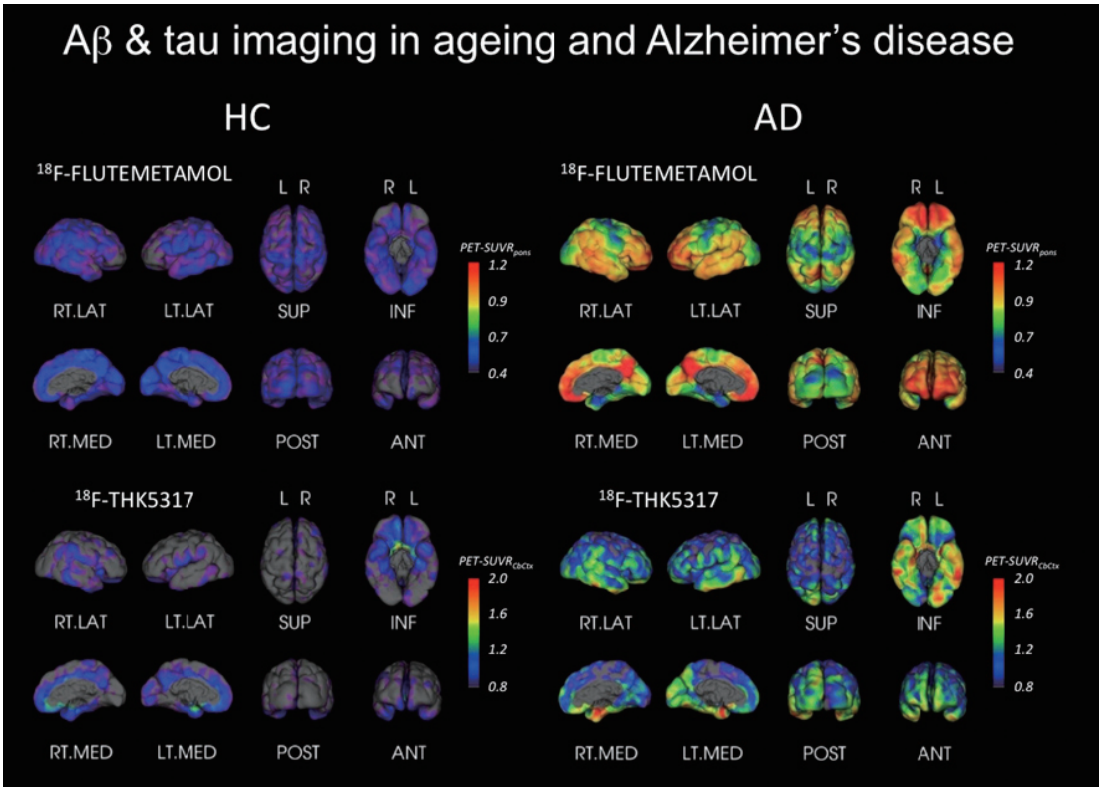
Title

In vivo evaluation of the pathology of Alzheimer's disease: Ab and tau imaging

The last decade has witnessed the development and characterization of tracers for the evaluation of the pathology of Alzheimer's disease in vivo. The introduction of selective tracers for aggregated and misfolded proteins, namely Ab and later tau, are providing the tools to change the landscape of dementia research and refine our understanding of Ab and tau deposition in the brain, allowing to investigate the causes, refine diagnosis and improve treatment of major neurodegenerative conditions such as Alzheimer's disease, Chronic Traumatic Encephalopathy and frontotemporal lobar degeneration, where either or both play a role. In vivo Ab and tau imaging allow examination of the regional and global changes of these disease markers over time as well as their relationship with other relevant parameters such as cognitive performance, genotype, fluid biomarkers and neurodegenerative changes.
Selective Ab and tau imaging are enabling to establish the respective roles Ab and tau play –as well as interplay- in aging and disease, improving the specificity of the diagnosis while allowing early detection of AD pathology in at-risk individuals. Their value resides not only in being robust diagnostic, prognostic or progression markers, but also surrogate markers of disease, crucial for patient recruitment, and evaluation of target engagement and efficacy for anti-tau and anti-Aβ therapeutic trials.



Victor L Villemagne, MD

A/Prof Villemagne graduated Cum Laude in 1983. He continued his post-graduate studies at the Division of Nuclear Medicine at Johns Hopkins Medical Institutions. He furthered his molecular neuroimaging training at the National Institute on Drug Abuse, NIH, and the University of Pittsburgh. He now holds the appointment of Senior Research Fellow in Neuroscience at the PET Centre, Austin Health where, since 2003, he has performed several clinical and preclinical Aβ and tau PET imaging studies. A/Prof Villemagne has authored or co-authored ten book chapters, several requested reviews on dementia imaging, and more than 200 original research publications, with senior or first author papers on PET research in leading international peer-reviewed journals, particularly in the field of neuroreceptor and amyloid imaging studies. Among other honours, he has received the Foerderer Fund for Excellence Award from The Children's Hospital of Philadelphia in 2002, the JAAME Fellowship from Japan in 2007 and the ANSTO Nuclear Medicine Award in 2010. More recently, he received the de Leon Prize in Neuroimaging - Senior Scientist by The Alzheimer's Association of America (Boston, USA, 7/2013), the Christopher Clark Award for the Continuing Advancement in the Field of Human Amyloid Imaging, Miami (USA, 17/01/2014), and the EANM Springer Prize for Best Paper (Germany, 10/2015).

