

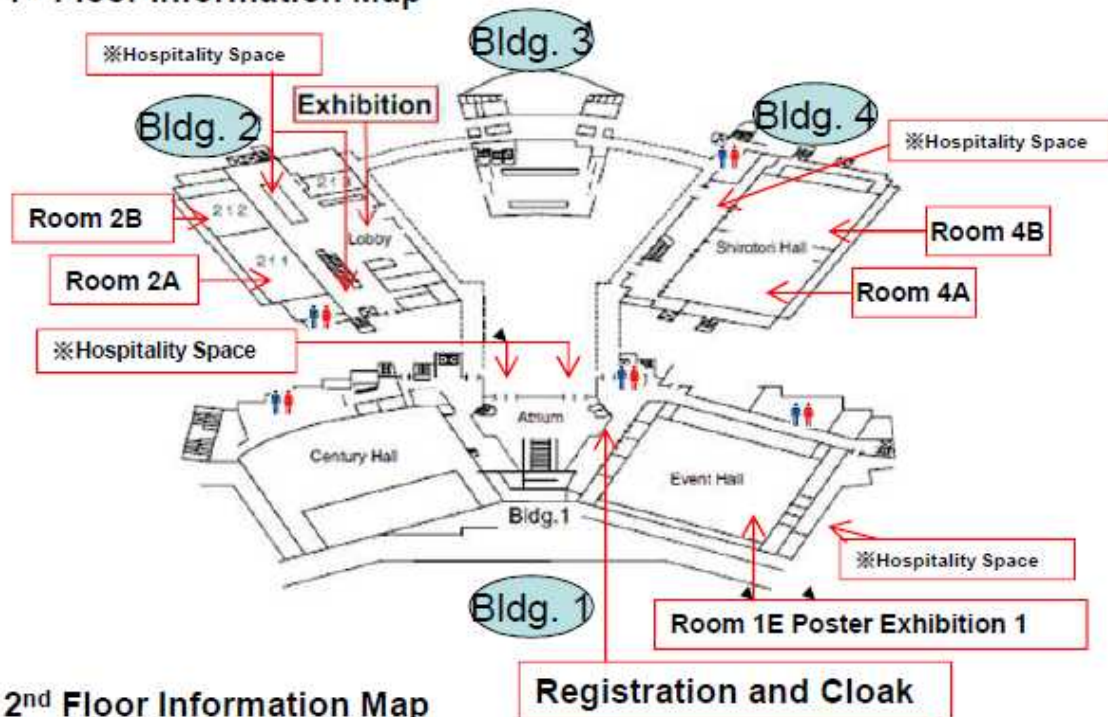
52nd Annual Meeting of Japanese Society of Neurology

From Pathogenesis to Therapy – Perspective for the Next 50 years

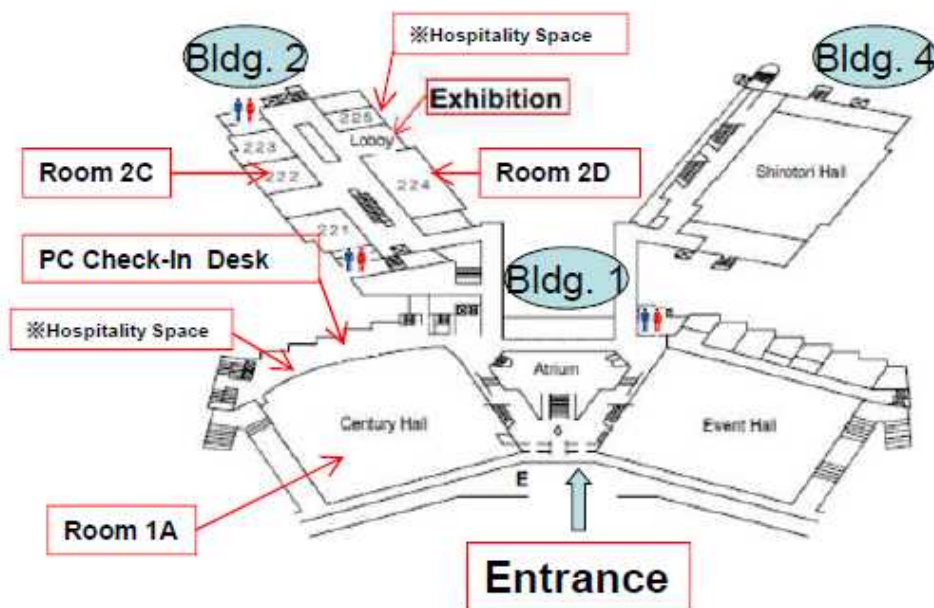


Date: May 18 (Wed) – 20 (Fri), 2011 Venue: Nagoya Congress Center
President: Gen Sobue, MD (Department of Neurology, Nagoya University Graduate School of Medicine)

1st Floor Information Map

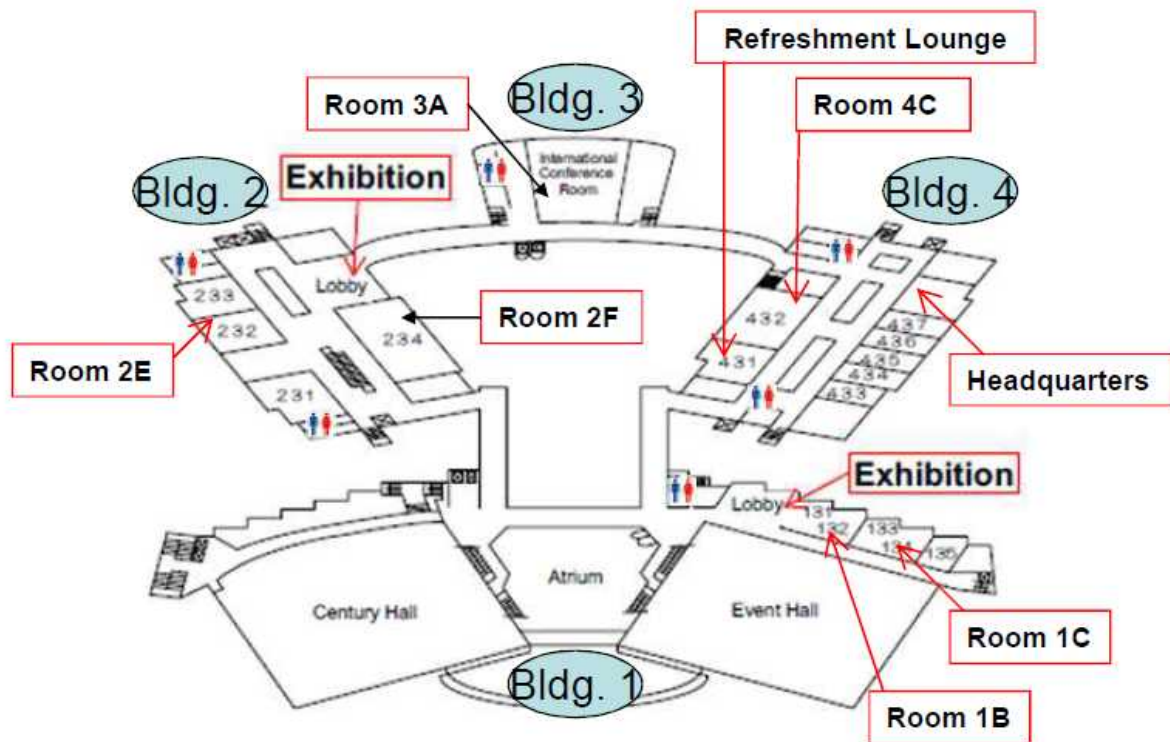


2nd Floor Information Map

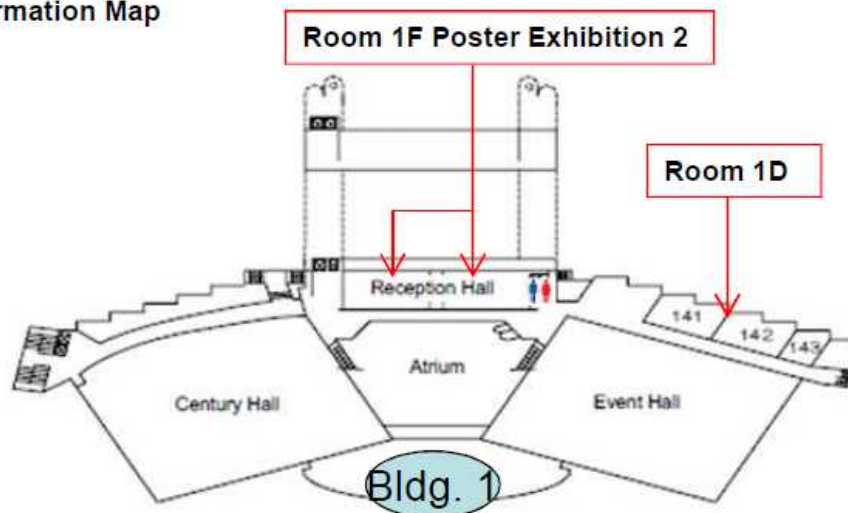


※Free Internet Access (via LAN) is Available at Every Hospitality Space and Refreshment Lounge

3rd Floor Information Map



4th Floor Information Map



Featured Speakers from Overseas

Ralf Baron (Univesitäätsklinikum Schleswig-Holstein, Germany)
Oscar Benavente (University of British Columbia, Canada)
Don W. Cleveland (Ludwig Institute, University of California at San Diego, USA)
Liyang Cui (Former President of the Chinese Society of Neurology, China)
Mostafa El Alaoui Faris (President of the 20th World Congress of Neurology, Marrakesh, 2011, Morocco)
Kenneth H. Fischbeck (Neurogenetics Branch, NINDS, NIH, USA)
Cynthia M Fox (National Center for Voice and Speech, USA)
Mark Frasier (Michael J Fox Foundation for Parkinson's Research, USA)
Robert Griggs (President of American Academy of Neurology; University of Rochester School of Medicine and Dentistry, USA)
Shu-Leong Ho (University of Hong Kong Queen Mary Hospital, Hong Kong)
Beom S. Jeon (International Delegate of the Korean Neurological Association, Korea)
Jong Sung Kim (University of Ulsan; Asan Medical Center, Korea)
Chong S. Lee (ASAN Medical Center, Korea)
Chin-Song Lu (Chang Gung Medical Center at Linkou, Taiwan)
Lennart Mucke (Gladstone Institute of Neurological Disease and UCSF, USA)
David Pleasure (Institute for Pediatric Regenerative Research and Department of Neurology, UC Davis, USA)
Jeffrey D. Rothstein (Johns Hopkins University, USA)
Gerard Said (Hospital de la Salpetriere, France)
Donald H. Silberberg (University of Pennsylvania, USA)
Michael J. Strong (The University of Western Ontario, Canada)
Louis Tan (National Neuroscience Institute, Singapore)
Michael W. Weiner (San Francisco VA Medical Center, UCSF, USA)

Alphabetical order

Academic Program with Featured Speakers

Special Lecture:

Past, present, and future of polyglutamine expansion disease

16:45~18:30, Tuesday, May 17, Room 3A (International conference Room, 3rd Floor Bldg.3)

Speaker: Kenneth H. Fischbeck (Neurogenetics Branch, NINDS, NIH, USA)

AAN-JSN Joint Symposium

Keynote Session: Future perspective of the partnership between AAN and JSN

14:30~15:00, Wednesday, May18, Room 1A (Century Hall, 2nd Floor, Bldg.1)

