THE UEHARA INTERNATIONAL SYMPOSIUM 2021

The Uehara Memorial Foundation's most recent symposium covered brain-periphery interactions, AN INCREASINGLY SIGNIFICANT AREA in life sciences and medicine.

The body's homeostasis is maintained by the interactions between elaborate and reciprocal communication systems between the brain and peripheral tissues and organs. We are beginning to understand that failure in these systems causes abnormal homeostasis of multiple organs and tissues and potentially leads to various diseases, making brain-periphery interactions one of the main emerging themes in life sciences and medicine. This year's symposium provided a showcase for cutting-edge research on brain-periphery interactions in basic and clinical medicine by experts invited from Japan and overseas. The participants exchanged new knowledge and views, and are expected to contribute extensively to medicine from basic research to clinical applications in the near future.

The first session, 'Brain and Metabolic Control', launched the symposium with a wonderful presentation by Hiroshi Inoue (Kanazawa University, Japan). Using sophisticated chemogenetic and genetic approaches, he showed that hepatic glucose production is regulated by the parasympathetic nervous system, and also by the vagus nerve through α-7 nicotinic acetylcholine receptor in Kupffer cells, demonstrating the importance of the brain-liver interaction. Ichiro Manabe (Chiba University, Japan) covered a significant interaction between the heart and kidney through the Klf-5-regulated renal production of GM-CSF. On the other hand, the renal artery sympathetic nerve plays an important role in response to cardiac pressure overload, suggesting a critical function of the brain-heart-kidney network. Joel K. Elmquist (UT Southwestern Medical Center, USA) focused on the importance of SF-1 in the ventromedial hypothalamus (VMH) and demonstrated that SF-1-positive VMH neurons control the response to exercise in skeletal muscle through the sympathetic nervous system. He also conducted a genetic screen in fruit flies to identify SF-1 target genes and found some interesting candidates. In the last two talks, metabolic interactions between the brain and peripheral organs, mainly the liver, were discussed. Hideki Katagiri (Tohoku University, Japan) introduced two types of brain-periphery interaction involved in metabolic regulation. He showed that the liver sends signals in response to metabolic states, such as obesity and food shortage, to the brain via neuronal and humoral mechanisms, causing the proliferation of pancreatic β cells and the suppression of brown adipose thermogenesis, respectively. Jens C. Brüning (Max Planck Institute, Germany) presented evidence demonstrating that insulin action in hypothalamic agoudi-related peptide (AgRP) neurons regulates glucose production in the liver. In addition, sensory food perception primes hepatic endoplasmic reticulum-homeostasis via activation of hypothalamic proopiomelanocortin (POMC) neurons. Upon high fat-feeding, POMC neurons are locally inhibited by activation of arcuate prepronociceptin (PNOC)-expressing neurons, leading to hyperphagia. Furthermore, maternal high fat-feeding during lactation increases body weight and fat mass of offspring involving impaired programming of hypothalamic and striatum neurocircuits.

Session 2, entitled 'Neuro-Immune Crosstalk for Mucosal Defense,' started with a fly genetic study by Shoichiro Kurata (Tohoku University, Japan) to elucidate neural control of gut homeostasis. Using an enhancer-trap screening, they discovered that a specific type of neurons projecting to the gut epithelium maintains gut homeostasis

LIFE SCIENCE SUPPORT

The Uehara Memorial Foundation was established in 1985 to commemorate the late Shokichi Uehara, who laid the foundation for the Taisho Pharmaceutical Co., Ltd. and was its president, and later its chairman. The foundation also marked the company's 70th anniversary. Since then, it has been supporting research in life science fields. Its research grants, including the Uehara Prize, recognize outstanding accomplishments, and further grants are offered for overseas study. The foundation also provides living expenses for international students studying in Japan. In the 37 years since it was established, the foundation has provided more than 10,000 grants and other forms of assistance, totalling about ¥33 billion ($US303 million).

Organizing international symposia is the foundation's most significant activity, sponsoring specific projects every three years. The results of the projects are reported in a special symposium, attended by leading international experts in the field. This year's symposium 'Brain-Periphery Interactions in Health and Diseases', was scheduled for June 2020, in Tokyo, but postponed until June 7 to 9, 2021 and held online, due to the pandemic.

AKIRA UEHARA

President, The Uehara Memorial Foundation

CEO, Taisho Pharmaceutical Holdings Co., Ltd.