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5. N Okamura, […] VL Villemagne. Noninvasive assessment of Alzheimer's disease neurofibrillary pathology using [18F-]THK-5105 PET. Brain. 137(Pt 6):1762-1771, 2014. *This is the follow-up paper using an improved derivative for selective tau imaging, assessed in a cohort of Alzheimer's disease patients and age-matched controls.*

Kazuhiko Yanai and Nobuyuki Okamura

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Title

Molecular PET imaging of disease-related pathology in Alzheimer disease

Alzheimer's disease (AD) and other neurodegenerative dementia belong to a family of protein misfolding diseases. These diseases are characterized by the accumulation of insoluble protein aggregates containing an enriched β-sheet structure. AD is pathologically characterized by the extensive deposition of amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs). Noninvasive monitoring of these protein deposits promises to be a useful technique for the pre-symptomatic detection of disease-related pathology and for the preventive intervention and assessment of therapeutic effects. Several PET tracers for imaging Aβ plaques have been successfully developed and commercially available. Amyloid PET studies in human subjects have shown a robust difference between the retention pattern in AD patients and healthy controls. Abnormal tracer retention in the neocortical areas predicts the progression of cognitive decline in the subjects with mild cognitive impairment and cognitively normal individuals. Recent PET studies with tau-selective PET tracers further demonstrated the radiotracer retention in sites with predilection for the deposition of NFTs and distinctly differentiated AD patients from elderly individuals. Furthermore, these tracer retention was closely associated with clinical symptom of dementia and brain atrophy. In contrast with the successful imaging of Aβ and tau, specific radiotracers are currently under development for in vivo imaging of α-synuclein and TDP43. Thus, an increasing interest has been focused on searching for novel PET imaging probes targeting at these protein deposits. In this talk, our recent progress will be presented in the development and clinical application of novel PET probes for early detection of disease-specific pathology in the brain.

Naruhiko Sahara

National Institute of Radiological Sciences, Chiba, Japan,

Title

Utility of tau imaging probe PBB3 in human and mouse brains

Intracellular deposition of microtubule-associated protein tau is a prominent neurological feature of neurodegenerative diseases referred to as tauopathies. Recent advances in positron emission tomography (PET) imaging research have led to significant breakthroughs with newly developed probes for tau depositions. This technology allows us to noninvasively examine the tau pathogenesis in living brains of humans and animal models. Our previous study has demonstrated that PET imaging with a tau radioligand, [^{11}C]PBB3, clearly visualizes tau deposits, which is closely aligned with disease symptoms of Alzheimer's disease (AD). In addition to the clinical study of AD diagnosis, utility of tau PET imaging has been examine for differential diagnoses of non-AD tauopathies. Among those clinical studies, patients and brain sections of frontotemporal dementia with parkinsonism linked to tau on chromosome 17 (FTDP-17-*MAPT*) were analyzed for tau PET imaging. All FTDP-17-*MAPT* patients showed increased [^{11}C]PBB3 uptake in cerebral cortex and medial temporal lobe. Distributions of [^{11}C]PBB3 in FTDP-17-*MAPT* patients are highly dependent on tau mutations and differ from those in AD. Autoradiography confirmed the specific binding of [^{11}C]PBB3 on tau lesions of autopsy brains with tau mutations. Histological studies of brain sections confirmed the binding of PBB3 to distinct tau pathologies such as NFTs composed of 3R+4R tau, glial inclusions composed of 4R tau and Pick body-like inclusions composed of 3R tau. On the other hand, the utility of small-animal in vivo imaging was examined for pursuing links between tau deposition and neurodegeneration. A longitudinal PET and magnetic resonance imaging (MRI) of transgenic (Tg) mice modeling tauopathy from 2 to 13 months of age confirmed that tau accumulation, neuroinflammation and forebrain atrophy became noticeable at 6 months of age. Postmortem immunohictochemical assays revealed that elevated microglial markers were associated with tau inclusions in the neocortex and hippocampus of aged Tg mice. These results indicate that temporospatial relationships among tau deposition, neuroinflammation and neuronal loss can be pursued by in vivo imaging of animal models, offering a translational research platform for investigational and therapeutic approaches to the mechanisms of tau-induced neurodegeneration.

Poster presentation

P1-1. Development of SPECT imaging probes targeting b-amyloid and tau

Name: Masahiro Ono
Institution: Department of Patho-Functional Bioanalysis, Graduate School of Pharmaceutical Sciences, Kyoto University

The objective in this study is to develop novel SPECT imaging probes targeting β-amyloid plaques (Aβ) and neurofibrillary tangles (tau) pathology, which are the major neuropathological changes in Alzheimer's disease (AD). Several PET imaging probes targeting Aβ (PIB, Flutemetamol etc.) and tau (THK-5351, PBB-3, T807 etc.) in the brain have been tested clinically and demonstrated potential utility. To diagnose a number of AD patients before the onset, it is necessary to apply new in vivo imaging technique with routine diagnostic use in addition to the PET diagnosis. Since much more hospitals possess SPECT facilities compared with PET, Aβ and tau imaging probes labeled with isotopes for SPECT will have more widespread clinical applicability. In the present study, I will report the development of novel SPECT imaging agents based on the benzoimidazopyridine scaffold targeting tau.

P1-2. Elucidation of the mechanisms of impairment of cortical plasticity in dementia and application to the new strategy for early diagnosis

Name: Takenobu Murakami
Institution: Neurology/Advanced Clinical Research Center, Faculty of Medicine, Fukushima Medical University

At the cellular and slice preparation level, accumulation of amyloid-beta protein (Aβ) in the brain causes impairment of synaptic plasticity, triggering dementia in Alzheimer's disease (AD). We propose that unveil of the mechanisms of synaptic breakdown induced by the Aβ is crucial for early detection of AD, and this may lead to prevention of dementia onset. In the present study, we induce the cortical synaptic plasticity at the systems level of the human primary motor cortex in early stages of AD, mild cognitive impairment and age-matched normal healthy controls by using transcranial magnetic stimulation. We speculated that the degree of the cortical plasticity will reflect the severity of the disorder. We have started recruiting participants, and now two patients have been registered. Here we will show the preliminary data of this project.

