14th international symposium at MNRC

New insights into the treatment of neurological diseases

February 13 (Monday), 2012 15:00 - 18:00

Shiga University of Medical Science (SUMS)

Staff Lobby

ABSTRACTS

Molecular Neuroscience Research Center (MNRC)

Shiga University of Medical Science

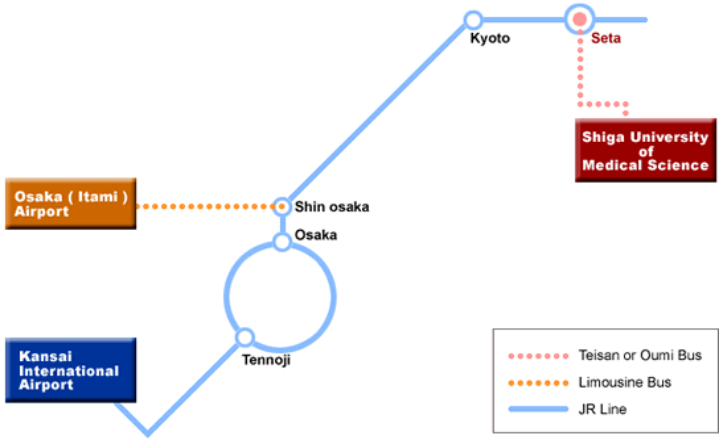
Access

From Kansai International Airport (KIX)

1. Take Airport Express "Haruka" bound for JR Kyoto station (approx. 75-80 min).

2. At Kyoto station, change to JR Biwako line (local train), and get off at JR Seta station (approx. 20min).

3. Take Teisan or Oumi bus bound for Shiga-idai, and get off at Shiga-Idai-Mae (approx. 15min).



From Osaka International Airport (ITM)

1. Take a limousine bus bound for JR Shin-Osaka station (approx. 25min).

2. At Shin-Osaka station, change to JR Kyoto line (rapid or local train).
(note:If you get on the Super rapid train, the train can not stop at Seta Station.)

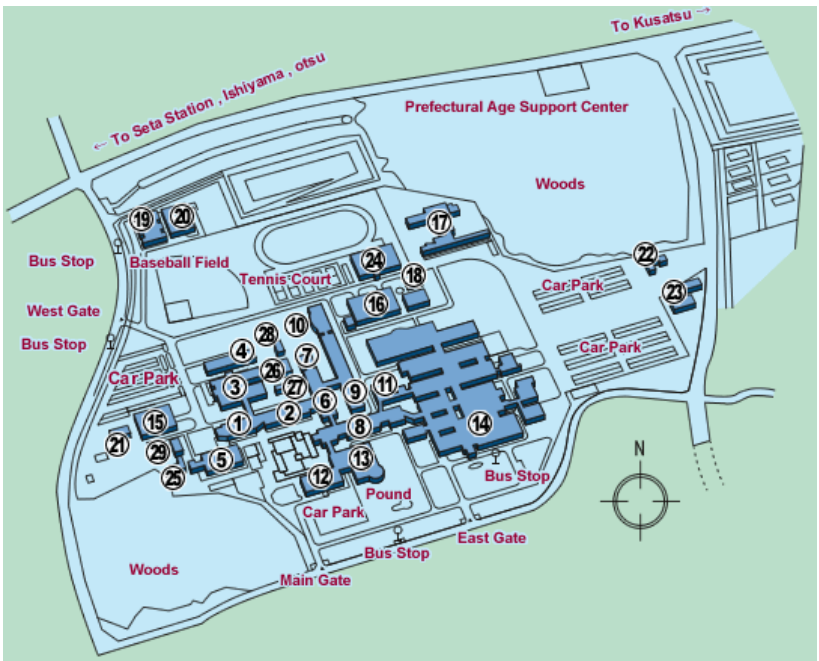
3. Get off at JR Seta station (approx. 50min). Take Teisan or Oumi bus bound for Shiga-Idai, and get off at Shiga-Idai-Mae (approx. 15min).