1. The Japanese Society of Neurology and the American Academy of Neurology: Response to Global Imperatives

Speaker: Robert Griggs (President of American Academy of Neurology; University of Rochester School of Medicine and Dentistry, USA)

2. American Academy of Neurology (AAN) and Japanese Society of Neurology (JSN) : Beyond the Pacific

Speaker: Hidehiro Mizusawa (President/CEO of the Japanese Society of Neurology; Tokyo Medical and Dental University, Japan)

ALS

15:00~16:45, Wednesday May 18, Room 1A (Century Hall, 2nd Floor, Bldg. 1)

1. Clinical or Patient-Oriented Research to Find the Pathogeneses and Cause of ALS

Speaker: Hiroshi Mitsumoto (Columbia University, USA)

2. The basis for selective neuronal vulnerability in ALS: mechanisms and therapy for ALS

Speaker: Don W. Cleveland (Ludwig Institute, University of California at San Diego, USA)

3. Oligodendroglia are an unexpected major contributor to ALS and Neurodegeneration

Speaker: Jeffrey D. Rothstein (Johns Hopkins University, USA)

4. Optineurin in ALS

Speaker: Hideshi Kawakami (Research Institute for Radiation Biology & Medicine, Hiroshima University)

5. Failure of RNA editing and the pathogenesis of ALS

Speaker: Shin Kwak (The University of Tokyo, Japan)

Alzheimer's Disease

15:00~16:45, Wednesday, May 18, Room 4B (Shirotori Hall South, 1st Floor, Bldg. 4)

1. Mechanisms and Treatment of Neuronal Dysfunction in Models of Alzheimer's Disease

Speaker: Lennart Mucke (Gladstone Institute of Neurological Disease and UCSF, USA)

2. Biomarkers for Predicting and Monitoring Progression of Alzheimer's Disease: The Alzheimer's Disease Neuroimaging Initiative

Speaker: Michael W. Weiner (San Francisco VA Medical Center, UCSF, USA)

3. Molecular pathology and disease-modifying therapies for Alzheimer's disease

Speaker: Takeshi Iwatsubo (Department of Neuropathology, Graduate School of Medicine, The University of Tokyo, Japan)

4. The future of Alzheimer's disease : opportunities and challenges in drug development

Speaker: Yoko Fujimoto (Pfizer Japan Inc.)

Hot Topics

9:30~10:20, Wednesday, May 18, Room 1A (Century Hall, 2nd Floor, Bldg. 1)

2. Updates of pathological mechanisms and therapies of multiple sclerosis

2-1. Pathophysiology of Progressive Multiple Sclerosis: Studies in a Genetically Manipulated Murine Model

Speaker: David Pleasure (Institute for Pediatric Regenerative Research and Department of Neurology, UC Davis, USA)

Neuroscience Session

10:45~11:30, Thursday, May 19, Room 3A (International Conference Room, 3rd Floor, Bldg. 3)

1. Lee Silverman Voice Treatment ; Rehabilitative Therapy for People with Parkinson's

Speaker: Cynthia M Fox (National Center for Voice and Speech)



East Asian Neurology Forum

Keynote Session: Future Perspective of East Asian Neurology

13:10~14:40, Thursday, May 19, Room 3A (International Conference Room, 3rd Floor, Bldg. 3)

1. Message from the WCN to the East Asian Neurology

Speaker: Mostafa El Alaoui Faris (President of the 20th World Congress of Neurology, Marrakesh, 2011, Morocco)

2. Role of the Chinese Society of Neurology in East Asia

Speaker: Liying Cui (Former President of the Chinese Society of Neurology, China)

3. Role of the Korean Neurology Association in East Asia

Speaker: Beom S. Jeon (International Delegate of the Korean Neurological Association, Korea)

3. Role of the JSN in East Asia

Speaker: Hidehiro Mizusawa (President of the Japanese Society of Neurology, Japan)

4. Designated Comments

Speaker: Ryuji Kaji (Trustee, World Federation of Neurology)

Parkinsonism: Up-to-date

14:40~16:45, Thursday, May 19, Room 3A (International Conference Room, 3rd Floor, Bldg. 3)

1. Neuroimaging and Diagnosis of Parkinsonism

Speaker: Chong S. Lee (ASAN Medical Center, Korea)

2. Treatment of early Parkinson's disease

Speaker: Louis Tan (National Neuroscience Institute, Singapore)

3. Treatment of advanced Parkinson's disease

Speaker: Shu-Leong Ho (University of Hong Kong Queen Mary Hospital, Hong Kong)

4. Non-motor feature in Parkinson's disease

Speaker: Tetsuya Maeda (Department of Neurology, Research Institute for Brain and Blood Vessels Akita)

5. Genetics of Parkinson's disease in Asia

Speaker: Chin-Song Lu (Chang Gung Medical Center at Linkou, Taiwan)

Message from Michael J Fox Foundation

14:40~16:45, Thursday, May 19, Room 3A (International Conference Room, 3rd Floor, Bldg. 3)

1. Accelerating the Cure for Parkinson's Disease: MJFF Mission and Funding Philosophy

Speaker: Mark Frasier (Michael J Fox Foundation for Parkinson's Research, USA)

Symposium

1. Definition and Treatment of Branch Atheromatous Disease (BAD); Various Perspectives

13:15~14:45, Thursday, May 19, Room 1B (Room 131+132, 3rd Floor, Bldg. 3)

SY-01-2. Branch atheromatous Disease: an important cause of small subcortical infarction in Asia

Speaker: Jong Sung Kim (University of Ulsan; Asan Medical Center, Korea)

SY-01-3. Branch atheromatous disease: Prognosis and management. The SPS3 experience

Speaker: Oscar Benavente (University of British Columbia, Canada)

7. *Atypical types of Dementia*

8:30~10:30, Thursday, May 19, Room 3A (International Conference Room, 3rd Floor Bldg. 3)

SY-07-4. Dementia with motor neuron disease

Speaker: Michael J. Strong (The University of Western Ontario, Canada)

8. *Chronic Pain update*

13:15~14:45, Thursday, May 19, Room 4A (Shirotori Hall North, 1st Floor Bldg. 4)

SY-08-1. Neuropathic pain-definition, mechanisms diagnosis and management

Speaker: Ralf Baron (Univesit  tsklinikum Schleswig-Holstein, Germany)

11. *Strategies for recruitment of medical students to neurology field and training them to become full-fledged neurologists*

14:45~16:45, Thursday, May 19, Room 2C (Room 222+223, 2nd Floor, Bldg. 2)

Keynote Lecture. Attracting the best and brightest to careers in neurology

Speaker: Donald H. Silberberg (University of Pennsylvania, USA)

17. *The Challenge of Refractory Neuropathies*

Keynote Lecture. Perspectives in refractory diabetic and amyloid small-fiber neuropathy

4:45~16:45, Thursday, May 19, Room 4C, Room 432, 3rd Floor, Bldg. 4)

Speaker: Gerard Said (Hospital de la Salpetriere, France)

Luncheon Seminar

11:45~12:45, Wednesday, May 18, Room 3A (International Conference Room, 3rd floor, Bldg. 3)

LS-09. Ending Alzheimer's Together

Speaker: Eric M. Reiman (Banner Alzheimer's Institute and Arizona Alzheimer's Consortium, USA)

12:00~13:00, Thursday, May 19, Room 3A (International Conference Room, 3rd Floor, Bldg. 3)

LS-21. What we have learned from preclinical models of Parkinson's disease?

Speaker: Etienne C. Hirsch (Hopital de la Pitie-Salpitriere, France)

12:00~13:00, Thursday, May 19, Room 4A (Shirotori Hall North, 1st Floor, Bldg. 4)

LS-22 Impact of new diagnostic criteria and new treatment of galantamine for Alzheimer's disease.

Speaker Serge Gauthier (Mcgill University, Canada)

12:00~13:00, Thursday, May 19, Room 4C (Room 432, 3rd Floor, Bldg. 4)

LS-24. Current Treatment Considerations & Future Treatment Paradigms for Multiple Sclerosis

Speaker Bernd C. Kieseier (Heinrich Heine University Dusseldorf, Germany)

12:00~13:00, Friday, May 20, Room 2E (Room 232+233, 3rd Floor, Bldg. 2)

LS-30. Early strengths translated into lasting benefits - new insights from Long Term Follow - up of Interferon beta- 1b -

Speaker: Peter Rieckmann (Bamberg Academic Hospital University of Erlangen, Germany)

12:00~13:00, Friday, May 20, Room 4A (Shirotori Hall North, 1st Floor, Bldg. 4)

LS-33. Memantine-a valuable and different treatment and different treatment for people with Alzheimer's disease

Speaker Roy W. Jones (RICE Royal United Hospital and University of Bath, UK)

Evening Seminar

18:30~20:00, Wednesday, May 18, Room 2E (Room 232+233, 3rd Floor, Bldg. 4)

ES-03 . 2010 Revisions to the "McDonald Criteria" 「 The 2010 revision of the McDonald Criteria - a step towards simplifying the diagnosis criteria for Multiple Sclerosis 」

Speaker: Michael Hutchinson (Consultant Neurologist at St Vincent's University Hospital, UCD, Ireland)

18:30~20:00, Friday, May 20, Room 4A (Shirotori Hall South, 1st Floor, Bldg. 4)

ES-07. Neuropathic Pain-from Lab to Clinic-

Speaker: Ralf Baron (Universitätsklinikum Schleswig-Holstein, Germany)

18:30~20:00, Thursday, May 19, Room 2C (Room 222+223, 2nd Floor, Bldg. 2)

ES-10. Botulinum Toxin for Spasticity and Cervical Dystonia : Learning the Art and Science

Speaker: Virgilio Gerald H. Evidente (Deep Brain Stimulation Program Mayo Clinic
Arizona, USA)

Special Lecture

16:45 ~ 8:30, Tuesday, May 17, Room 3A (International Conference Room, 3rd Floor, Bldg.3)



Past, present, and future of polyglutamine expansion disease

Kenneth H. Fischbeck

Neurogenetics Branch, NINDS, NIH, USA

The polyglutamine diseases are a set of nine neurodegenerative diseases caused by unstable CAG repeat expansions in widely expressed genes. Each disease has unique features due to the characteristics of the mutant protein and the population of neurons that degenerates, but there are common features of adult onset, gradual progression, and correlation of repeat length with age of onset and disease severity. Each disease has been reproduced by overexpression of the mutant protein in animal models. Intracellular inclusions of mutant protein are a common pathological feature in cell culture and animal models as well as in patients, and the expanded polyglutamine causes the proteins to aggregate in a repeat-length dependent manner. While there are indications of loss of normal function in some of the mutant proteins, the principal effect of the mutations is a toxic gain of function, which may cause transcriptional dysregulation, mitochondrial dysfunction, altered axonal transport, and other effects that lead to neuronal dysfunction and death. Various approaches to therapy have shown promise in animal models, including suppression of disease gene expression by RNA interference, targeted disruption of proteolytic processing or post-translational modification of the disease protein, enhancing the degradation of the mutant protein, and mitigating the downstream effects. Spinal and bulbar muscular atrophy, the first polyglutamine disease to be discovered, is unique in that the toxicity of the mutant protein (the androgen receptor) is ligand dependent. Androgen reduction therapy is effective in animal models. Demonstrating this effect in patients has been difficult because of the slow disease progression and perhaps also because the treatment needs to be started early in the disease course. The challenge now is to translate therapeutic interventions like this that show promise in pre-clinical studies into safe and effective treatment for patients in well designed clinical trials.