P1-3. Visualization of hippocampal microcircuit activity in a virtual navigation task to elucidate spatial-memory dysfunction in neural circuit breakdown process

Name: Kotaro Mizuta[1)], Masaaki Sato[1, 2)], Yukiko Sekine[1)], Masako Kawano[1)], Tanvir Isram[1)], Masamichi Ohkura[3)], Junichi Nakai[3)], Yasunori Hayashi[1, 3)]
Institution: [1)] Lab for Memory Mechanism, BSI RIKEN, Saitama, Japan, [2)] JST PRESTO, Saitama, Japan, [3)] Saitama Univ, Saitama, Japan

Neural circuit breakdown leads to decline of spatial cognitive function in Alzheimer's disease (AD) and hippocampus plays an essential role in memory formation for space. It is not well understood, however, how neural circuit for memory for space is formed and how the breakdown affects memory. To address this issue, head-fixed mice that express G-CaMP7 in hippocampal CA1 pyramidal neurons were trained on a virtual spatial memory task in which they stayed at a particular zone for 2 sec to receive reward. After training, two-photon calcium imaging revealed that a group of neurons demonstrated time-locked activity while the mice stayed at the zone. When the reward was removed, the activity of the neurons representing the zone was decreased. This suggests that the activity of these neurons has an important role in spatial memory.

P1-4. Disrupted functional connectivity in Parkinson's disease patients with severe olfactory dysfunction

Name: Hirohisa Watanabe[1, 2)], Bagarinao Epifanio[2)], Noritaka Yoneyama[2)], Kazuhiro Hara[2)], Kazuya Kawabata[2)], Kazunori Imai[2)], Masaaki Hirayama[2)], Takashi Tsuboi[2)], Masahisa Katsuno[2)], Gen Sobue[1, 3)]

Institution: [1)] Brain and Mind Research Center, Nagoya University, Japan, [2)] Department of Neurology, Nagoya University Graduate School of Medicine, Japan , [3)] Nagoya University Graduate School of Medicine, Japan

Severe olfactory dysfunction (OD) is closely associated with the development and progression of dementia in Parkinson's disease (PD). Aim of this study is to identify the specific brain atrophic patterns in PD patients with severe OD using VBM and to elucidate the brain network dynamics in PD linking between severe OD and dementia using resting state functional MRI (rs-fMRI). We classified PD patients into severe OD group (PD-ODP) and mild or no OD group (PD-ODN) using OSIT-J. PD-ODN showed mild abnormal functional connectivities but no significant GM volume loss. PD-ODP had mild GM volume loss in higher olfactory function regions and significant decreased and increased functional connectivities in resting state networks. In addition, PD-ODN and PD-ODP showed increased GM volumes in predominant posterior insular We identified the dynamic changes of increased and decreased brain GM volume and functional connectivity indicating the disruption and compensation processes underlying the pathogenesis of PD-ODP.

P1-5. Involvement of striatal projection system in TAR DNA-binding protein 43kDa-related frontotemporal lobar degeneration

Name: Yuichi Riku[1)], Hirohisa Watanabe[1)], Mari Yoshida[2)], and Gen sobue[3)]

Institution: [1)] Department of Neurology, Nagoya University, [2)] Institute for Medical Science of Aging, [3)] Aichi Medical University, and Graduate School of Nagoya University

Although frontotemporal lobar degeneration (FTLD) primarily involves the frontotemporal neocortices, the striatum is also preferentially affected. There have been limited pathological observations on differential involvement of the striosome-matrix compartments in the striatum and the striatal efferent projection systems in FTLD patients. We analyzed pathologically confirmed 59 patients with FTLD-TDP and ALS. In results, the striosome was prominently affected, and presynaptic terminals of efferent projection fibers from the striatum were remarkably depleted and involved by TDP-43 pathology. These findings were marked in FTLD patients, but some ALS patients also exhibited definite changes. The striosome receives inputs from the limbic forebrain, and striatal projections are necessary for the cortico-striatal circuits. The neural circuits involving the limbic forebrain are particularly essential for management of psychobehavior functions. Our results propose that the impairment of the striosome and striatal projection may contribute to psychobehavioral presentations in FTLD-TDP and ALS.

P1-6. Involvement of the caudate nucleus head and its networks in sporadic amyotrophic lateral sclerosis

Name: Michihito Masuda

Institution: Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan

A clinical diagnostic marker is lacking for sporadic patients with TDP-43 pathology. Our objective was to assess the specific and common lesions of brain structure and the early involved network connectivity in sporadic ALS patients. Fifty-one patients with sporadic ALS were subdivided into three groups: seven patients who satisfied FTD criteria (ALS-FTD), 25 of ALS with cognitive deficiency (ALS-CD) and 19 of ALS with normal cognitive function (ALS-NC). We investigated MRI analysis. VBM revealed atrophic changes in the caudate head and ventrolateral frontal lobe in the ALS-FTD group. TBSS revealed white matter changes, particularly in the areas surrounding the caudate head in the ALS-CD and ALS-FTD groups. Probabilistic diffusion tractography showed a significant decrease in structural connectivity between the caudate head and the other frontal cortex, even in the ALS-NC group. Our results indicated that networks of the caudate head were the most vulnerable to lesion in sporadic ALS patients.

P2-1. Altered tau isoform ratio caused by loss of FUS and SFPQ function leads to FTLD phenotypes, aberrant adult neurogenesis, and tau pathology.

Name: Shinsuke Ishigaki, Yusuke Fujioka, Yuichi Riku, Daiyu Honda, Satoshi Yokoi, , Hirohisa Watanabe, Masahisa Katsuno, Gen Sobue

Institution: Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Fused in sarcoma (FUS) is genetically and clinicopathologically linked to amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). We found that the intranuclear interaction between FUS and splicing factor, proline- and glutamine-rich (SFPQ) was disrupted in both familial and sporadic FTLD/ALS brains. Both FUS and SFPQ regulate alternative splicing of the Mapt gene at exon 10, which generates two isoforms of microtubule-associated protein tau (Tau), 4-repeat Tau (RD4) and 3-repeat Tau (RD3). Silencing of FUS or SFPQ resulted in an increased ratio of RD4/ RD3. Mice with hippocampus-specific FUS- or SFPQ-knockdown exhibited FTLD-like behavioral impairments, as well as reduced adult neurogenesis followed by tau pathology and neurodegeneration. The aberrant behaviors and reduced adult neurogenesis were rescued by co-silencing RD4. Our findings suggest a novel pathophysiological link between FUS and Tau in FTLD/ALS through the regulation of RD4/RD3 isoforms and their functional role in altered adult neurogenesis.