PROGRAM

WELCOME ADDRESS
Akira Uehara (President, The Uehara Memorial Foundation (CEO, Taisho Pharmaceutical Holdings Co., Ltd.)

OPENING REMARKS
Shuh Narumiya (Chair of the Organizing Committee) (Professor, Kyoto University)

SESSION 1: BRAIN AND METABOLIC CONTROL
Chairperson: Ichiro Manabe & Hideki Katagiri

S1-1. Role of Brain–Liver Interaction in Hepatic Glucose Metabolism
Hiroshi INOUE (Kanazawa University, Japan)

S1-2. Neuro–Immune-Metabolic Regulation of Cardiac Homeostasis and Disease
Ichiro MANABE (Chiba University, Japan)

S1-3. SF-1 in the Hypothalamus: A Molecular Link between Energy Balance and Exercise
Joel K. ELMQUIST (UT Southwestern Medical Center, USA)

S1-4. Neuronal Information Highways for Systemic Regulation of Glucose Metabolism
Hideki KATAGIRI (Tohoku University, Japan)

S1-5. Brain Insulin Action in CNS-dependent Control of Metabolism
Jens C. BRÜNING (Max Planck Institute, Germany)

SESSION 2: NEURO–IMMUNE CROSSTALK FOR MUCOSAL DEFENSE
Chairperson: Norifumi Iijima

S2-1. Neural Control of Gut Homeostasis in *Drosophila*
Shoichiro KURATA (Tohoku University, Japan)

S2-2. Neuro–Immune Control of Mucosal Virus Infection
Norifumi IIJIMA (NIBIOHN, Japan)

SESSION 3: GLIA AND PERIPHERY
Chairperson: Rieko Muramatsu & Takaomi C. Saido

S3-1. Roles of Astroglial IFITM3 and MHCI in Brain Dysfunction Associated with Systemic Immune Activation
Kiyofumi YAMADA (Nagoya University, Japan)

S3-2. Circulating Factors Regulate Central Nervous System Regeneration
Rieko MURAMATSU (National Center of Neurology and Psychiatry, Japan)

S3-3. Physiological and Pathological Functions of Microglia for Brain Periphery Interactions
Hiroaki WAKE (Nagoya University, Japan)

S3-4. Microglia at the Crossroads of Cortical Wiring and Environmental Signals
Sonia GAREL (IBENS, France)

S3-5. The Effect of Plasmacytoid Dendritic Cell Depletion on Alzheimer's Disease Pathology
Takaomi C. SAIDO (RIKEN, Japan)

S3-6. Redox Balance in Central Nervous System and Its Impact on Aging-related Diseases
Hozumi MOTOHASHI (Tohoku University, Japan)

S3-7. Novel Genetic Tools for Studying Microglia in the CNS
Marco PRINZ (University of Freiburg, Germany)

S3-8. The Immune System Hold the Key to Defeat Alzheimer's Disease: The Role of Monocyte-derived Macrophages
Michal SCHWARTZ (The Weizmann Institute of Science, Israel)

SESSION 4: IMMUNE ACTIVATION IN BRAIN DEVELOPMENT
Chairperson: Yukiko Gotoh

S4-1. Peripheral Cytokines at Perinatal and Prenatal Stages Perturb Neurocognitive Development: Implication in Schizophrenia
Hiroyuki NAWA (Wakayama Medical University, Japan)

S4-2. Modulatory Roles of the Immune System in Shaping Animal Behaviors
Jun R. HUH (Harvard Medical School, USA)

S4-3. First-line Defense Mechanisms against Viral Infection
Yukiko GOTOH (The University of Tokyo, Japan)

SESSION 5: EMOTIONAL BRAIN AND PERIPHERY
Chairperson: Tomoyuki Furuyashiki

S5-1. Stress and Brain–Gut Interactions: Role of Corticotropin Releasing Factor Signaling
Yvette TACHÉ (UCLA, USA)

S5-2. Roles of Brain and Peripheral Inflammation in Stress and Depression
Tomoyuki FURUYASHIKI (Kobe University, Japan)

S5-3. Artificial Hibernation/ Life-protective State Induced by Thiazoline-related Innate Fear Odors via Sensory TRPA1 Activation
Ko KOBAYAKAWA (Kansai Medical University, Japan)