[Biography]

Current Position :

Chief, Neurogenetics Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD

Education :

1968-72 Harvard University, Cambridge, MA
A.B. magna cum laude in Biochemical Sciences, June 1972
A.M. in Biology, June 1972
1972-76 Johns Hopkins University, Baltimore, MD
M.D., May 1976

Post-Graduate Training and Fellowship Appointments :

1976-77 Intern in Medicine, Case Western Reserve University Hospital, Cleveland, OH
1977-80 Resident in Neurology, University of California, San Francisco, CA
1980-82 Research Fellow in Neurology, University of Pennsylvania, Philadelphia, PA

Appointments :

1982-89 Assistant Professor of Neurology, University of Pennsylvania
1989-95 Associate Professor of Neurology, University of Pennsylvania
1990-98 Secondary Appointment in Genetics, University of Pennsylvania
1992 Boerhaave Visiting Professor, University of Leiden, The Netherlands
1995-98 Professor of Neurology, University of Pennsylvania
1998- Chief, Neurogenetics Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD

AAN-JSN Joint Symposium K-1 : Future perspective of the partnership between AAN and JSN

Chair : Ichiro Kanazawa President of the Science Council of Japan,
International University of Health
and Welfare Graduate School

14 : 30~15 : 00, Wednesday, May 18, Room 1A (Century Hall, 2nd Floor, Bldg.1)



The Japanese Society of Neurology and the American Academy of Neurology : Response to Global Imperatives

Robert Griggs

President of American Academy of Neurology ; Department of Neurology, University of Rochester School of Medicine and Dentistry, USA

Neurologists throughout the world share interests in the treatment of patients, in the training of the young, and in discovering new therapies. This meeting brings experts from the United States to share insights in neurological diseases with scientists in the Japanese Society of Neurology. One month ago Japanese clinical neuroscientists traveled to Honolulu to share their work with attendees at the AAN meeting addressing scientists from around the world. Thus, neurologists join all of medicine in shared opportunities for globalization : Fostering improvements in less-developed countries and building collaborations among the advanced countries of the world.

The term "translational" research has recently come into wide use in medical science. I believe that neurologists have failed to match other specialties in translating our science into improved outcomes for our patients. Translational research has been classified as T1, T2 and T3 : T1-translating science into mice and then first into humans ; T2-includes controlled clinical trials that establish the benefit of a treatment in patients, and T3-insuring that patients receive the treatments and that their health improves. For T1 and T2 we have many successes. But for T3 research we have clung to an outmoded belief that well-meaning neurologists will invariably help their patients receive the highest quality of care. We have no evidence for this assertion and much evidence against it. Japanese and American neurologists must commit to developing the systems that make the prevention and treatment of neurological disease uniformly available in our countries and globally. We have a very long way to go.

【Biography】

Current Position :

President of the American Academy of Neurology, Professor of Neurology, Medicine, Pathology and Laboratory Medicine, and Pediatrics, Professor in the Center for Human Experimental Therapeutics, University of Rochester School of Medicine and Dentistry, Rochester, New York

Education :

1960 University of Delaware, B.A., Chemistry, Phi Beta Kappa
1964 University of Pennsylvania, M.D., Alpha Omega Alpha

Faculty Appointments :

1971-1974 Assistant Professor of Neurology, Medicine, and Pediatrics, University of Rochester School of Medicine and Dentistry ; Rochester, New York
1974-1979 Associate Professor of Neurology, Medicine, Pathology and Pediatrics, University of Rochester School of Medicine and Dentistry ; Rochester, New York
1979-present Professor of Neurology, Medicine, Pathology and Laboratory Medicine, and Pediatrics, University of Rochester School of Medicine and Dentistry ; Rochester, New York
2010-present Professor in the Center for Human Experimental Therapeutics, University of Rochester School of Medicine and Dentistry, Rochester, New York

AAN-JSN Joint Symposium K-2 : Future perspective of the partnership between AAN and JSN

14 : 30~15 : 00, Wednesday, May 18, Room 1A (Century Hall, 2nd Floor, Bldg.1)



American Academy of Neurology (AAN) and Japanese Society of Neurology (JSN) : Beyond the Pacific

Hidehiro Mizusawa

President/CEO of the Japanese Society of Neurology, Department of Neurology,
Tokyo Medical and Dental University

JSN was founded in 1902 by Prof. Miura, a neurologist and Prof. Uchimura, a psychiatrist. In 1935, JSN changed its name to the Japanese Society of Psychiatry and Neurology (JSPN). In 1955, supported by NINDS, Professors Kurland (NIH), McAlpine (University of London) and Reese (University of Wisconsin) arrived in Japan to study multiple sclerosis. They stimulated the strong desire of neurologists all over the country to create an organization independent of JSPN as they travelled from Hokkaido to Kumamoto. Accordingly, at the 5th Annual Meeting of the Medical Neurology Study Group in 1959, a renewed JSN was established and immediately recognized as the Japanese branch of WFN followed by the 1st JSN's annual meeting in 1960. To be sure, neurologists of US and WFN have played an important role in shaping Japanese neurology from the start. Many Japanese neurologists have studied neuroscience and clinical neurology in US, and the relationship between AAN and JSN has grown steadily across the Pacific. I am sure that mutual cooperation between the two societies will continue to lead to exciting new developments and will contribute not only to the well-being of both countries but also to improving QOL in other parts of the world.

【Biography】

Current Position : President/CEO of the Japanese Society of Neurology, Professor of Neurology and Neuroscience, Graduate School of Medical and Dental Sciences, Director of the Center for Brain Integration Research, Director of the School of Medicine Faculty of Medicine, Tokyo Medical and Dental University, Tokyo

Education :

1976 University of Tokyo, M.D.
1983 University of Tokyo, Ph.D.

Faculty Appointments :

1981 Assistant Professor of the 1st Internal Medicine, Hamamatsu Medical School
1982 Assistant Professor of Neurology, University of Tokyo Hospital
1983 Staff Neurologist, Yokufukai Hospital
1984 Junior Associate Professor of Neurology, Tsukuba University School of Clinical Medicine
1990 Associate Professor of Neurology, Tsukuba University School of Clinical Medicine
1996 Professor of Neurology, Tokyo Medical and Dental University Faculty of Medicine

AAN-JSN Joint Symposium 1-1 : ALS

Chair : Gen Sobue Nagoya University Graduate School of Medicine
Don W. Cleveland Ludwig Institute, University of California at
San Diego, USA

15 : 00~16 : 45, Wednesday, May 18, Room 1A (Century Hall, 2nd Floor, Bldg.1)



Clinical or Patient-Oriented Research to Find the Pathogeneses and Cause of ALS

Hiroshi Mitsumoto

Department of Neurology, Columbia University, USA

ALS is considered the worst of all the intractable diseases. Recent progress in ALS basic research, particularly in the areas of identifying new genetic causes and molecular mechanisms of neuronal degeneration, and gaining access to iPSCs, is truly magnificent. Yet, it is also disheartening that the pathogenesis and cause of ALS still eludes us. For the past 20 years, randomized clinical trials have become the major component of clinical research in ALS, testing more than 30 potential medications; however, with the exception of riluzole, all have failed to show any beneficial effects. These potential drugs are developed based on a variety of hypotheses largely derived from studies in ALS animal models or cell-based studies. These studies are indeed a critical part of ALS research; nevertheless, we, as ALS clinicians, need to promote more active clinical research aimed at finding the disease mechanisms and cause in patients with ALS because the mystery of the disease exists in the patients themselves. Yet, studying patients with ALS poses many insurmountable limitations. Clinicians and scientists need to find a way to surpass these limitations and conduct innovative research with ALS patients that is not only translational, but also more transformative. In accordance with this effort, a strong collaboration among all parties involved, such as basic scientists, clinicians, funding agencies and patient advocacy groups, is essential. As the first step, we propose to hold a conference in which all involved come together to discuss the current status of ALS research and future directions. ALS phenotypes, biomarkers, epidemiology, genes and epigenetics, and the required infrastructure for effective ALS clinical research to come (database, biobank, and research study groups) must be reviewed. This approach is an alternative way to facilitate the production of effective medications to treat ALS.

【Biography】

Current Position :

Dr. Hiroshi Mitsumoto, Wesley J. Howe Professor of Neurology, Columbia University College of Physicians and Surgeons, is Director of the Eleanor and Lou Gehrig MDA/ALS Research Center and Neuromuscular Division at the Neurological Institute of New York, a position he has held since 1999.

Education and Appointments :

He was educated in Japan, graduated at the top of his class from Toho University School of Medicine in 1968, and came to this country in 1972 to complete his medical internship at Johns Hopkins/Baltimore City Hospitals and his neurology residency at Case Western Reserve University under the mentorship of Dr. Joseph M. Foley. Subsequently, Dr. Mitsumoto completed a fellowship in neuropathology at the Cleveland Clinic Foundation and undertook neuromuscular research as an MDA fellow at Tufts University with Dr. Walter G. Bradley. In 1981, he joined Case Western Reserve University, and in 1983, he was named Director of the Neuromuscular Section and the ALS Center at the Cleveland Clinic. Throughout his career, he has devoted his clinical and research efforts to the care of patients with ALS and the investigation of animal models of ALS.

AAN-JSN Joint Symposium 1-2 : ALS

15 : 00~16 : 45, Wednesday, May 18, Room 1A (Century Hall, 2nd Floor, Bldg.1)



The basis for selective neuronal vulnerability in ALS : mechanisms and therapy for ALS

Don W. Cleveland

Ludwig Institute, University of California at San Diego, USA

An inherited form of ALS is caused by mutations in ubiquitously expressed superoxide dismutase (SOD1). The disease mechanism is through an acquired toxicity unrelated to dismutase activity. Use of selective gene excision or viral encoded siRNA has demonstrated that toxicity is non-cell autonomous, with mutant SOD1 within motor neurons driving disease onset, while damage within neighboring astrocytes and microglia accelerates disease progression. These findings validate therapies to slow disease progression, including cell replacement through injection of stem cell derived astrocytic progenitors. Another approach now in trial is suppression of mutant SOD1 expression following infusion of DNA antisense oligonucleotides that direct destruction of SOD1 mRNA widely within the nervous system. Identification of ALS-causing mutations in TDP-43 and FUS/TLS, two RNA/DNA binding proteins, combined with TDP-43 mislocalization in most incidences of sporadic ALS, has initiated a paradigm shift in defining disease mechanism. TDP-43 binding sites on mRNAs from 6,304 genes have been identified as the brain RNA targets for TDP-43. Loss of nuclear TDP-43 that is seen in neurons of sporadic ALS patients is shown to affect levels of >600 mRNAs (including FUS/TLS and progranulin) and 965 splicing events in the nervous system. RNAs whose levels are most depleted by reduction in TDP-43 are derived from genes with very long introns and which encode proteins involved in synaptic activity, providing a basis for neuronal vulnerability to loss of TDP-43 function. Finally, TDP-43 is shown to auto-regulate its own synthesis (in part by directly binding and enhancing splicing of an intron within the 3'untranslated region of its own mRNA, thereby triggering nonsense mediated RNA degradation), providing a mechanism by which cytoplasmic aggregation will trigger runaway synthesis of TDP-43 that amplifies the initiating aggregates.