P2-2. CADASIL Notch3 protein is not transendocytosed and degraded in lysosome.

Name: Satoshi Hiura[1)], Koki Hamada[1)], Toshiki Mizuno[2)], Motoyuki Itoh[1)]

Institution: [1)] Department of Biochemistry, Graduate School of Pharmaceutical Sciences, Chiba university, Japan. [2)] Department of Neurology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Japan

CADASIL is an autosomal dominant hereditary disease and Notch3 gene is known as a causative gene. However, its pathogenesis is still unclear and there is no effective cure. Notch signaling acts in developing tissues and maintaining homeostasis. Ligand membrane proteins such as Jagged or Delta on neighboring cells bind Notch receptor and promote cleavage of Notch receptor to extracellular domain (NECD) and intracellular domain (NICD). NICD is translocated into the nucleus and activates downstream gene transcription. NECD is considered to be pulled by ligands and transendocytosed into ligand expressing cells. Co-culture of CADASIL mutant Notch3 expressing cells with ligand expressing cells resulted in increase in the accumulation of mutant NECD compared to that of wild type. In addition, CADASIL Notch3 protein was stabilized by chloroquine, a lysosome inhibitor, more strongly than wild type Notch3. Taken together, these data suggest that CADASIL Notch3 protein is not transendocytosed and degraded in lysosomes.

P2-3. Analysis of synaptic activity dependent release of tau protein from neuron.

Name: Kaoru Yamada

Institution: The University of Tokyo

Although tau is predominantly present in the cytoplasm, accumulating evidence suggests that it is also physiologically released into the extracellular space. However the underlying mechanism, which mediates tau release from neurons remained unknown. The previous studies have demonstrated that release of tau is regulated by neuronal activity. In order to elucidate molecular mechanisms underlying activity-dependent release of tau, we set out to characterize the secreted forms of tau species using primary cortical neurons. Consistent with the previous observations, the elevated synaptic activity by a-latrotoxin rapidly and significantly increased de novo release of endogenous tau without altering LDH activity. We observed both full-length tau as well as truncated species in the media. In contrast to intracellular tau, extracellular tau was dephosphorylated at certain cites. The substantial difference between extracellular and intracellular tau observed in this study may indicate the presence of tau species susceptible to release.

P2-4. Analysis of ubiquitin linkage types in VCP mutation-induced neurodegeneration

Name: Yuri Shibata, Jun-ichiro Inoue
Institution: The Institute of Medical Science, The University of Tokyo

Many neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD), are characterized by the ubiquitin-positive protein aggregates. Mutations in the valosin-containing protein (VCP) have recently been identified in familial ALS and Inclusion Body Myopathy, Paget's disease and Frontotemporal Dementia (IBMPFD), and VCP mutations lead to defects in autophagy-mediated protein degradation. Although it has been shown that overexpression of pathogenic VCP mutant causes accumulation of ubiquitin-positive aggregates, it remains unclear which types of polyubiquitin linkages are conjugated to this aggregates. We tried to purify polyubiquitinated proteins from VCP mutant-expressing cells using Tandem Ubiquitin Binding Entity (TUBE) and determine their chain types by linkage-specific deubiquitinating enzymes. We also examined whether these deubiquitinating enzymes inhibit the VCP mutant-mediated aggregate formation..

P2-5. Pathological effects of amyloid beta oligomers on synaptic plasticity

Name: Hiromitsu Tanaka, Daiki Sakaguchi, Tomoo Hirano
Institution: Department of Biophysics, Graduate School of Science, Kyoto University

Hippocampal long-term potentiation (LTP) has been regarded as a cellular basis of learning and memory, and has also been suggested to be involved in Alzheimer's disease. We have recently succeeded in formation of postsynaptic-like membrane (PSLM) directly on the glass surface in hippocampal neuronal culture by coating the glass with a kind of presynaptic adhesion molecule Neurexin, and performed live-cell imaging of AMPA-type glutamate receptors (AMPA receptors) tagged by fluorescent protein with total internal reflection fluorescence microscopy. This method has enabled us to record the location and movement of AMPA receptors around PSLM with a high signal-to-noise ratio. Using this new method, we analyzed the change of synaptic delivery of AMPA receptors caused by amyloid beta (Aβ) oligomers, and suggested that Aβ oligomers inhibit the increase the number of GluA1-containing AMAPA receptors and suppress the hippocampal LTP expression.

P2-6. Nardilysin prevents amyloid plaque formation by enhancing a-secretase activity in an Alzheimer's disease mouse model

Name: Mikiko Ohno[1)], Yoshinori Hiraoka[2)], Stefan F. Lichtenthaler[3, 4, 5)], Kiyoto Nishi[1)], Sayaka Saijo[1)], Hidekazu Tomimoto[6)], Wataru Araki[7)], Ryosuke Takahashi[8)], Toru Kita[9)], Takeshi Kimura[1)], and Eiichiro Nishi[1)]
Institution: [1)] Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [2)] Department of Pharmaceutical Sciences, Kobe Gakuin University, Kobe, Japan, [3)] German Center for Neurodegenerative Diseases (DZNE), site Munich, Germany, [4)] Neuroproteomics, Klinikum rechts der Isar, Technische Universität München, 81675 Munich, Germany, [5)] Munich Cluster for Systems Neurology (SyNergy), Munich, Germany, [6)] Department of Neurology, Graduate School of Medicine, Mie University, Mie, Japan,, [7)] National Institute of Neuroscience, NCNP, Tokyo, Japan, [8)] Department of Neurology, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [9)] Kobe Medical Center General Hospital, Kobe, Japan