SESSION 6: SENSORIMOTOR INTEGRATION
Chairperson: Yoshihiro Yoshihara

S6-1. Elucidation of Excitatory/ Inhibitory Imbalance in the Central and Peripheral Systems of Psychiatric Disorders
Shinichiro NAKAJIMA (Keio University, Japan)

S6-2. The Claustrum Orchestrates Cortical Slow-wave Activity
Yoshihiro YOSHIHARA (RIKEN, Japan)

S6-3. The Circuits Linking Interoception, Emotion and Pain—The Role of Parabrachio-amygdaloid Network
Fusao KATO (Jikei University, Japan)

S6-4. Dissecting the Phenotype of *Dystonia Musculorum* Mice
Hirohide TAKEBAYASHI (Niigata University, Japan)

SESSION 7: BRAIN–PERIPHERY COMMUNICATIONS IN AGING
Chairperson: Shin-ichiro Imai

S7-1. The NAD World 3.0: The Importance of eNAMPT/NMN-mediated Inter-tissue Communications in Mammalian Aging/Longevity Control
Shin-ichiro IMAI (IBRI, Japan; Washington University (St. Louis), USA)

S7-2. The Hypothalamus and Aging
Dongsheng CAI (Albert Einstein College of Medicine, USA)

S7-3. Brain Aging and Rejuvenation through Circulatory Factors
Tony WYSS-CORAY (Stanford University, USA)

SESSION 8: IMMUNE CONTROL OF BRAIN PATHOLOGY
Chairperson: Akihiko Yoshimura

S8-1. Brain-draining Lymphatics and Neurological Disorders
Jonathan KIPNIS (Washington University (St. Louis), USA)

S8-2. The Biochemical Dialog between Major Physiological Systems Mediated by Immune Cells
Sidonia FAGARASAN (RIKEN, Japan)

S8-3. Neural Repair after Ischemic Brain Injury by Innate and Adaptive Immunity
Akihiko YOSHIMURA (Keio University, Japan)

CLOSING REMARKS
Tomoyuki Furuyashiki (Vice Chair of the Organizing Committee) (Professor, Kobe University)

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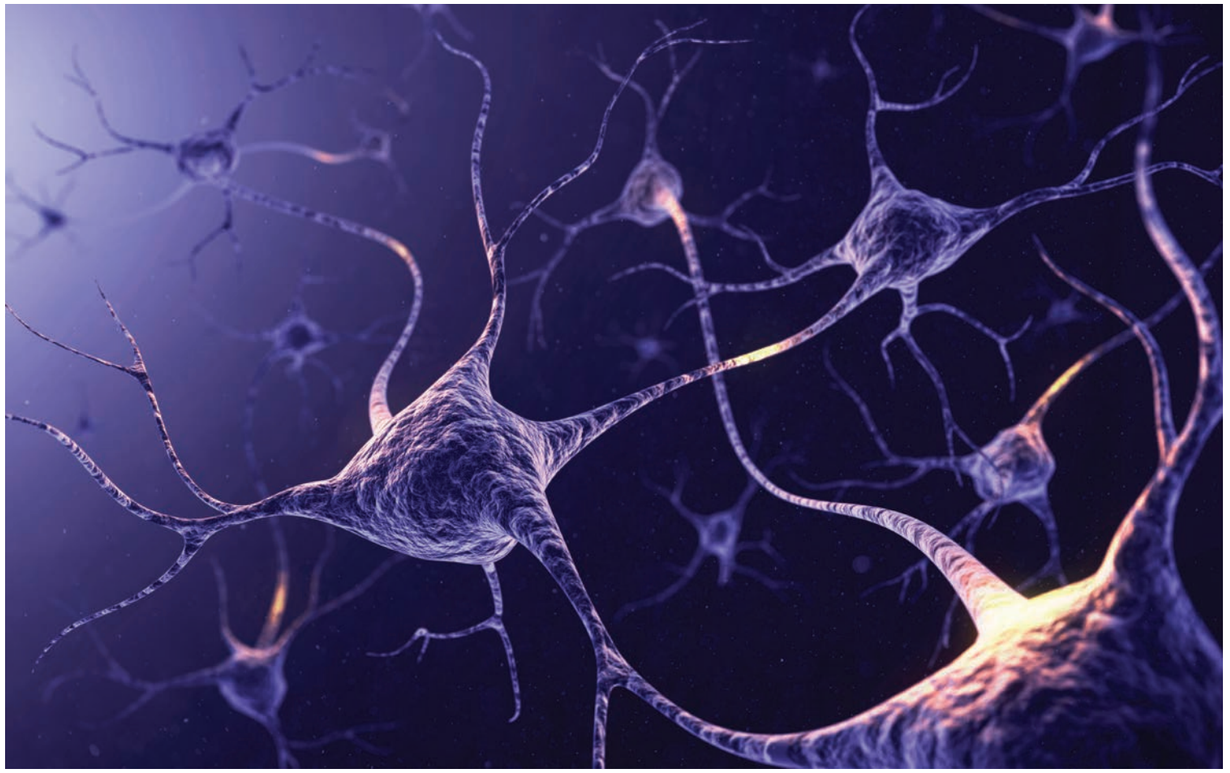
for survival. Norifumi Iijima (National Institutes of Biomedical Innovation, Health and Nutrition, Japan) presented his findings on roles of cellular and humoral immunity in the vaccination against herpes simplex virus (HSV)-2, a neurotropic virus. He discovered that the establishment of tissue-resident memory T cells in vaginal tissues, rather than a systemic antibody-based vaccine provides rapid clearance of the virus, the finding exploitable for the development of a new HSV vaccine.