[Biography]

Current Position :

Professor, Departments of Medicine, Neuroscience and Cellular and Molecular Medicine, Univ. of California, San Diego

Education :

1972	B.S. in physics with highest honors, New Mexico State University
1977	Ph.D. in Biochemical Sciences, Princeton University
1978-1981	Postdoctoral, Department of Biochemistry and Biophysics, University of California at San Francisco

Positions Held :

1981-1985	Assistant Professor, 1985-1988 Associate Professor, 1988-1995 Professor, Department of Biological Chemistry, Johns Hopkins University School of Medicine
1991-1995	Professor, Department of Neuroscience, Johns Hopkins University School of Medicine
1995-present	Professor, Departments of Medicine, Neuroscience and Cellular and Molecular Medicine, Univ. of California, San Diego
1995-present	Head, Laboratory of Cell Biology, Ludwig Institute for Cancer Research
2003-present	Head, Laboratory for ALS Research in San Diego
2008-present	Chair, Department of Cellular and Molecular Medicine, Univ. of California, San Diego

AAN-JSN Joint Symposium 1-3 : ALS

15 : 00~16 : 45, Wednesday, May 18, Room 1A (Century Hall, 2nd Floor, Bldg.1)



Oligodendroglia are an unexpected major contributor to ALS and Neurodegeneration

Jeffrey D. Rothstein

Johns Hopkins University, USA

Oligodendroglia support axon survival and function through mechanisms independent of myelination and their dysfunction leads to axon degeneration in several human diseases. The cause of this degeneration has not yet been determined, but lack of energy metabolites such as glucose or lactate is one prominent hypothesis. Lactate is transported exclusively by monocarboxylate transporters, and changes to these transporters dramatically affect lactate production and utilization. Here we show that one specific lactate transporter, monocarboxylate transporter 1, is present primarily within oligodendrocytes and that even minor disruption of this transporter produces axon damage and neuron loss in animal and cell culture models. In addition, this same transporter is reduced in patients with, and mouse models of, amyotrophic lateral sclerosis (ALS). The exact role of oligodendrocytes in axon function and neuron survival has been elusive, and we believe that our study defines one important mechanism by which oligodendrocytes support neurons and axons.

[Biography]

Current Position : Professor of Neurology and Neuroscience, and the Graduate Training Program in Cellular and Molecular Medicine (2000-), Director- Brain Science Institute, Johns Hopkins University (2011-)
Director and Founder, Robert Packard Center for ALS Research, Johns Hopkins University
Director of the ALS/MDA Clinic, Johns Hopkins University
Deputy Director, Johns Hopkins Institute for Clinical and Translational Research (2009-)

Education :

1977 Colgate University, Hamilton, NY A.B. Neuroscience
1979 University of Chicago, Chicago, IL M.A. Neurochemistry-Biopsychology
1984 University of Illinois Health Sciences Center, Chicago, IL Ph.D. Physiology and Biophysics-Neurochemistry
1985 University of Illinois-College of Medicine, Chicago, IL M.D.

Academic Appointments :

1989-1990 Instructor, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD
1989-1993 Visiting Faculty, Department of Pharmacology, Georgetown University School of Medicine, Washington D.C.
1991-1993 Assistant Professor, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD
1994-2000 Associate Professor, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD
1994-2000 Associate Professor, Graduate Training Program in Cellular and Molecular Medicine, Johns Hopkins University School of Medicine, Baltimore, MD
1997-2000 Associate Professor, Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD
1998 Vice Chairman of Neurology, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD

AAN-JSN Joint Symposium 1-4 : ALS

15 : 00~16 : 45, Wednesday, May 18, Room 1A (Century Hall, 2nd Floor, Bldg.1)



Optineurin in ALS

Hideshi Kawakami¹, Hirofumi Maruyama¹, Hidefumi Ito^{2,3}

¹Department of Epidemiology, Research Institute for Radiation Biology & Medicine, Hiroshima University, ²Department of Neurology, Kyoto University Graduate School of Medicine, ³Department of Neurology, Kansai Medical University

Amyotrophic lateral sclerosis (ALS) is a middle-age onset and progressive disorder characterized by degeneration of motor neurons of the primary motor cortex, brainstem, and spinal cord. Most cases of ALS are sporadic, but about 10% are familial. The genes known to be causative of classical familial ALS (FALS) are superoxide dismutase 1 (SOD1), ANG encoding angiogenin, TARDP encoding TAR DNA-binding protein TDP-43, and FUS/TLS (fused in sarcoma/translated in liposarcoma). However, these genetic defects occur in only about 20~30% of FALS cases, and most genes causing FALS are unknown. We found 3 types of mutation of in the gene encoding optineurin (OPTN), earlier reported to be a causative gene of primary open-angle glaucoma (POAG), in ALS patients. They included a homozygous deletion of exon 5, a homozygous Q398X nonsense mutation, and a heterozygous E478G missense mutation within its ubiquitin-binding domain. Cell transfection analysis showed that the nonsense and missense OPTN mutations abolished the inhibition of activation of NF- κ B, and the E478G OPTN mutation revealed a cytoplasmic distribution different from that of the wild type or a POAG mutation. A case with the E478G mutation showed OPTN-immunoreactive cytoplasmic inclusions. Furthermore, SOD1-positive inclusions of SOD1 ALS cases, TDP-43 positive inclusions of sporadic ALS, and FUS-positive inclusions of sporadic and FUS ALS cases were also noticeably immunolabeled by anti-OPTN antibodies. Our findings strongly suggest that OPTN is involved in ALS pathogenesis. Our findings also indicate that NF- κ B inhibitors could be used to treat ALS and that transgenic mice bearing various OPTN mutations will be relevant for the development of new drugs to treat ALS.

【Biography】

Current Position :

Professor, Department of Epidemiology, Research Institute for Radiation Biology & Medicine, Hiroshima University (2005-)

Education :

1984 Hiroshima University, Faculty of Medicine
1988 Kyoto University Graduate School of Medicine

Appointments :

1989 Resident, Utano National Hospital, Department of Neurology
1993 Assistant Professor, Hiroshima University, Faculty of Medicine Department of 3rd Internal Medicine
2003 Associate Professor, Hiroshima University Graduate School of Biomedical Sciences, Department of Clinical Neuroscience & Therapeutics
2004 Associate Professor
 Hiroshima University Hospital Department of Neurology

AAN-JSN Joint Symposium 1-5 : ALS

15 : 00~16 : 45, Wednesday, May 18, Room 1A (Century Hall, 2nd Floor, Bldg.1)



Failure of RNA editing and the pathogenesis of ALS

Shin Kwak

Department of Neurology, Graduate School of Medicine, The University of Tokyo

GluA2 is a subunit of the AMPA receptor, playing a key role in the regulation of the Ca^{2+} permeability after adenosine (A)-to-inosine (I) conversion at the glutamine/arginine (Q/R) site where the Q codon (CAG) is substituted by the R codon (CIG = CGG). AMPA receptors containing Q/R site-edited GluA2 is Ca^{2+} -impermeable, whereas those containing Q/R site-unedited GluA2 is Ca^{2+} -permeable. A-to-I conversion at the GluA2 Q/R site is specifically mediated by adenosine deaminase acting on RNA 2 (ADAR2). Because all the GluA2 expressed in neurons are edited at the Q/R site in mammals throughout the life from embryonic stages, and because motor neurons in conditional ADAR2 knockout mice undergo slow death due to expression of Q/R site-unedited GluA2, ADAR2-mediated GluA2 Q/R site-editing is crucial for neuronal survival.

We demonstrated that significant proportions of motor neurons of sporadic ALS patients expressed Q/R site-unedited GluA2 resulting from insufficient ADAR2 expression. These molecular abnormalities are disease-specific and lesion-selective in motor neurons of patients with sporadic ALS. Notably, in contrast to the fact that all the motor neurons express ADAR2-immunoreactivity in normal subjects, all the motor neurons exhibiting the abnormal processing of TAR DNA-binding protein (TDP-43) lack the ADAR2-immunoreactivity, whereas those exhibiting normal TDP-43 localization possess ADAR2-immunoreactivity in patients with sporadic ALS. Therefore, there is a molecular link between absence of ADAR2-immunoreactivity (or ADAR2 activity) and abnormal TDP-43 processing in ALS motor neurons.

Taken together, it is likely that reduced ADAR2 activity with expression of unedited GluA2 is involved in the neuronal cell death in sporadic ALS.

[Biography]

Current Position :

Associate Professor/Neurologist, Department of Neurology, Division of Clinical Neuroscience, Graduate School of Medicine, The University of Tokyo, (1997-)

Degrees :

1977 M.D. University of Tokyo
1984 Ph. D. Faculty of Medicine, University of Tokyo

Education and Training :

1977-9 Resident at University and City Hospitals
1980 Research Associate in Tsukuba University
1986-7 Visiting Scientist at Friedrich-Miescher Institut, Basel, Switzerland

Positions and Employment :

1984 Associate, Department of Neurology, University of Tokyo Hospital
1989 Chief of laboratory, Division of Degenerative Neurological Disorders, National Institute of Brain Research
1994 Assistant Professor, Department of Neurology, University of Tokyo Hospital

AAN-JSN Joint Symposium 2-1 : Alzheimer's disease

Chair : Takeshi Iwatsubo Department of Neuropathology, Graduate School
of Medicine, The University of Tokyo

Michael W. Weiner Department of Radiology, San Francisco
VA Medical Center/UCSF, USA

15 : 00~16 : 45, Wednesday, May 18, Room 4B (Shirotori Hall South, 1st Floor, Bldg.4)



Mechanisms and Treatment of Neuronal Dysfunction in Models of Alzheimer's Disease

Lennart Mucke

Gladstone Institute of Neurological Disease and UCSF, USA

Alzheimer's disease (AD), the most frequent neurodegenerative disorder, causes a relentlessly progressive dementia. It is associated with synaptic impairments and is widely thought to be caused by the abnormal accumulation of amyloid- β peptides ($A\beta$) in the brain. How exactly $A\beta$ causes synaptic and cognitive deficits remains to be elucidated. The analysis is complicated by the many different assembly states $A\beta$ can assume, which include dimers and trimers, higher-order oligomers, protofibrils, and fibrillar amyloid plaques. Evidence obtained in human amyloid precursor protein (hAPP) transgenic mice and other models suggests that oligomers and protofibrils are likelier causes of synaptic and cognitive failure than amyloid plaques, but the mechanisms by which the most pathogenic $A\beta$ assemblies cause neuronal dysfunction are uncertain. These mechanisms may involve binding of $A\beta$ assemblies to cell surface molecules with signal transduction capacity or less specific interactions with membranes that alter permeability. We recently identified the receptor tyrosine kinase EphB2 as a key target of $A\beta$ oligomers. Binding of $A\beta$ oligomers to EphB2 triggered the proteasome-dependent degradation of EphB2. Because EphB2 regulates the function of glutamate receptors and synapses, this mechanism likely contributes to $A\beta$ -induced synaptic dysfunction and cognitive decline. Indeed, preventing depletion of neuronal EphB2 levels in the dentate gyrus of hAPP mice also prevented their synaptic deficits, cognitive impairments and behavioral abnormalities. Other strategies that make the brain more resistant to $A\beta$ -induced neuronal dysfunction include reducing levels of the microtubule-binding protein tau, the tyrosine kinase Fyn, or the group IVA isoform of phospholipase A2. Prevention of aberrant excitatory neuronal activity appears to be the common mechanism underlying the therapeutic benefit of these distinct manipulations. References : J. Neurosci. 24 : 4692, 25 : 9694, and 31 : 700 ; Nature 469 : 47 ; Nat. Neurosci. 11 : 1311 and 13 : 812 ; Neuron 55 : 697 ; Science 316 : 750. Supported by the NIH (NIA and NINDS)