Amyloid-b (Ab) peptide, one of the senile plaques in patients with Alzheimer's disease (AD), is derived from proteolytic cleavage of amyloid precursor protein (APP) by b- and g-secretases. Alpha-cleavage of APP by a-secretase has a potential to preclude the generation of Ab because it occurs within the Ab domain. We previously reported that a metalloendopeptidase, nardilysin (N-arginine dibasic convertase; NRDc) enhances a-cleavage of APP, which results in the decreased generation of Ab in vitro. To clarify the in vivo role of NRDc in AD, we intercrossed transgenic mice expressing NRDc in the forebrain with AD model mice. Here we demonstrate that the neuron-specific overexpression of NRDc prevents Ab deposition in the AD mouse model. The activity of a-secretase in the mouse brain was enhanced by the overexpression of NRDc, and was reduced by the deletion of NRDc. Our results indicate that NRDc controls Ab formation through the regulation of a-secretase.

P2-7. The role of sortilin in the pathogenesis of prion disease

Name: Suehiro Sakaguchi, Keiji Uchiyama
Institution: Division of Molecular Neurobiology, The Institute for Enzyme Research, Tokushima University

Prions, which are mainly formed by the abnormal isoform of prion protein, designated PrPSc, are transmissible agents of prion diseases. PrPSc is produced from the normal cellular isoform of PrP, PrPC. Lowering PrPSc load in the brain increased the lifespan of prion-infected mice. However, molecular mechanism regulating PrPSc load in prion-infected neurons remains largely unknown. Recently, a number of genome-wide association studies and biochemical studies have identified the VPS10P proteins including sortilin as risk factors for neurodegenerative diseases, including Alzheimer's disease. In the present study, we show that prion infection stimulates lysosomal degradation of sortilin. We also identified that sortilin is a negative regulator of PrPSc load in prion-infected cells. These results indicate that PrPSc by itself positively regulates its load by inducing lysosomal degradation of the negative regulator sortilin.

P2-8. p62-mediated selective autophagy in neurons

Name: Gen Matsumoto
Institution: Nagasaki University School of Medicine, Department of Anatomy and Neurobiology

Aging is one of the major risk factors for age-related neurodegenerative disorders. It has been implicated that aging reduces a property of the neuronal protein degradation system, causing the accumulation of undigested proteins. The autophagy adaptors including p62/SQSTM1 play important roles in the degradation of aggregated proteins or damaged organelles through selective autophagy. We recently reported that p62 phosphorylation at S403 is required for the promotion of autophagosomal engulfment of damaged mitochondria through PINK1/Parkin-mediated mitophagy pathway as well as protein aggregates. To understand the neurological significance of p62, we measured the absolute mRNA amount of all autophagy adaptors in primary cultured neurons and mice brain and found that p62 mRNA is the most abundant autophagy adaptor in neurons, suggesting that the p62 majorly participates in the selective autophagy process in brain. We discuss about a therapeutical possibility against neurodegenerative diseases by modulating the p62-phosphorylation in neurons.

P2-9. Relative contributions of degradation in the brain and elimination across the blood-brain barrier to cerebral clearance of human amyloid-β peptide(1-40) monomer in the mouse brain

Name: Shingo Ito[1)], Sumio Ohtsuki[1)], Kohta Matsumiya[2)], Sho Murata[2)], Yuki Katsukura[2)], Junichi Kamiie[3)], Tetsuya Terasaki[2)]
Institution: [1)] Department of Pharmaceutical Microbiology, Faculty of Life Sciences, Kumamoto University, Japan, [2)] Division of Membrane Transport and Drug Targeting, Graduate School of Pharmaceutical Sciences, Tohoku University, Japan, [3)] Laboratory of Veterinary Pathology, School of Veterinary Medicine, Azabu University, Japan

Cerebral clearance of the soluble amyloid-β peptide (Aβ) monomer involves both degradation in the brain and brain-to-blood elimination across the blood-brain barrier (BBB). Although this information may be important to understand the pathogenesis of Alzheimer's disease, the relative contributions of these processes are poorly understood. We show that cerebral Aβ clearance through degradation is 2-3-fold greater than that through brain-to-blood elimination across the BBB. Processes sensitive to insulin and phosphoramidon, inhibitors of neprilysin and insulin-degrading enzyme (IDE) are involved not only in degradation, but also in the elimination of human Aβ(1-40) across the BBB. In vitro transport studies demonstrated the involvement of IDE in the internalization of hAβ(1-40) monomer in the BBB. In conclusion, our results suggest a dominant contribution of degradation to cerebral hAβ(1-40) clearance. Additionally, elimination of hAβ(1-40) from the mouse brain across the BBB involves an insulin-sensitive process mediated by IDE expressed in brain capillary endothelial cells.

P2-10. Pathological stabilization of tau through phosphorylation at Ser262/356 by Par-1/MARK contributes to abnormal metabolism and toxicity of tau caused by Aβ42

Name: Kanae Ando[1, 2], Akiko Maruko-Otake[2], Yosuke Ohtake[2], Motoki Hayashishita[1], Michiko Sekiya[3] and Koichi M. Iijima[3]

Institution: [1] Department of Biological Sciences, Graduate School of Science and Engineering, Tokyo Metropolitan University, [2] Department of Neuroscience, Thomas Jefferson University, Philadelphia, PA, USA, [3] Department of Alzheimer's Disease Research, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan

Abnormal metabolism of microtubule-associated protein tau has been associated with neurodegenerative diseases including Alzheimer's disease (AD). It is believed that β-amyloid (Aβ) triggers tau abnormality, such as detachment from microtubules and phosphorylation at disease-specific sites in AD brains. However, the initial step of tau mismetabolism leading to generation of toxic tau species is not clear. Using transgenic Drosophila co-expressing human tau and Aβ, we found that Aβ increases levels of microtubule-unbound tau in the cytosol regardless of its phosphorylation status and enhances tau phosphorylation at Ser262/356 via PAR-1/MARK. Phosphorylation at Ser262/356 preferentially stabilizes tau species that are not phosphorylated at GSK3-target sites in the cytosol, and blocking this pathological stabilization of tau suppressed enhancement of tau toxicity caused by Aβ. These results suggest that tau mislocation to the cytosol followed by stabilization by phosphorylation at Ser262/356 via PAR-1/MARK is an initial step of tau mismetabolism leading to toxicity.

