

Japan-U.S. Brain Research Cooperation Program
Information Exchange Seminar Program FY2012: Report

Field: Neurobiology of Disease

1. Seminar title: Trans-Pacific Workshop on Stroke 2012
2. Dates from October 17, 2012 to October 18, 2012
3. Location: Wyndham Riverfront Hotel, New Orleans, LA, USA

4. Coordinators

Japanese Coordinator

Name: Hiroaki Ooboshi

Title: Professor

Affiliation: Department of Internal Medicine, Fukuoka Dental College

U.S. Coordinator

Name: Midori A. Yenari

Title: Professor

Affiliation: Department of Neurology, UCSF

5. Participants:

Japan: Invited participants 9 people Others 0 people

(Please give names, titles and affiliations of invited participants)

Koji Abe, Professor, Department of Neurology, Okayama University
Hiroaki Ooboshi, Professor, Department of Internal Medicine, Fukuoka Dental College
Shunya Takizawa, Professor, Department of Neurology, Tokai University
Kazuo Kitagawa, Assoc. Professor, Department of Neurology, Osaka University
Mami Noda, Assoc. Professor, Department of Pharmacology, Kyushu University
Tetsuro Ago, Assist. Professor, Department of Medicine & Clinical Science, Kyushu University
Shigeru Tanaka, Assist. Professor, Department of Neuropharmacology, Hiroshima University
Eisuke Dohi T, Staff, Department of Neurology, Hiroshima University
Nozomi Akimoto, Grad. Student, Department of Pharmacology, Kyushu University

U.S.: Invited participants 21 people Others 0 people

(Please give names, titles and affiliations of invited participants)

Midori Yenari, Professor, Department of Neurology, UCSF
Jialing Liu, Professor, Department of Neurosurgery, UCSF
Shobu Namura, Professor, Department of Neurobiology, Morehouse School of Medicine
Kyra Becker, Professor, Department of Neurology, University of Washington
David S. Miller, Director, National Institutes of Health
Nicholas G. Bazan, Professor, Neuroscience Center, Louisiana State University
Ludmila Belayev, Professor, Neuroscience Center, Louisiana State University
David W. Busija, Professor, Department of Pharmacology, Tulane University
Byron Ford, Professor, Department of Neurobiology, Morehouse School of Medicine
Jeff M. Gidday, Assoc. Professor, Department of Neurosurgery, University of Washington
Raphael Guzman, Assist. Professor, Department of Neurosurgery, Stanford University

Chris B. Shaffer, Assist. Professor, Department of Biomedical Engineering, Cornell University
Prasad V.G. Katakam, Fellow, Department of Pharmacology, Tulane University
Masahito Kawabori, Fellow, Department of Neurology, UCSF
Yosuke Akamatsu, Fellow, Department of Neurosurgery, UCSF
Chin Cheng Lee, Fellow, Department of Neurosurgery, UCSF
Allison Kunze, Fellow, Department of Neurology, University of Washington
Donghui Li, Fellow, Department of Neurobiology, Morehouse School of Medicine
Zhenfeng Xu, Fellow, Department of Neurobiology, Morehouse School of Medicine
Alberto E. Musto, Fellow, Neuroscience Center, Louisiana State University
Nozomi Nishimura, Fellow, Department of Biomedical Engineering, Cornell University

6. Seminar Outline and Significance:

Stroke is a leading cause of death and disability in many industrialized nations, and the United States and Japan are no exception. In the US, recanalizing therapies such as pharmacological thrombolysis and mechanical thrombectomy have been FDA approved. However, these therapies are limited to small numbers of patients, leaving the majority of stroke victims with few treatment options. Because stroke often leads its victims with significant disability, the need to identify effective treatment strategies is obvious. Within the past few decades, laboratory researchers from both the US and Japan have striven to understand and identify relevant therapeutic targets and strategies to treat stroke. While investigators from both countries often attend the same international scientific meetings, there are rare chances for investigators to meet and discuss individual research interests at a level where collaborations could be formed. This is likely due to the large and sometimes intimidating venues used by larger conferences, as well as language and cultural barriers. Thus, it is hoped that in a smaller, more intimate setting, investigators will have a chance to explore areas of common research interests and begin to develop ideas for joint investigations.