[Biography]

Current Positions :

Director, Gladstone Institute of Neurological Disease (1998-)

Joseph B. Martin Distinguished Professor of Neuroscience (2000-), Professor of Neurology, Step 6, University of California, San Francisco (1998-)

Education :

1976-1980 Free University Berlin, School of Medicine, Berlin, Germany

1980-1982 George August University, School of Medicine, Göttingen, Germany

1982 M.D. (Magna Cum Laude), George August University

Positions :

1990-1994 Assistant Member, 1994-1996 Associate Member, Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA

1996-1998 Head and Associate Investigator, Gladstone Molecular Neurobiology Program, The J. David Gladstone Institutes,

1996-1998 Associate Professor, Department of Neurology, Neuroscience Program, and Biomedical Sciences Program, University of California, San Francisco

1997-present Neurology Attending, San Francisco General Hospital

AAN-JSN Joint Symposium 2-2 : Alzheimer's disease

15 : 00~16 : 45, Wednesday, May 18, Room 4B (Shirotori Hall South, 1st Floor, Bldg.4)



Biomarkers for Predicting and Monitoring Progression of Alzheimer's Disease : The Alzheimer's Disease Neuroimaging Initiative

Michael W. Weiner¹, Paul Aisen², Ronald Petersen³, Clifford Jack, Jr.³, William Jagust⁴, John Trojanowski⁵, Leslie Shaw⁵, Andrew Saykin⁶, Arthur Toga⁷, Laurel Beckett⁸, Anthony Gamst²

¹Department of Radiology, San Francisco VA Medical Center/UCSF, USA, ²University of California, San Diego, ³Mayo Clinic, Rochester, MN, ⁴University of California, Berkeley, ⁵University of Pennsylvania, Philadelphia, PA, ⁶Indiana University-Purdue University, Indianapolis, IN, ⁷University of California, Los Angeles, ⁸University of California, Davis

ADNI is an observational longitudinal clinical trial to determine the value of imaging and biomarkers for disease modifying Alzheimer's treatment trials. It aims to : improve methods for clinical trials, determine optimum methods and validate imaging and biomarker data. To date we have longitudinally studied : MCI (n = 400) ; AD (n = 200) ; Controls (n = 220). The rate of hippocampus atrophy and whole brain atrophy both appear to have high statistical power for measuring change over time. Brain atrophy also predicts future decline. FDG PET measures also have high predictive value of MCI conversion to AD and cognitive decline, and some FDG PET measures have high power as outcomes. Complete GWAS data has been obtained on all subjects. Normal healthy elders with APOE4 and/or low CSF A β amyloid have worse memory scores and higher rates of hippocampal atrophy than the non carrier controls or subjects with high CSF A β ; this is consistent with the hypothesis that some controls have preclinical AD pathology. ADNI data has been used to create clinical trial designs of subjects with "early AD". Similar ADNI-like projects, with similar methods, are underway worldwide. Our renewal includes enrollment of new subjects including "early" MCI and F18 amyloid imaging on all subjects. Website is ADNI-info.org and all clinical, cognitive, imaging, and biomarker data is available without embargo on UCLA/LONI/ADNI. Updated analysis of ADNI data, including most recent followup data, will be presented.

【Biography】

Current Position :

Professor of Radiology, Medicine, Psychiatry, and Neurology, University of California at San Francisco

Research Career :

Dr. Weiner attended Johns Hopkins University and the State University of New York, and worked at Mount Sinai Hospital in New York (Resident), and Yale University (Fellow). After service in the US Air Force, in 1971 at the University of Wisconsin he was awarded a VA Research Associate at the Madison VA. Subsequently he was awarded a VA Clinical Investigatorship and relocated to the Palo Alto VA/Stanford University, where he subsequently received the Young Investigator Award of the American College of Cardiology in 1976. In 1980 he performed the first experiment using implanted coils to obtain ³¹P NMR spectra from the kidney of living rats, beginning his work using NMR/MRI for research. Since 1980 he has been at the San Francisco VA/UCSF. He is currently Director of the Center for Imaging of Neurodegenerative Diseases, a 10,000 square foot building with 2 research MRIs and over 70 staff including 9 faculty.

AAN-JSN Joint Symposium 2-3 : Alzheimer's disease

15 : 00~16 : 45, Wednesday, May 18, Room 4B (Shirotori Hall South, 1st Floor, Bldg.4)



Molecular pathology and disease-modifying therapies for Alzheimer's disease

Takeshi Iwatsubo

Department of Neuropathology, Graduate School of Medicine, The University of Tokyo

Deposition of amyloid β peptides ($A\beta$) as senile plaques is the most characteristic neuropathological feature of Alzheimer's disease (AD), which is implicated in its pathogenesis and deemed as the prime target for the disease-modifying therapy (DMT). $A\beta$ deposition is determined by the production and clearance. $A\beta$ is produced by sequential proteolytic cleavages by β - and γ -secretases. γ -Secretase, harboring presenilins (PS) as the catalytic center, forms the C terminus of $A\beta$ that determines its propensity to aggregate: missense mutations in PS genes cause familial AD by altering the preferred γ -secretase cleavage sites in a way to increase production of pathogenic $A\beta_{42}$ species. γ -Secretase forms a hydrophilic pore within the membrane lipid bilayer, and inhibitors of β - and γ -secretases with different targets and mode of action are being developed. $A\beta$ immunotherapy facilitates the clearance of $A\beta$ from brain parenchyma through the activities of anti- $A\beta$ antibodies with different characteristics. Efforts to clinically develop the DMTs for AD, including establishment of imaging and fluid biomarkers that surrogate the AD pathology, will also be discussed in relation to the emerging trends of very early treatment at the preclinical AD stage.

【Biography】

Current Position :

Professor, Department of Neuropathology, Graduate School of Medicine, The University of Tokyo

Research Career :

Dr. Iwatsubo is a neuropathologist/neurologist who has contributed to the elucidation of the pathomechanism of human neurodegenerative disorders, especially AD, using multidisciplinary approaches. He demonstrated that $A\beta_{42}$ is the initially and predominantly deposited species in senile plaque amyloid by immunohistochemistry using specific antibodies. He then demonstrated that mutations in presenilin genes cause familial AD by increasing the production of $A\beta_{42}$, elucidated the process of formation of γ -secretase complex, and showed that the γ -secretase complex harbors a water-permeable pore through which intramembrane proteolysis takes place. He also developed a method to isolate and purify Lewy bodies from human brains and showed that α -synuclein, especially a hyperphosphorylated form, is a component of Lewy bodies. He is recently leading the Japanese ADNI, a nationwide longitudinal imaging/biomarker study on MCI and AD, aiming at bridging the basic disease neuroscience to the clinic, and developing standard surrogate markers for clinical trials of disease-modifying drugs for AD.

AAN-JSN Joint Symposium 2-4 : Alzheimer's disease

15 : 00~16 : 45, Wednesday, May 18, Room 4B (Shirotori Hall South, 1st Floor, Bldg.4)



The future of Alzheimer's disease : opportunities and challenges in drug development

Yoko Fujimoto
Pfizer Japan Inc.

Based on the progress of the understanding of pathogenesis of Alzheimer's disease (AD), accompanied with strong medical and social needs, anti-AD drugs is one of the most active areas for drug development by pharmaceutical companies. Disease-modifying therapy that acts on essential pathological processes of the disease progression is the major target for treatment. Therapies that alter A β pathway are widely believed to have disease modifying effects and are expected to lead to a breakthrough for the treatment of AD.

Unfortunately, however, a series of failures of phase 3 clinical trials for targeting A β pathway were announced during the past several years. These disappointing results raise the possibility that therapeutic interventions applied earlier in the pathophysiological process of AD would be more likely to achieve disease-modification. This approach seems most reasonable, since the patho-physiological process of AD is known to begin considerably prior to the diagnosis of clinical dementia.

In order to allow for early intervention, a wide range of challenges remain such as technical and ethical issues of diagnosis at the pre-clinical phase and initiation of drug treatment before having any clinical symptoms. Considering the fact that the issue of aging societies is imminent and that more than 25 percent of people aged 85 or over are likely to suffer from AD, the structure of medical system will also be exposed to reconsideration because of the large impact on budgets. Therefore it seems essential that everyone who is involved from the academic field, regulatory and industry collaboratively discuss the issues, address future direction and undertake the challenge of anti-AD drug development in order to realize the true value of advances in science and medical innovation for the patient, caregivers and society.

【Biography】

Current Position : Director, Japan Disease Area Leader, Neurology, Clinical Research, Pfizer Japan Inc. (2007-)

Education :

1986-1992 Medical School, Tokyo Medical and Dental University
2002-2006 PhD school of Neuroscience, Tokyo Medical and Dental University

Professional Experience :

1992-1993 Resident in Dep. of Neurology, Tokyo Medical and Dental University
1993-1994 Physician in Internal Medicine, Tokyo Metropolitan Hospital of Bokuto
1994-1995 Physician of Internal Medicine, Saitama Rehabilitation Center,
1995-1997 Physician (Neurologist) in Dep. of Neurology, Tokyo Neurological Hospital
1997-2001 Research Fellow Dep. Of Immunology, Duke University
2002-2003 Medical Advisor, Clinical Research, Pharmacia
2003-2007 Japan Project Team Leader for Varenicline (Champix), Clinical Research, Pfizer

Special Lecture

9:30 ~ 10:20, Wednesday , May 18, Room 1A (Century Hall, 2nd Floor, Bldg.1)



Pathophysiology of progressive multiple sclerosis : studies in a genetically manipulated murine model

David Pleasure, Athena Soulika, Peter Bannerman, Takayuki Itoh
Institute for Pediatric Regenerative Research and Department of Neurology, UC Davis, USA

Current therapies for multiple sclerosis (MS) diminish relapse frequency, but do not prevent disease progression. Neuroimaging and autopsy studies indicate that MS progression is more closely correlated with axon loss than with demyelination. It is crucial, therefore, to understand the pathogenesis of axonal degeneration in MS. We analyzed axonal pathology in a chronic experimental autoimmune encephalomyelitis (EAE) MS model elicited by immunizing genetically manipulated mice with myelin oligodendrocyte glycoprotein peptide 35–55 (MOG peptide). There were two temporally and spatially distinct patterns of axonopathy : a) foci of axonal disruption within inflammatory lesions during the acute phase of the illness ; and b) progressive, symmetrically distributed loss of transgenically labeled axons with the corticospinal tracts (CSTs) during the chronic phase of the illness. This delayed CST axonal loss resembled that reported by Deluca et al (Brain, 2004) in CSTs of chronic MS patients. Further analysis of spinal cords of the MOG peptide EAE mice showed that the CST axon loss was not length-dependent. While there was prominent dendritic disruption in projection neurons in motor cortex, only a small proportion of these neurons were lost. Though foci of systemic inflammatory cells were absent from CNS during the chronic phase of MOG peptide EAE, there was long-lasting induction of CNS Toll-like receptors (TLRs) and associated innate immune signaling molecules. We hypothesize that cumulative axon loss and persistent neurological deficits in MOG peptide EAE and MS result from both acute axonal injury within focal inflammatory lesions and a diffuse neurodegenerative process driven by persistent CNS innate immune activation. If this hypothesis is correct, preventing MS progression will require development of therapeutic strategies aimed at suppressing prolonged induction of CNS innate immunity.