P2-11. I2020T LRRK2 iPSC-derived neurons exhibit increased Tau phosphorylation

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Leucine-rich repeat kinase 2 (LRRK2) is the causative molecule of the autosomal dominant hereditary form of Parkinson's disease (PD), PARK8, which was originally defined in a study of a Japanese family (the Sagamihara family) harboring the I2020T mutation in the kinase domain. In the present study, to elucidate the pathogenetic effect of mutant LRRK2, we first generated and analyzed iPSC derived from PD patients in the Sagamihara family. We found that patient iPSC-derived neurons exhibited activation of GSK-3β and high Tau phosphorylation relative to control-iPSC-derived neurons. Furthermore, the postmortem brain of the patient from whom the iPSC had been established exhibited deposition of neurofibrillary tangles as well as increased Tau phosphorylation in neurons. These results indicate that I2020T LRRK2 iPSC-derived neurons replicate to some extent the pathologic phenotype evident in the brain of PARK8 patients.

P2-12. Misregulation of thiol-disulfide status in Cu,Zn-superoxide dismutase with mutations causing amyotrophic lateral sclerosis

Name: Yoshiaki Furukawa, Itsuki Anzai, Mariko Ogawa, and Eiichi Tokuda
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Dominant mutations in Cu,Zn-superoxide dismutase (*SOD1*) gene cause a familial form of amyotrophic lateral sclerosis (ALS). Abnormal accumulation of mutant SOD1 proteins in spinal cords is known as a pathological hallmark of SOD1-related ALS, and mutation-induced misfolding of SOD1 has been proposed. Despite this, it remains obscure how SOD1 becomes misfolded by ALS-causing mutations. We first show that the cysteine residues in SOD1 are essential to the induction of toxicity in a *C. elegans* model. SOD1 has four Cys residues of total, two of which form an intramolecular disulfide bond. We then show that pathogenic mutations increase thermal fluctuation of SOD1 and thereby facilitate shuffling of the disulfide bond among Cys residues. Further shuffling of the disulfide bond between SOD1 molecules results in the formation of SOD1 oligomers cross-linked via disulfide bond(s). Thiol-disulfide chemistry in SOD1 would hence be a target to suppress the misfolding of mutant SOD1 *in vivo*.

P2-13. Aberrant calcium signaling in endoplasmic reticulum

Name: Kozo Hamada
Institution: RIKEN, Brain Science Institution

The endoplasmic reticulum (ER) is a key organelle for protein folding and calcium signaling, which is responsible for various cellular processes including neuronal plasticity, ER stress, and apoptosis. The inositol 1,4,5-trisphosphate receptor (IP3R) acts as ER-resident calcium channels in which four subunits assemble to form an ion channel activated by binding of IP3. Defective allosteric regulation in IP3R is considered crucial to ER dysfunction, but the specific mechanism remains unknown. We demonstrate that a pleiotropic enzyme transglutaminase type 2 (TG2) targets the allosteric coupling domain of IP3R type 1 (IP3R1) and negatively regulates IP3R1-mediated calcium signaling by locking the subunit configurations. The control point of this regulation is the covalent posttranslational modification of Gln2746 residue which TG2 tethers to the adjacent subunit. Modification of Gln2746 and ER dysfunction were observed in neurodegenerative disease models, suggesting a pathological role of this modification in the disease.

P2-14. Transcription factors HSF1, HSF2 and NFATc2 suppress Huntington's disease progression

Name: Naoki Hayashida
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Huntington's disease (HD) is one of the well-known neurodegenerative diseases. Glutamine repeats at N-terminal of huntingtin protein (Htt) are less than 40 in healthy individuals, but more than 150 in patients. The protein containing long Glutamine tract is called as polyQ, and polyQ-Htt protein aggregates and acquires toxicity in cell nuclei. These aggregates are formed in neurons, astrocytes, and microglia, and consequently injure the neuronal functions.
Heat shock transcription factor 1 (HSF1) is required for well-known chaperone heat shock proteins (HSPs) induction, and HSF2 is important in central nervous system development. Nuclear factor of activated T-cell cytoplasmic 2 (NFATc2) is a critical transcription factor in immune system, but recently, my colleagues and I revealed NFATc2 is an essential HSF1 target gene (Hayashida et al., EMBO J 2010). Here, I show these transcription factors suppress HD progression through the different functions.

P2-15. Quantitative analysis of GSK3Beta activity in cells.

Name: Ambika Krishnankutty[1)], Taeko Kimura[1)], Ryo Yonezawa[1)], Koichi Ishiguro[2)], Akiko Asada[1)], Taro Saito[1)] and Shin-ichi Hisanaga[1)]

Institution: [1)] Department of Biological Sciences, Tokyo Metropolitan University, Tokyo.
[2)] Juntendo University, Tokyo.

Alzhimer's disease (AD) is characterized by the intracellular accumulation of hyperphosphorylated tau. The phosphorylation is catalysed mainly by GSK3β and CDK5. Phosphorylation by GSK3β is accelerated by prime phosphorylation by CDK5. However, it is not known how these two kinases cooperates. The kinase activity of GSK3β is usually estimated by Ser9 phosphorylation using phospho-specific antibody. Ser9 phosphorylation is a marker of inactive GSK3β but not active GSK3β. In this study, we measured the absolute activation of GSK3β in various cultured cells using Phos-tag SDS-PAGE. The active and inactive forms of GSK3β were separated in Phos-tag SDS-PAGE. Insulin treatment of cultured cell lines increased Ser9 GSK3β but most part of GSK3β still remained in the active state. We would like to report GSK3β activation in different types of cells and brains.