The workshop was intended to update investigators on the current status of research as it pertains to cerebrovascular injury and treatment in stroke at both the laboratory and clinical level. The workshop identified key areas of investigation and gaps in scientific knowledge that could be bridged by the formation of collaborations between labs of each nation.

7. Seminar Results and Future Implications:

One area largely under investigated by the scientific community, yet an area with high promise for clinical translation is that of cerebrovascular factors in brain ischemia. Compared to brain cell death pathways which have been extensively studied for the past decade or so, less is known about how ischemia affects the blood vessels in the brain, and whether therapeutic strategies to protect these vessels may translate into effective treatments. Recent work in the field has shown that significant complications of stroke are due to a disrupted blood brain barrier (BBB) through which blood cells and other serum elements can enter the brain and lead to further damage than that by ischemia alone. More recent research has focused on the role of inflammation, which can exacerbate cerebrovascular injury. Mechanisms how ischemia affects the cerebrovasculature and the BBB were discussed by the attendees, and such understanding would lead to the identification of effective therapies.

Newly-identified cytoprotective agents were introduced by many researches in this workshop. The development of tolerance, whereby sublethal insults protect against lethal insults has been of great interest to the field for at least a decade or more. While most work has focused on the development of tolerance to the brain parenchyma itself, or to neurons, studies that have shown vascular tolerance were presented to exert brain protection. A major challenge unique to the central nervous system is being able to deliver therapies effectively, since the brain is normally protected by a BBB which is often impermeable to many drugs. Thus, this workshop covered areas where improving drug delivery through this barrier can be achieved without having to resort to invasive procedures. The strategies to enhance protein/drug binding and transport through the BBB to allow entry of a potential therapy without causing lasting brain injury were discussed.

The area of cell-based therapy has been a topic of international interest given the promise of stem cells to cure major classes of human illness. The US and Japan have contributed significantly to the scientific knowledge in this area. The use of stem cells or other cells which contain reparative potential has been

studied in stroke models by investigators from both nations. The delivery method of stem cells to the brain, e.g., intravascular approaches, was also discussed. Angiogenesis was another important topic regarding how the brain repairs and/or forms new vessels after stroke and whether these vessels necessarily function normally. Translational issues were also discussed, since being able to deliver these therapies is the goal of research in the field. The workshop also covered state of the art non-invasive imaging.

The presentation and discussion in this workshop was published in the prestige journal (Ann NY Acad Sci 1278:25-32,2013).

8. Other (implementation issues, feedback, etc.)

The meeting was viewed by most of the attendees as a successful beginning to the development of collaborative efforts between the two countries in the investigation of the pathomechanisms of ischemic stroke. The size and format of the meeting were well received, especially by the Japanese participants and junior investigators, who often feel intimidated when asked to speak at large conferences. The location and timing surrounding the Society for Neuroscience meeting was convenient for the U.S. participants, particularly the basic researchers and students.

This meeting clearly demonstrated the need for future meetings that could expand upon the topics covered. For example, edaravone has been used with stroke patients in Japan, and U.S. participants expressed an interest in learning more about the experiences of Japanese clinicians, with an eye toward larger-scale international studies. Neural repair using iPS was another actively discussed topic. Because of its accessibility, pluripotency, and autologous nature, iPS technology has tremendous potential for treating neurodegenerative diseases, including stroke. Future investigations that apply iPS technology to the treatment of stroke patients may be an important area of collaboration between investigators in the two countries. Establishing standardized preclinical models and unbiased study methods would allow comparison of biological robustness of findings across laboratories, which is important when considering clinical translation. Related to this issue, developing a reproducible nonhuman primate model of stroke will certainly be useful for testing promising neuroprotectants, such as neuregulin-1, DHA, and NPD1. Collaborations with physicists and chemists are needed, as shown by the examples of *in vivo* imaging.