Cumpus map

(2) Basic Medicine Education and Research Building

2F: Staff Lobby

(7) Molecular Neuroscience Research center (MNRC)



- Programs -

1) 15:00–15:05 Opening Remarks: *Tadao Bamba*
(President and Dean, Shiga University of Medical Science)

2) 15:05–17:55 Presentations

1. 15:05–15:15
Introduction; "The aim of the symposium"
Ikuo Tooyama *(Director of MNRC, Shiga University of Medical Science)*

2. 15:15–16:05
"A Neuroprotection Framework in Cerebral Ischemia Based on a 'Stroke in a Dish' Model"
Joseph S Tauskela *(University of Ottawa, NRC, Canada)*

3. 16:05–16:25
"Mitochondrial Ferritin reduces oxidative stress-induced neuronal death in Alzheimer's disease"
Hongkuan Yang *(MNRC, Shiga University of Medical Science)*

(Break 10 min)

4. 16:35–17:05
"Expression profiles of cytokines in the brain of Alzheimer's disease patients"
Yoshihiro Konishi *(Department of Clinical Research, National Hospital Organization Tottori Medical Center, Japan)*

5. 17:05–17:55
"Human Brain Discovery Research: Brain Banks and Translational Neuroscience"
Thomas G Beach *(Banner Sun Health Institute, USA)*

3) 17:55–18:00 Closing Remarks: *Takanori Hattori*
(Vice President and Dean, Shiga University of Medical Science)

1. Introduction; "The aim of the symposium"

Ikuo Tooyama, MD, PhD
(Director of MNRC, Shiga University of Medical Science)

Abstract

Although neuronal regeneration in the brain has recently received some attention, the activity is limited in the adult brain. Thus, it is very important to protect neuronal death in the neurological disorders including stroke and neurodegenerative disorders such as Alzheimer's disease. In order to protect neuronal death, it must clarify the mechanism of cell death. Several mechanisms are proposed. These include toxic proteins, oxidative stress and neuroinflammation. Each phenomenon does not occur alone but they are simultaneously seen in the affective areas. In Alzheimer's disease brain, for example, extracellular amyloid beta plaques and intracellular neurofibrillary tangles induce oxidative stress and inflammation. In this symposium, we invite excellent researchers from USA, Canada and Japan to talk the recent advances in the mechanism of neuronal death and its treatment.

2. A Neuroprotection Framework in Cerebral Ischemia Based on a 'Stroke in a Dish' Model

Joseph S Tauskela, PhD
(University of Ottawa, NRC, Canada)

Abstract

Neuroprotection in stroke remains a major challenge, with the exception of ederavone (Japan), suggesting shortcomings in optimization of therapeutics at the preclinical level. A neuroprotection 'framework' is proposed to address key issues: (i) timing – treatment too delayed to counter rapidly developing excitotoxicity; (ii) efficacy – lack of prioritization of biological targets/therapeutics; (iii) adverse effects – inability to predict. A neuroprotection framework was developed using an increasingly stringent stroke-like model of oxygen-glucose deprivation (OGD) in cortical neuron cultures. First, preconditioning stimuli to activate endogenous stress responses prior to lethal OGD protect neurons by a common mechanism, which is suppression of cellular glutamate release. Second, this cellular glutamate release is not prevented during more prolonged OGD, but this 'ceiling' of neuroprotection can be overcome by administration of an anti-excitotoxic receptor antagonist drug cocktail when this delayed glutamate release occurs. Third, neuroprotection against supra-lethal OGD requires a more potent anti-excitotoxic cocktail, and not antagonists of other channels implicated in cerebral ischemia. Investigations of spatiotemporal patterns of network activity using multi-electrode arrays are in progress to assess efficacy:toxicity ratios of neural network function. Summarizing, the neuroprotective framework currently consists of combination therapy which temporally suppresses pre- and post-synaptic components of glutamatergic excitotoxicity. Preconditioning 'buys time' before requiring 'rescue' later in OGD, with rescue achieved by using an increasingly aggressive receptor antagonist cocktail as the stringency of OGD increases.

3. Mitochondrial Ferritin reduces oxidative stress-induced neuronal death in Alzheimer's disease

Hongkuan Yang, MD
(MNRC, Shiga University of Medical Science)