P2-16. Gain-of-function Profilin 1 mutations linked to familial amyotrophic lateral sclerosis cause seed-dependent intracellular TDP-43 aggregation

Name: Yoshinori Tanaka, Takashi Nonaka, Genjiro Suzuki, Fuyuki Kametani, Masato Hasegawa

Institution: Dementia Research Project, Tokyo Metropolitan Institute of Medical Science

Mutations in the profilin 1 (PFN1) gene have been identified as a cause of familial amyotrophic lateral sclerosis (ALS), however, the molecular mechanisms have not been clarified. Here, we show that ALS-linked PFN1 mutants form cytoplasmic aggregates positive for p62 and ubiquitin, and these aggregates sequester endogenous TDP-43, the central molecule of both sporadic and some familial forms of ALS. Co-expression of PFN1 mutants and TDP-43 increased the levels of insoluble and phosphorylated TDP-43. Interestingly, insoluble TDP-43 prepared from cells expressing PFN1 mutants and TDP-43 induced formation of intracellular TDP-43 aggregates in other cells, indicating that TDP-43 accumulated in the presence of the PFN1 mutants is converted to prion-like species. These findings provide new insight into the mechanisms of neurodegeneration in ALS, suggesting that gain-of-toxic-function PFN1 gene mutation leads to conformational change of TDP-43.

P2-17. New insights in quantitative analysis of phosphorylation of Tau in AD model mouse and Tauopathy brains by Phos-tag SDS-PAGE

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Institution: [1)] Department of Biological Sciences, Tokyo Metropolitan University, Tokyo, Japan
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[3)] Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan4Juntendo University, Tokyo, Japan

Aggregates of hyperphosphorylated Tau are commonly found in brains of tauopathies. Therefore, understanding of the pathological environment that induces hyperphosphorylation of Tau is important. Here, we applied Phos-tag SDS-PAGE to characterization of Tau phosphorylation in vivo. P301L mutant Tau in JNPL3 mice was hyperphosphorylated only in Sarkosyl-insoluble aggregates. We also analysed phosphorylation of Tau in AD and CBD patients. AD at Braak stage V had a slightly higher phosphorylated Tau, whereas AD at Braak stage VI showed hyperphosphorylation states of Tau. Unexpectedly, there were relatively large amounts of unphosphorylated Tau in normal human brains. Further, Sarkosyl-soluble Tau was not hyperphosphorylated in AD and CBD patient's brains, whereas Sarkosyl-insoluble Tau was highly phosphorylated. The phosphorylation profiles of AD and CBD patients was different a little. These results suggest that the phosphorylation states of Tau in brains are not so high and may be hyperphophorylated after when it is incorporated into aggregates.

P2-18. The loss of FUS leads to brain atrophy accompanied with neuronal loss.

Name: Yusuke Fujioka[1)], Shinsuke Ishigaki[1)], Misato Yoshikawa[2)], Satoshi Yokoi[1)], Daiyu Honda[1)], Hirohisa Watanabe[1)], Masahisa Katsuno[1)], Akihiko Takashima[2)], Gen Sobue[1)]

Institution: [1)] Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan, [2)] Natl. Ctr. for Geriatrics and Gerontology, Aichi, Japan

FUS is a causative gene for familial ALS and FTLD. In ALS/FTLD, distinct profiles of brain atrophy are major characteristics in the lesion with FUS pathology. To determine whether silencing of FUS causes neurodegeneration, we established a FUS knock-down (shFUS) mouse model by injecting adeno-associated virus (AAV) encoding shRNA against FUS into the bilateral hippocampus. We measured the size of hippocampus by 3.0T MRI at 6, 12 and 18 months post-injection to investigate long-term effects of shFUS. The Mn2+ enhanced MRI performed at 12 months post-injection showed supranormal excitability at the bilateral hippocampus. The volume of hippocampus of shFUS mice was significantly decreased at 18 months post-injection. These results indicate that the loss of FUS leads to abnormal excitability of neurons followed by brain atrophy accompanied with neuronal loss in an age-dependent manner, which mimics the phenotypes of FTLD.

P2-19. Silencing of FUS induces the morphologic abnormities of dendritic spines

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Institution: Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Spine morphology is correlated with synaptic plasticity and physiological function, but not fully elucidated especially in ALS/FTLD. We examined the morphological change of dendritic spines of FUS-silenced neurons. Mouse primary neurons were infected with lentivirus expressing shRNA against mouse FUS (shFUS). Total spine number and mature spine ratio were significantly reduced in shFUS neuron. PSD-95 positive particles around dendrites was also significantly reduced and internalized. To establish the profile of proteins binding to PSD-95, protein extracts from primary neurons infected with shFUS or shCont were immunoprecipitated with PSD-95 antibody and analyzed by LC/MS. The MS study revealed that in total, 902 proteins bound to PSD-95, and 139 proteins were identified as proteins with more than 2-fold change of score number. These results suggest the pathophysiological change of the excitatory synapse in FUS-associated ALS/FTLD.