Session 3, 'Glia and Periphery,' introduced cutting-edge findings on the role of glia for the brain-periphery interaction. Kiyofumi Yamada (Nagoya University, Japan) presented a contribution of astrocytes to the brain dysfunction associated with a response to systemic immune activation, showing functions of an interferon-stimulated gene *IFITM3*, as well as the major histocompatibility complex class I (H-2D). Rieko Muramatsu (NCNP, Japan) addressed how circulating factors—FGF21 and apelin—promote remyelination of demyelinated lesions in the central nervous system by stimulating the proliferation and differentiation of oligodendrocyte precursor cells. She suggested that a reduced concentration of apelin may be responsible for the inadequate remyelination apparent in aged mice. Hiroaki Wake (Nagoya University, Japan) identified dual roles of microglia in the regulation of permeability of the blood-brain barrier (BBB) via in vivo imaging. He showed that systemic inflammation results in the recruitment of microglia to the cerebral vasculature, with the microglia initially maintaining BBB integrity by making the claudin-5–dependent contact with endothelial cells. However, the microglia subsequently disrupt BBB function by mediating phagocytosis of astrocytic endfeet. The potential role of BBB leakage in recruiting peripheral blood cells during the later phases of inflammation was also discussed. Sonia Garel (CNRS, INSERM, Université PSL, France) talked about the role of microglia in the regulation of the forebrain circuits. Depletion or functional perturbation of microglia impairs the timely positioning of specific subsets of interneurons as well as their subsequent functional integration into the neocortex, with these effects having physiological and behavioural consequences. She also showed that responses of microglia to the microbiome are sexually dimorphic, which has major implications for our understanding of sexual biases in the occurrence of microglia-related neurodevelopmental disorders. The remaining talks focused on novel glial roles and functions in neuroinflammation and neurodegenerative disease. Using his original Alzheimer's disease (AD) mouse model (AppNL-G-F/NL-G-F), Takaomi C. Saido (RIKEN, Japan) showed distinct microglia subclasses exert differential effects on amyloid β peptide deposition. In particular, his findings suggest that microglia expressing sialic-acid-binding immunoglobulin-like lectin (Siglec)-H contribute to amyloid β peptide deposition and AD pathogenesis. Hozumi Motohashi (Tohoku University, Japan) highlighted the importance of redox balance in the central nervous system for age-related diseases. She presented an interesting finding that neuron-specific deficiency of CARS2, a mitochondrial sulfur metabolizing enzyme, decreases glutathione in the liver, suggesting the presence of a sulfur metabolic network connecting the central nervous system and the liver. Marco Prinz (University Hospital Freiburg, Germany) found hexosaminidase b (Hexb), a lysosomal enzyme that is stably expressed in microglia even under pathological conditions. He generated HexbtdTomato and HexbCreERT2 mouse lines and showed that they could be novel genetic tools useful for selectively visualizing and targeting microglia, respectively. Michal Schwartz (The Weizmann Institute of Science, Israel) presented the data relevant to immunotherapy against Alzheimer's disease (AD) and dementia. Immune checkpoint blockade arrests and even reverses cognitive loss with reduction of inflammation and brain pathology in several murine models of AD and age-related dementia. The mechanism includes monocyte recruitment by interferon gamma signalling in the choroid plexus.