【Biography】

Current Position :

Professor, Neurology and Pediatrics, and Director, IPRM, UC Davis School of Medicine

Education :

1959	Yale College, New Haven CT BA History
1963	P&S, Columbia, NY, NY MD Medicine
1964–6	Neurological Institute, Columbia, NY, NY Neurology
1966–9	NINDS, NIF, Bethesda, MD Neurology
1992	Marine Biological Laboratory, Woods Hole MA Developmental Biology

Positions :

1969–2005	Department of Neurology, University of Pennsylvania
1977–2005	Professor of Neurology, Pediatrics and Orthopaedics, University of Pennsylvania
1994–2000	Director, Pediatric Neurology, Children's Hospital of Philadelphia
1994–2004	Loeb Endowed Chair, then Notebaert Endowed Chair, Children's Hospital of Philadelphia
1996–2004	Director, Joseph Stokes Research Institute, Children's Hospital of Philadelphia
1999–2004	Senior Vice President for Research, Children's Hospital of Philadelphia
2005–present	Professor, Neurology and Pediatrics, and Director, IPRM, UC Davis School of Medicine

Neuroscience Session

10:45 ~ 11:30, Thursday, May 19, Room 3A (International Conference Room, 3rd Floor, Bldg.3)



Lee Silverman Voice Treatment ; Rehabilitative Therapy for People with Parkinson's

Cynthia M Fox¹, Lorraine A. Ramig^{1,2,3}

¹National Center for Voice and Speech, ²University of Colorado, Boulder, CO, ³Columbia University, New York, NY

Despite optimal pharmacological and surgical management, nearly ninety percent of the 6 million individuals with Parkinson disease (PD) worldwide have significant speech deficits that negatively impact their quality of life. Over the past twenty years, an efficacious speech treatment for PD (Lee Silverman Voice Treatment/LSVT LOUD) has been developed with outcome data supporting long lasting improvements (out to 2 years) that are correlated with brain reorganization as revealed by recent neural imaging studies. Furthermore, recent advances in neuroscience emphasize the need for human studies of exercise-based interventions in Parkinson disease (PD) that promote activity-dependent neuroplasticity. The potential disease modifying effects of exercise in animal models of PD, and key aspects of exercise that contribute to neuroplasticity, compel the need for well-defined exercise-based behavioral speech and physical treatments in humans with PD.

This presentation will : 1) highlight elements of exercise that drive neuroplasticity and briefly discuss the potential impact of exercise-based speech and physical therapies in humans with PD, 2) present the background and motivation for voice treatment in Parkinson disease, 3) describe the creation of an efficacious treatment and efficacy data, 4) discuss the evolution in our understanding of LSVT LOUD and application to the limb motor system, and 5) introduce technology as a tool to increase accessibility to intensive speech treatment. Funded, in part, by NIH R01 DC01150.

[Biography]

Current Position :

Research associate at the National Center for Voice and Speech
Co-founder and Chief Clinical Officer of LSVT Global, Inc

Education and Appointments :

Cynthia Fox, Ph.D., CCC-SLP received her doctorate degree in Speech and Hearing Sciences from the University of Arizona, Tucson. She is an expert on rehabilitation and neuroplasticity and the role of exercise in the improvement of function consequent to neural injury and disease. Dr. Fox is a leader in administration of LSVT LOUD speech treatment for people with Parkinson disease (PD). She began working with Dr. Lorraine Ramig 15 years ago conducting efficacy research on LSVT LOUD in people with PD. She was the first to apply this treatment to other disorders, such as multiple sclerosis and pioneered the application to pediatric populations. Dr. Fox has worked closely on the development of a physical therapy program (LSVT BIG) that was modeled after LSVT LOUD. Dr. Fox is a research associate at the National Center for Voice and Speech and Co-founder and Chief Clinical Officer of LSVT Global, Inc.

East Asian Neurology Forum1

Keynote Session : Future Perspective of East Asian Neurology

Chairs : Jun Kimura, Department of Neurology, University of Iowa

Ryosuke Takahashi, Department of Neurology, Kyoto University

13 : 10~14 : 40, Thursday, May 19, Room 3A (International Conference Room, 3rd Floor, Bldg.3)



Message from the WCN to the East Asian Neurology

Mostafa El Alaoui Faris

President of the 20th World Congress of Neurology,
Marrakesh, 2011, Morocco

【Biography】

Current Position :

President of the 20th World Congress of Neurology, Marrakesh–November 2011

Head of the Department of Neurology and Neuropsychology–Hôpital des Spécialités
Rabat, Morocco

Academic Appointments and Society Memberships :

Professor of Neurology and Neuropsychology at Mohamed V University Medical
School–Rabat, Morocco

Founder of the Master of Clinical Neuropsychology

Supervisor of Stroke Research Program of Hassan II Academy of Science and Tech-
nology

President of the 20th World Congress of Neurology, Marrakesh–November 2011

President of the Moroccan Society of Neurology

Chairman of Maroc–Alzheimer Association



Role of the Chinese Society of Neurology in East Asia

Liying Cui

Former President of the Chinese Society of Neurology, China

【Biography】

Current Position :

Professor of Neurology and chief of neurological department in Peking Union Medical College Hospital

Education :

Dr. Cui had been trained in Duke University medical center as a Visiting professor in EMG lab. from Oct 1992 to Oct. 1993 and in California University medical center in Irvine as a clinical neurophysiological fellow from Nov 1993 to Oct. 1995. Study of Olfactory Evoked Potentials in normal subjects and patients with congenital anosmia, Parkinson disease, Alzheimer's disease, schizophrenia were done and two papers were published already.

Appointments :

Former president of Chinese Society of Neurology

President of Chinese Society of EMG & Clinical Neurophysiology.

Research Career :

Research experience includes EMG and nerve conduction velocity studies in normal subjects and patients with neuropathy and myopathy, Single fiber EMG in myasthenia gravis and amyotrophy lateral sclerosis, transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS) in research and clinical application including stroke, ALS, GBS and multiple system atrophy.



Role of the Korean Neurology Association in East Asia

Beom S. Jeon

International Delegate of the Korean Neurological Association, Korea

【Biography】

Current Position :

Chairman of Neurology and Medical Director of the Movement Disorder Center, Seoul National University Hospital

Director, Center for Healthcare Policy and Communication, Seoul National University College of Medicine

President of the Korean Movement Disorder Society

International Delegate of the Korean Neurological Association

Education and Research Career :

Dr. Jeon graduated from Seoul National University College of Medicine, and completed his neurology residency both at Seoul National University Hospital (1983-1987) and at the University of Minnesota (1987-1991), and then had movement disorder fellowship under Dr. Stanley Fahn at Columbia University (1991-1993). He also studied basic neurosciences under Dr. Robert Burke as H. Houston Merritt Fellow (1997-1998) at Columbia University. Dr. Jeon has extensively studied genetics in Korean patients with parkinsonism, and is currently interested in medical and surgical treatment of advanced parkinsonism.



Role of the JSN in East Asia

Hidehiro Mizusawa

President of the Japanese Society of Neurology, Japan

【Biography】

Current Position :

President/CEO of the Japanese Society of Neurology, Professor of Neurology and Neuroscience, Graduate School of Medical and Dental Sciences, Director of the Center for Brain Integration Research, Director of the School of Medicine Faculty of Medicine, Tokyo Medical and Dental University, Tokyo

Education :

1976 University of Tokyo, M.D.

1983 University of Tokyo, Ph.D.

Faculty Appointments :

1981 Assistant Professor of the 1st Internal Medicine, Hamamatsu Medical School

1982 Assistant Professor of Neurology, University of Tokyo Hospital

1983 Staff Neurologist, Yokufukai Hospital

1984 Junior Associate Professor of Neurology, Tsukuba University School of Clinical Medicine

1990 Associate Professor of Neurology, Tsukuba University School of Clinical Medicine

1996 Professor of Neurology, Tokyo Medical and Dental University Faculty of Medicine



Designated Comments

Ryuji Kaji

Trustee, World Federation of Neurology

【Biography】

Current Position :

Professor and Chairman, Department of Neurology, University of Tokushima Graduate School of Medicine, JAPAN

Education :

1979 Graduated from Kyoto University School of Medicine (M.D.), Residency in Neurology and Medicine at Tokyo Metropolitan Geriatric Hospital

1981 PhD course in Medical Science (1985, PhD degree)

1985 Post-doctoral fellow in Department of Neurology, Hospital of the University of Pennsylvania

Appointments :

1986 Visiting Professor of Neurology at the Hospital of the University of Pennsylvania

1987 Assistant Professor of Neurology at the Louisiana State University Medical Center

1989 Assistant, Department of Neurology, Kyoto University School of Medicine

1991 Lecturer, Department of Neurology, Kyoto University Graduate School of Medicine

2000- Current Position

East Asian Neurology Forum : Message from Michael J Fox Foundation

Chair : Mitsutoshi Yamamoto Department of Neurology, Kagawa Prefectural
Central Hospital

Beom S. Jeon Seoul National University Hospital, Korea

14 : 40~16 : 45, Thursday, May 19, Room 3A (International Conference Room, 3rd Floor, Bldg.3)



Accelerating the Cure for Parkinson's Disease : MJFF Mission and Funding Philosophy

Mark Frasier

Research Programs, Michael J Fox Foundation for Parkinson's Research, USA

The Michael J Fox Foundation (MJFF) was founded in 2000 with a simple mission : to accelerate therapeutics and ultimately find a cure for Parkinson's Disease. MJFF utilizes a unique model of funding research that combines a strategic focus on identifying the critical path for developing a cure for PD with sound scientific judgement. MJFF works with stakeholders from academia, government and regulatory authorities, and pharmaceutical and biotechnological companies all over the world to support research that will make the maximum impact in accelerating therapeutics. This lecture will outline the MJFF mission, articulate the current MJFF research priorities, and discuss the specific funding opportunities for scientists and clinicians focused on Parkinson's Disease research. The lecture will also highlight the unique funding model and discuss new efforts focused on developing research tools such as clinical scales, antibodies, and biomarkers to accelerate PD research.