P2-20. FUS regulates AMPA receptor function and FTLD/ALS-associated behavior via GluA1 mRNA stabilization

Name: Daiyu Honda[1)], Tsuyoshi Udagawa[1)], Yusuke Fujioka[1)], Motoki Tanaka[2)], Satoshi Yokoi[1)], Hirohisa Watanabe[1)], Masahisa Katsuno[1)], Masahiro Sokabe[2)], Shinsuke Ishigaki[1)], and Gen Sobue[1)]

Institution: [1)] Department of Neurology, Nagoya University Graduate School of Medicine, [2)] Mechanobiology Laboratory, Nagoya University Graduate School of Medicine

Fused in sarcoma (FUS) is an RNA/DNA binding protein associated with amyotrophic lateral sclerosis (ALS) and fronto-temporal lobar degeneration(FTLD). Here we evaluate intrinsic roles of FUS on synaptic functions and animal behaviors. FUS was depleted in primary neurons by shRNA-expressing lentiviruses or in hippocampus by injecting shRNA-expressing AAVs bilaterally. Expression profiling of synaptic proteins revealed that FUS depletion down-regulates GluA1. FUS binds GluA1 mRNA in the vicinity of the 3' terminus and controls poly (A) tail maintenance, thus regulating stability. GluA1 reduction upon FUS knockdown reduces mEPSC amplitude both in cultured neurons and in vivo. FUS knockdown in hippocampus attenuates dendritic spine maturation and causes behavioral aberrations including hyperactivity, disinhibition, and social interaction defects, which are partly ameliorated by GluA1 reintroduction. These results highlight the pivotal role of FUS in regulating GluA1 mRNA stability, post-synaptic function, and FTLD-like animal behaviors.

P3-1. Identification of propagation system using α-syn in PARK4 iPS cells

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In recent years, the propagation hypothesis that pathological misfolding protein spreads from cell to cell have been proposed as a central pathology of Parkinson's disease (PD).
Although several mouse models have been developed, these models did not elucidate the pathogenesis of PD so far. It has been accepted that the marmoset model of PD is closer to the human PD. Thus, in the present study, we focus on the marmoset model of PD by using iPS cells.
We have prepared the dopaminergic neurons differentiated from the iPS cells of PARK4 as familiar PD patients to produce and purify α-synuclein proteins. Similarly, we also purifiedα-synuclein proteins from the PD patient's red blood cells. By the injection with these α-synuclein proteins into the genetically modified mouse and marmoset having a mutation in humans, we will identify the mechanism of the propagation system in PD.

P3-2. Pathophysiological analysis of neurodegenerative disorders using disease specific iPSCs

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Institution: [1)] Department of Neurology, School of Medicine, Aichi Medical University, [2)] Department of Physiology, School of Medicine, Keio University, [3)] Department of Neurology, Graduate School of Medicine, Nagoya University, [4)] Graduate School of Medicine, Nagoya University

Disease specific human iPSCs, established from patients' somatic cells, would provide valuable disease models recapitulating disease onset and progression by the differentiation into the cells affected in the disease. We established iPSCs from somatic cells taken from patients of spinal bulbar muscular atrophy (SBMA), an adult onset lower motor neuron disease caused by the abnormal expansion of polyglutamine tract (CAG repeat) in Androgen receptor (AR). We derived patient-specific motor neurons, and examined their pathological changes focusing on the alteration of gene expressions and mutant AR aggregations during the course of differentiation. As a result, we found that several disease related genes may be associated with early disease progression of SBMA. By further analyses, the elucidation of the underlying mechanisms of motor neuron degeneration in SBMA, and the identification of novel disease related genes and molecular markers, which may contribute to early disease diagnosis and novel therapeutics are expected.

P3-3. *In vivo* PET imaging of mitochondrial abnormalities in a mouse model of tauopathy

Name: Anna M. Barron[1)], Bin Ji[1)], Masayuki Fujinaga[1)], Ming-Rong Zhang[1)], Tetsuya Suhara[1)], Naruhiko Sahara[1)], Hideo Tsukada[2)], Makoto Higuchi[1)]

Institution: [1)] Molecular Imaging Center, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan. [2)] Central Research Laboratory, Hamamatsu Photonics K.K., Hamamatsu, Shizuoka, Japan.

Damaged mitochondria may be one of the earliest manifestations of Alzheimer`s disease (AD), with region-specific reductions in cerebral metabolism and mitochondrial dysfunction observed long before the onset of symptoms both clinically and in mouse models of the disease. In this study functional imaging was used to examine neuronal metabolic abnormalities in a mouse model of tauopathy (rTg4510) in vivo, using a novel PET probe for mitochondrial complex I (18F-BCPP-EF) which mediates the first step in oxidative phosphorylation. A marked reduction in 18F-BCPP-EF uptake was observed in hippocampal and forebrain regions of rTg4510 mice, coinciding with tau neuropathology as assessed by [11C]PBB3 PET. Further, hippocampal 18F-BCPP-EF uptake positively correlated with hippocampal volume assessed by MRI, indicating an association between mitochondrial complex I and neuronal loss. These findings indicate that mitochondrial complex I may be a useful imaging biomarker for the identification of early-stage metabolic changes associated with AD neuropathology and neuronal loss.

Access Map

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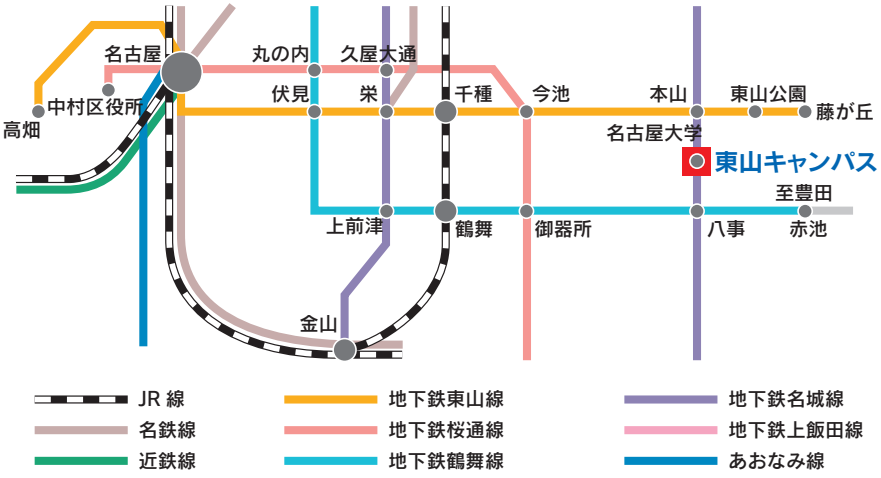

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