Abstract

Iron, as the most abundant metal in the brain, is an essential cofactor for many key proteins involved in the normal function of neuronal tissues, as well as many other important metabolic processes. Excess iron accumulation and deposition in the brain is a major hallmark in aging. Dysregulation of iron is considered to be involved in the pathogenesis of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and Friedreich's ataxia (FRDA), as iron is tightly associated with oxidative stress and neurotoxicity.
Mitochondrial Ferritin (MtFt), a novel protein which was initially found in sideroblastic anemia, has recently been revealed to have a strong link to the pathological mechanism and neuroprotective effect of several neurodegenerative diseases. Due to its ferroxidase activity and its ability to store iron, MtFt protects against oxidative stress.
In human cerebral cortex, MtFt mRNA was detected mainly in neurons and to a lesser degree in glial cells. The expression level of MtFt was increased in Alzheimer's disease patients compared to control cases. In cultured neuroblastoma cells, the expression of both MtFt mRNA and protein was increased by treatment with H_2O_2 or a combination of β-amyloid and H_2O_2. In addition, the overexpression of MtFt in neuroblastoma cells showed a significant neuroprotective effect against H_2O_2-induced oxidative stress. In contrast, MtFt silencing not only increased cell sensitivity to β-amyloid and H_2O_2–induced oxidative stress, but also led to cell growth defects. These results suggest that MtFt is involved in the pathology of AD and may play a neuroprotective role against oxidative stress.
Little information is available concerning the precise roles of MtFt in neurodegenerative diseases, particularly Alzheimer's disease. Further research into the role of MtFt may provide new insight into the pathogenesis of AD and may provide novel therapeutic strategies for many neurodegenerative diseases.

4. Expression profiles of cytokines in the brains of Alzheimer's disease patients

Yoshihiro Konishi, MD, PhD
(Department of Clinical Research, National Hospital Organization
Tottori Medical Center, Japan)

Abstract

Neuroinflammation is involved in the Alzheimer's disease (AD) pathology. Our major focus was to clarify whether neuroinflammation plays important roles in AD pathogenesis, particularly prior to the manifestation of overt dementia. We analyzed cytokine expression profiles of the brain, with focus on non-demented patients with increasing AD pathology, referred to as high pathology control (HPC) patients, who provide an intermediate subset between AD and normal control subjects, referred to as low pathology control (LPC) patients. With real-time PCR techniques, we found significant differences in interleukin (IL)-1ß, 10, 13, 18, and 33, tumor necrosis factor (TNF)α converting enzyme (TACE), and transforming growth factor (TGF)ß1 mRNA expression ratios between HPC and AD patients, while no significant differences in the expression ratios of any cytokine tested here were observed between LPC and HPC patients. The cytokine mRNA expression ratios were determined as follows: first, cytokine mRNA levels were normalized to mRNA levels of a housekeeping gene, peptidyl-prolyl isomerase A (PPIA), which showed the most stable expression in a given set of samples among ten housekeeping genes tested here; then, the normalized data of cytokine levels in the temporal cortex were divided by those in the cerebellum, which is resistant to AD pathology. Subsequently, the expression ratios of the temporal cortex to cerebellum were compared among LPC, HPC and AD patient groups (n = 10 in each group). Our results indicate that cytokines are more mobilized and implicated in the later AD stage when a significant cognitive decline occurs and develops than in the developmental course of AD pathology prior to the manifestation of overt dementia.

5. Human Brain Discovery Research: Brain Banks and Translational Neuroscience.

Thomas G Beach, MD, PhD
(Banner Sun Health Institute, USA)

Abstract

Medical science in general is currently perceived as underperforming over the last few decades. This is because of the relatively slow rate of development of new and improved disease treatments. Most often, this has been blamed on regulatory and economic factors that generate a so-called "valley of death", hindering new drug candidates from being quickly translated to clinical trials and regulatory approval. To bring a new medicine from bench to bedside requires about seven to ten years of clinical trials costing around $800 million dollars. We propose, however, that for neurodegenerative diseases, a relative decline of human brain discovery research is also a contributor to this perplexing problem. The currently approved pharmacological agents for treating Alzheimer's disease and Parkinson's disease were identified through direct examination of postmortem human brain tissue more than 30 years ago. Subsequently, research funding has shifted almost entirely to in vitro and animal models of disease. While these are powerful and necessary approaches, they lack a connection with reality if findings are never cross-validated through studies of diseased and control human brains. Despite the relative lack of funding, human brain discovery research has continued to make important contributions to our understanding of neurodegenerative disease, and brain banks have played an essential role. It is likely that the pace of discovery will dramatically accelerate over the coming decades as increasingly powerful methods such as genomics, gene expression profiling, proteomics and metabolomics are applied. To optimize the promise of these new technologies, however, it is critical that brain banks receive increased governmental and/or private support. The Banner Sun Health Research Institute Brain and Body Donation Program (BBDP), established in 1987 in Sun City, Arizona, is unique in the world for having uniformly short postmortem intervals, with a median PMI of 3.0 hours for the entire collection from more than 1400 autopsies. This has been the major factor in allowing the Program to prosper through research contracts, grants and user fees despite a relative lack of government funding. Significant human brain research discoveries that have been made possible through the use of BBDP tissue will be highlighted.

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