【Biography】

Current Position :

Director, Research Programs, Michael J Fox Foundation for Parkinson's Research, New York, NY (2006-)

Education :

1994-1998 University of Dayton, Dayton, OH, Bachelor of Science, Biochemistry
1999-2004 Loyola University Chicago, Chicago, IL, Ph.D., Pharmacology

Appointments :

1998 Intern, Wacker Chemical Company, Burghausen, Germany
1998-1999 Chemist, Nestle Corporation, Dublin, OH
2004-2006 Postdoctoral Fellow, Eli Lilly and Company, Indianapolis, IN

East Asian Neurology Forum 1-1 : Parkinsonism : Up-to-date

Chair : Mitsutoshi Yamamoto Department of Neurology, Kagawa Prefectural Central Hospital

Beom S. Jeon Seoul National University Hospital, Korea

14 : 40~16 : 45, Thursday, May 19, Room 3A (International Conference Room, 3rd Floor, Bldg.3)



Neuroimaging and Diagnosis of Parkinsonism

Chong S. Lee¹, Kim Jae Seung², Oh Jungsu², You Sooyeoun¹

¹ASAN Medical Center, Korea, ²Department of Nuclear Medicine, Asan Medical Center, University of Ulsan College of Medicine

While Parkinson's disease (PD) constitutes the majority of degenerative parkinsonism, atypical parkinsonism is increasingly recognized in living patients thanks to recent developments of neuroimaging. Multiple system atrophy (MSA) is characterized by a triad of parkinsonism, dysautonomia and cerebellar ataxia. Revised diagnostic criteria of MSA require at least two symptoms, one of which must be dysautonomia. However, in the early stage of disorder, it is not uncommon to find monosymptomatic MSA, the diagnosis of which is assisted by neuroimaging. Pathological studies showed that a substantial number of tau parkinsonism was diagnosed clinically as PD, underscoring the fact that tau parkinsonism is overly underdiagnosed. 18 F-FDG PET may show reduced FDG metabolism in the medial frontal cortex, the caudate and possibly in the midbrain. PET with 18F-FP-CIT, a DAT ligand, is also useful to separate tau parkinsonism from alpha-synuclein parkinsonism.

Parkinsonism-dementia complex is another confusing area, in which a clear-cut guideline for clinical diagnosis is lacking. The most common cause of degenerative parkinsonism-dementia complex is Lewy body dementia, followed by the tau disorder. Lewy body dementia is characterized by hypometabolism of FDG in the occipital cortex, distinct from Alzheimer disease. 11C-PIB, amyloid ligand, is often, but not always, positive in Lewy body dementia. There was no difference in the regional pattern of FDG metabolism between PIB(+) and PIB(-) Lewy body dementia. Tauopathy with parkinsonism-dementia complex shows profound FDG hypometabolism in the frontal and temporal cortices, sparing occipital cortex.

Psychiatric symptom in PD is an emerging area of interest. Impulse control disorder is associated with hypometabolism of FDG in the ventral striatum.

In conclusion, it seems promising that a combination of 18F-FP-CIT and 18F-FDG PET is useful to separate tauopathy from alpha-synucleinopathy. Furthermore, it remains to see whether these neuroimaging studies can detect PD patients who are prone to dementia or psychiatric symptoms.

【Biography】

Current position :

Professor of Neurology, Asan Medical Center, University of Ulsan College of Medicine (2006-)

Education and Appointments :

1978-1982	Seoul National University, College of Medicine, MD
1987-1991	University of British Columbia, Neurology, FRCPC
1991-1996	Fellow, University of British Columbia/Neurodegenerative Disorders Centre
1994-1995	Postdoc Fellow, University of British Columbia/Neurodegenerative Disorders Centre
1997-2006	Assistant Professor, University of British Columbia/Neurology
2006-present	Professor, Asan Medical Center/University of Ulsan College of Medicine

East Asian Neurology Forum 1-2 : Parkinsonism : Up-to-date

14 : 40~16 : 45, Thursday, May 19, Room 3A (International Conference Room, 3rd Floor, Bldg.3)



Treatment of early Parkinson's disease

Louis Tan

National Neuroscience Institute, Singapore

The general considerations when initiating drugs in early PD patients include the disease severity, age of patients, quality of life, employment status, and co-morbid conditions. The traditional view is to initiate treatment only when there is functional impairment and the basis for this is the lack of proven neuroprotective drugs in PD. The alternate view is to initiate treatment early. Proponents of such an approach argue that at the point of diagnosis, patients already suffer significant disability and have an impaired quality of life. Furthermore, in trials on early PD patients, patients who begin treatment earlier have sustained and better motor outcomes. There are now a number of drugs with some evidence of a disease modifying effect. These drugs include the monoamine oxidase-B inhibitors (selegiline and rasagiline) and coenzyme Q10. The evidence for this will be presented. Other medications that have a mild symptomatic effect and may be used in early PD are anti-cholinergics and amantadine. For better symptomatic control, dopamine agonist or levodopa may be prescribed. The rationale and evidence for the use of the various medications will be presented during the talk together with a proposed approach to the management of early PD.

【Biography】

Current Position :

Senior Consultant, Department of Neurology, National Neuroscience Institute, Singapore

Co-Director, Parkinson's Disease and Movement Disorders Centre, Singapore

Adjunct Associate Professor, Duke-NUS Graduate Medical School, Singapore

Education and Research Career :

Upon graduating from the National University of Singapore and completing his neurology training at Tan Tock Seng Hospital, Dr. Louis Tan underwent a movement disorders fellowship at the Parkinson's Institute in Sunnyvale, California. He was a founding member and the past-secretary of the Asian and Oceanian Section of the *Movement Disorder Society*. He is currently the Co-Chair of the AOS Education Committee, and also a member of the *Movement Disorders Journal's* editorial board.

Research Interest :

His areas of specialty and research interests are Parkinson's disease and movement disorders. He is also interested in the epidemiology, clinical studies and clinical trials in Parkinson's disease and other movement disorders.



Treatment of advanced Parkinson's disease

Shu-Leong Ho

University of Hong Kong Queen Mary Hospital, Hong Kong

The problems encountered in Parkinson's disease (PD) increase as the disease advances. They involve the degeneration of dopaminergic and non-dopaminergic neuronal pathways resulting in various motor and non-motor disabilities. Motor disabilities include increasing bradykinesia, rigidity, tremor and gait instability, which respond well to dopaminergic-based therapies such as dopamine agonists and levodopa. On-off and gait freezing are motor disabilities which may not respond well to such dopaminergic therapies. Non-motor disabilities include PD dementia, PD psychosis, depression, anxiety and sleep disorders. In some patients, these non-dopaminergic features may cause more disability than parkinsonian motor features, especially in more advanced stages of the disease. All these problems are further complicated by chronic complications of levodopa therapy, such as early wearing off, dyskinesias and motor fluctuations which become more disabling as the disease progresses, and dopamine dysregulation syndrome with dopamine agonists. The treatment approach in advanced PD has to be individualized as different PD patients have different problems with various severity. This will include a careful and detailed assessment of their disabilities and timing of their medications. The assessments include the use of patient diaries, inpatient monitoring, gait and speech therapy assessments. The management of such problems in advanced PD requires a combination of anti-parkinsonian drug adjustments and/or deep brain stimulation therapy, appropriate symptomatic therapy for non-motor complications, and a multidisciplinary approach involving nursing, physical, psychological and social intervention. This talk will not cover non-motor disabilities as that is covered in a later talk.

【Biography】

Current Position :

The Henry G Leong Professor of Neurology and Chief of Division of Neurology at the University of Hong Kong, Queen Mary and Tung Wah Hospitals

Research Interest :

Dr. Ho's research interest lies in the pathogenesis and treatment of neurodegenerative disorders, specifically Parkinson's disease and amyotrophic lateral sclerosis.



Non-motor feature in Parkinson's disease

Tetsuya Maeda

Department of Neurology, Research Institute for Brain and Blood Vessels Akita

Parkinson's disease (PD) is one of the most common human movement disorders, presenting the cardinal motor features including bradykinesia, rigidity, tremor at rest and postural instability. These motor symptoms become clinically evident when more than 60% of dopaminergic cells in the substantia nigra pars compacta (SNc) are lost, whereas it is now well-recognized that pathologically, PD is a widespread systemic disease. Correspondingly, PD is manifested by the motor symptoms as well as the non-motor symptoms, such as apathy, pain, sexual difficulties, bowel incontinence, and sleep disorders, while these are still under-recognized and, consequently, undertreated.

The non-motor phenomena of PD are consisted of such a wide spectrum of symptoms based on the widespread pathological changes. Recent studies targeting these symptoms endeavor to quantify and manage them using with specific validated tools available for their assessment, including the nonmotor symptoms questionnaire, the non-motor symptoms scale, the revised unified PD rating scale, and the scales for outcomes in PD.

In the clinical course of PD, the non-motor symptoms are apparent not only in advanced stages but also in early stages. Some symptoms such as olfactory dysfunction, constipation, rapid-eye movement sleep behavior disorder, and depression might exist prior to the motor symptoms by several years or more. This non-motor progression is consistent with the recent concept that Lewy body pathology and consequent neuronal dysfunction begin in the olfactory bulb and lower medulla. The expansion of the prominent pathological changes might induce the corresponding dopaminergic dysfunction and clinical symptoms. In a clinical practice, any possible treatments, whether dopaminergic or not, have to be considered to improve patients' living quality. In fact, non-dopaminergic treatment might contribute to a management of some non-motor symptoms of PD. In this review, an overview of this clinically inevitable issue of PD is provided.

【Biography】

Current Position :

Chief in Clinical Neurology, Senior Scientist, Department of Neurology, Research Institute for Brain and Blood Vessels Akita (2009-)

Education :

1993 M.D., Hirosaki University School of Medicine
1997 Ph.D., Hirosaki University Graduate School of Medicine

Appointments :

1993 Resident in Neurology, 3rd Department of Internal Medicine, Hirosaki University, Hirosaki, Japan
1997 Senior Resident in Neurology, 3rd Department of Internal Medicine, Hirosaki University, Hirosaki, Japan
2002 Attending Neurologist, 3rd department of internal medicine, Hirosaki University, Hirosaki, Japan
2003 Research Scientist, Department of Neurology, Research Institute for Brain and Blood Vessels, Akita, Japan
2006 Senior Scientist, Department of Neurology, Research Institute for Brain and Blood Vessels, Akita, Japan



Genetics of Parkinson's disease in Asia

Chin-Song Lu

Chang Gung Medical Center at Linkou, Taiwan

Genetic etiology plays an important role in Parkinson's disease either in understanding the pathogenic mechanisms or in guiding the direction of pharmaceutical therapy. About 10% to 15% of Parkinson's disease is related to monogenic causes and genetic risk factors. In fact, different populations might be associated with different mutations of the causing genes and even with different genes. The genetic influence will be discussed in Asia PD population in the presentation.

Up to date, there are 18 possible loci have been reported. However, SNCA and LRRK2 genes are important monogenic causes in association with autosomal dominant inheritance. The clinical presentations of patients were similar to those of idiopathic PD, but dementia was frequently associated with duplicate or triplicate of SNCA. PRNK is the most common gene in association with autosomal recessive inheritance, followed by PINK1, DJI, ATP13A2, GIGYF2 and PLA2G6. They are usually presenting with young onset Parkinsonism.

Several genes and loci are still needed to be further investigated such as SPR, FBX07, PARK16, PARK17, and PARK18. In Asia, most of the monogenic causes have been well investigated here in Japan, such as PRNK, PINK1, DJ1 and LRRK2 genes, particularly by Professor Mizuno and his colleagues and also other investigators. The important risks of G2385R and R1628P in LRRK2 gene were initially documented in Taiwan and Singapore. The G2385R risk factor was further documented in Japan, Korea and China. On the contrary, the G2019S was rarely identified in Asian countries; despite it was the most important mutation in LRRK2 gene in the Western countries. Whether the heterozygous mutations of PRNK and PINK1 are able to cause clinical symptoms are still controversial.

The other genes might be also important in Asian PD are GBA, SCA2 and SCA3. Several loci detected recently by GWAS study from Japan might be potentially significant risks.

【Biography】

Current Position :

Chairman of the Department of Neurology and of the Neuroscience Research Center at Chang Gung Memorial Hospital and Medical Center at Linkou

Research Career :

Professor Lu's research interests cover many aspects of disorders of movement in neurology. His recent research projects include studies of [^{99m}Tc-TRODAT-1 SPECT imaging for diagnosis and to investigate the deep brain stimulation on subthalamic nucleus for treating Parkinson's disease ; analysis of Parkin mutations in non-familial Parkinson's disease in Taiwan ; the role of DYT1 in dystonia ; and phenotype and genotype of primary torsion dystonia in the Taiwanese population.

More recent, Professor Lu's important work is the discovery of G2385R and R1628P in LRRK2 gene and PLA2G6 as the important risk factors in Parkinson's Disease in Taiwanese. He also contributes the important research on DYT5, 6, 8, and 11 in dystonia in Taiwan.

Symposium1

13:15 ~ 14:45, Thursday , May 19, Room 1B (3rd Floor, Bldg.1)

SY-01-2

Branch atheromatous disease : an important cause of small subcortical infarction in Asia



Medical college, University of Ulsan ;
Department of Neurology, Asan Medical Center ; Stroke Center, Asan Medical Center, Korea
○Jong Sung Kim

Branch atheromatous disease (BAD) refers to atheromatous occlusion of a small, perforating vessel. BAD produces small subcortical infarction (SSI) and presents clinically with lacunar syndrome. However, this is pathophysiologically distinguished from traditional small vessel disease (SVD) caused by lipohyalinosis primarily affecting the distal part of perforators. According to vascular imaging findings, BAD may be divided into infarcts associated with parental artery disease (PAD) and those without. Although perforating vessels cannot be visualized by current imaging technologies, SSI abutting on the parenteral vessel can be considered a BAD caused by proximal atherosclerotic occlusion of a perforating vessel. Thus, in clinical practice, SSI may be divided into SSI with PAD (SSS+PAD), proximal SSI without PAD (pSSI-PAD) and distal SSI without PAD (dSSI-PAD). We examined the prevalence of SVD markers (leukoaraiosis and microbleeds) and atherosclerosis markers (cerebral atherosclerosis and coronary heart disease) among these groups, and found that SSSI+PAD had the highest prevalence of atherosclerosis markers and the lowest prevalence of SVD markers, whereas dSSI-PAD had the lowest prevalence of atherosclerosis markers and the highest SVD markers. pSSI-PAD showed intermediate features. The prevalence of these markers also differed according to the vascular territories; atherosclerosis markers significantly increased while SVD markers decreased as the vascular territory became lower (from middle cerebral artery, basilar artery to vertebral artery). These results illustrate that SSI has a heterogeneous pathogenesis. Since intracranial atherosclerosis is a major cause of stroke in Asia, the importance of BAD should be appropriately recognized.

SY-01-3

Branch atheromatous disease : prognosis and management. The SPS3 experience



Division of Neurology, University of British Columbia, Canada
○Oscar Benavente

Stroke due to pathology of small penetrating arteries is common and still remains controversial with respect to mechanisms, prognosis and treatment. Occlusion of small penetrating arteries results in lacunar infarcts which are cavitations not larger than 20 mm and are often located deep in the brain. The pathology of the affected arteries is quite diverse, including; subintimal foam cells, wall disorganization, fibrinoid necrosis and lipohyalinosis. Occasionally, obliteration of the parent artery produces giant lacunes. A distinct vascular pathology involving the basilar artery referred as branch atheromatous disease (BAD) is the etiology of a large proportion of pontine infarcts. Both entities (BAD and lipohyalinosis) are clinically identical and in addition, it is likely that the prognosis and response to treatment are the same. Therefore, from the practical point of view this differentiation is purely academic. The Secondary Prevention of Small Subcortical Strokes (SPS3) study is the first clinical trial designed to address clinical scientific questions in patients with symptomatic lacunar infarct defined by magnetic-resonance imaging, which are likely due to small vessel disease. Patients are simultaneously randomized in a 2 x 2 factorial design, to antiplatelet therapy-aspirin plus clopidogrel vs. aspirin and to two levels of blood pressure control- "intensive" (< 130 mmHg) vs. "usual" (130-149 mmHg). The primary outcome is recurrent stroke and secondary outcomes include cognitive decline and major vascular events. Recruitment has been completed with 3020 patients; results are expected by mid 2012.

Symposium7

8:30 ~ 10:30, Thursday , May 19, Room 3A (International Conference Room, 3rd Floor Bldg.3)

SY-07-4

Dementia with motor neuron disease



¹Department of Clinical Neurological Sciences, The Schulich School of Medicine & Dentistry, The University of Western Ontario, Canada, ²The Robarts Research Institute, Schulich School of Medicine & Dentistry, The University of Western Ontario

○Michael J. Strong¹, Wencheng Yang¹, May Gohar², Wendy L. Strong²

Background: The neurodegenerative process of amyotrophic lateral sclerosis (ALS) includes both selective degeneration of motor neurons and one or more syndromes of frontotemporal dysfunction (e.g., behavioural (ALSbi) or cognitive (ALSci) syndromes, a frontotemporal dementia (ALS-FTD)). There is widespread degeneration of the frontal, temporal and to a lesser extent parietal lobes in association with TDP-43 immunoreactive pathology. We have shown that tau protein metabolism is also altered in ALSci and now describe the topographic distribution of tau pathology in ALS.

Methods & Results: Tau is hyperphosphorylated (pThr175-tau) in ALSci and is associated with an upregulated of GSK-3b activity. We generated novel rabbit polyclonal antibodies to three tau phospho-epitopes (pSer208, 210, pThr217 and pThr175) and demonstrated pathological tau aggregates in both ALSci and ALS. The pattern of deposition suggests that phylogenetically more primitive regions (amygdala, entorhinal cortex, hippocampus) are involved prior to more anteriorly placed regions (i.e., anterior cingulate gyrus). Tau pathology was prominent in astrocytes. Neuronal pThr175-tau immunoreactive aggregates were associated with an up-regulation of TDP-43 expression but not with TDP-43 aggregates. Transient transfections with pseudo-phosphorylated tau (Asp-Thr175-tau) induces tau fibrils and an enhanced rate of cell death that could be inhibited the inhibition of GSK-3b activation.

Conclusions: While ALSci shows pathological processing of both TDP-43 and in tau protein, our observations suggest that ALSci is primarily a disorder of tau protein metabolism. This provides a basis on which to develop novel ALS therapies directed towards cognitive impairment.

Symposium8

13:15 ~ 14:45, Thursday , May 19, Room 4A (Shiratori Hall, 1st Floor Bldg.4)

SY-08-1

Neuropathic pain-definition, mechanisms diagnosis and management



Division of Neurological Pain Research and Therapy, Department of Neurology, Univesitätsklinikum Schleswig-Holstein, Germany
○Ralf Baron

Neuropathic pain represents a major medical problem and treatment has been unsatisfactory. Therefore, a new concept to classify neuropathic pain was proposed in which pain is analyzed on the basis of underlying mechanisms rather than on the basis of the causing etiology. The German Research Network on Neuropathic Pain established a large data-base of clinical as well as standardized quantitative sensory testing data. In all neuropathic etiologies several different somatosensory patterns could be analyzed. Thus, clear phenotypic subgroups exist in neuropathic pain which might be specifically tested in clinical trials.

The medical management of neuropathic pain consists of five main classes of oral medication (antidepressants, anticonvulsants with Na-blocking action, anticonvulsants with Ca-modulating actions, tramadol and opioids and topical medications (capsaicin and local anaesthetics). A early combination of compounds effecting different mechanisms is often useful. Venlafaxine and duloxetine which block both serotonin and norepinephrine reuptake was effective in patients with painful diabetic polyneuropathy. Pregabalin and gabapentin show efficacy postherpetic neuralgia, diabetic painful neuropathy, central pain states and other neuropathic pain entities. The mechanism is an action on the $\alpha 2$ β -subunit of neuronal calcium channels. Local anaesthetics block voltage-dependent sodium channels. Carbamazepine is effective in trigeminal neuralgia. The strength of evidence is lower in other types of neuropathic pain. Oxcarbazepine and also lamotrigine and topiramate were not superior to placebo in large trials on painful diabetic neuropathy. For lamotrigine there is evidence of efficacy for HIV sensory neuropathy and central poststroke pain.

Symposium11

14:45 ~ 16:45, Thursday , May 19, Room 2C (2nd Floor Bldg.2)

Keynote Lecture

Attracting the best and brightest to careers in neurology



University of Pennsylvania, USA

○Donald H. Silberberg

Widespread interest in the neurosciences has led to the development of undergraduate college majors in neuroscience so that many students entering medical school are very interested in a career in our field. Exposure to clinical neurology at the University of Pennsylvania School of Medicine (PennMed) begins with observation of real patients in the 1st year coupled with the course "Introduction to Neurosciences". In their 2nd year the neurological examination is taught by neurology faculty, preparing students for an intensive clerkship in their 3rd year. More advanced clinical courses are available, and some students pursue a combined MD/PhD before applying for residency training. Approximately 5 or 6 students per year, in a class of 160, apply for neurology residency. Others pursue neurosurgery or psychiatry. The top students apply to the top programs nationally. Our program attracts 225 applicants/year from US medical schools, for 7 places, not including Child Neurology.

Neurology residency training lasts 4 years, including 1 year of internal medicine. Penn's residency program is highly structured, as are other top programs, combining inpatient and outpatient responsibilities, and conferences that include all of the neurology subspecialties, neuropathology and neuroradiology. Almost all Penn trainees pursue post-residency clinical subspecialty and/or research fellowships, and enter academic departments throughout the US. These factors, in addition to the opportunity to participate in the care of individuals with a wide variety of neurological illnesses under the supervision of nationally and internationally known faculty, lead to recruitment of top students.

Symposium17

14:45 ~ 16:45, Thursday , May 19, Room 4C (3rd Floor Bldg.3)

Keynote Lecture

Perspectives in refractory diabetic and amyloid small-fiber neuropathy



Department of Neurology Hospital de la Salpetriere, France

○Gerard Said

Small fiber neuropathies (SFN) are characterized by alteration of unmyelinated and small myelinated nerve fibers with impairment of pain and temperature sensations, often associated with autonomic disturbances. Pains and numbness in distal lower limbs are the most common symptoms. Loss of temperature and pain sensations in distal lower limbs contrasts with relative preservation of light touch, position and vibratory sense, tendon reflexes and muscle strength. Nerve conduction and sensory action potentials may remain unaltered for a long time. Diabetes is responsible for most cases of SFN in the world. In severe cases progression of sensory deficit follows a length dependent pattern with gradual involvement of proximal lower limbs; upper limbs and anterior trunk. In this setting, nerve biopsy specimens show predominant involvement of unmyelinated and small myelinated fibers, and a dying back process followed by spontaneous axonal regeneration by sprouting. Ideally, only perfect control of blood glucose, as achieved by β -cell replacement by Langherans islets or pancreas transplantation can prevent further alteration of the PNS and allow efficient regeneration.

Familial amyloid polyneuropathy (FAP) is very similar to severe forms of diabetic polyneuropathy with a devastating course leading to death within 10 years on average. Fiber degeneration is linked to the presence of transthyretin-derived amyloid deposits in the endoneurium. Liver transplantation dramatically reduces the amount of circulating mutated transthyretin and, a drug recently introduced Tafamidis[®] seems to favorably influence the outcome. However genetic counseling remains highly recommended for prevention of FAP.