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Session 4, 'Immune Activation in Brain Development,' illustrated elaborate long-term consequences and mechanisms of immune activation in brain development and functions. Hiroyuki Nawa (Wakayama Medical University, Japan) reported a range of circuit-level alterations in a rodent model of schizophrenia induced by neonatal injection of epidermal growth factor (EGF), with dopaminergic aberrations being prominent among these alterations. Jun R. Huh (Harvard Medical School, USA) summarized a series of studies on the mechanisms that underlie autism spectrum disorder (ASD) induced by maternal immune activation (MIA). He implicated interleukin (IL)-17a as a key mediator of the effects of MIA on embryos, with this cytokine having been found to induce aberrant laminar organization and activation of the dysgranular zone of the primary somatosensory cortex. Of interest, however, expression of IL-17a induced in adult mice by bacterial lipopolysaccaride was found to temporarily rescue the social behaviour deficits induced by MIA, revealing a beneficial effect of inflammation on neurodevelopmental disorders (in particular, those associated with a primed immune system). He suggested that the role of IL-17a as a neuromodulator may be evolutionarily older than its function as an immunomodulator. Finally, he showed that MIA activates an integrated stress response in an IL-17a-dependent manner, resulting in a global reduction in mRNA translation and the development of behavioural abnormalities, only in male offspring. Although the mechanism underlying this sex-specific difference remains unclear, this phenomenon may account for the higher incidence of ASD in males. Yukiko Gotoh (The University of Tokyo, Japan) reported novel defense mechanisms against viral infection within the brain, specifically regarding the switch between type I interferon expression and apoptosis.

Session 5, entitled 'Emotional Brain and Periphery,' elaborated on central and peripheral mechanisms for stress responses contributing to survival and diseases. Yvette Taché (UCLA, USA) demonstrated central and peripheral roles of corticotropin-releasing factor (CRF) receptors for the brain-gut interaction under stress. She discovered that CRF and CRF receptor subtype 1 (CRFR1) in distinct brain areas mediate stress-related colonic motor stimulation and visceral hyperalgesia via the autonomic nervous system. Besides, peripheral CRF and CRF-R1 play crucial roles for stress-related colonic secretomotor activation and visceral hyperalgesia. These findings may be relevant to the pathology of irritable bowel syndrome, a stress sensitive functional bowel disorder. Tomoyuki Furuyashiki (Kobe University, Japan) demonstrated roles of inflammation for chronic social stress-induced emotional disturbance. He discovered that chronic stress activates microglia through innate immune receptors, leading to prefrontal neuronal atrophy and depressive-like behaviour via proinflammatory cytokines. In parallel, chronic stress mobilizes myeloid cells in an adrenergic receptor-dependent mechanism, contributing to emotional disturbance. Ko Kobayakawa (Kansai Medical University, Japan) revealed novel life-protective roles of innate fear odors through inducing an artificial hibernation state. He discovered that sensory presentation of thiazoline-related fear odours orchestrates hypothermia, hypometabolism, anti-hypoxia, and anti-inflammatory immune enhancement through Trpa1-mediated signals via trigeminal and vagal afferents, promoting survival under lethal conditions. These findings could be exploited to develop effective sensory interventions.

Session 6, entitled 'Sensorimotor Integration,' covers new attempts to understand how the brain integrates multimodal peripheral information in healthy and disease conditions. Shinichiro Nakajima (Keio University, Japan) presented his ongoing clinical studies collecting multidimensional data comprising of symptoms, brain connectivity, and brain and peripheral metabolic changes from various psychiatric patients. Multivariate analyses of these data will pave the way towards elucidating the heterogeneity and comorbidity of psychiatric disorders to rebuild the diagnostic system and develop rational treatments for mental illnesses. Yoshihiro Yoshihara (RIKEN, Japan) demonstrated crucial roles of the claustrum, a thin, sheet-like neural structure located between the insular cortex and the striatum, in shaping the pattern of cortical activity. He discovered that claustrum neurons fire during sleep and drowsy states and orchestrate slow-wave cortical activity by synchronous interneuron firing that leads to prolonged silencing of neocortical neurons. Fusao Kato (Jikei University School of Medicine, Japan) identified crucial roles of neuronal projections from the lateral parabrachial nucleus (LPB) to the central amygdala (CeA) and their plasticity as a hub for aversive sensory information and defensive/survival responses. He demonstrated that inflammatory pain potentiates LPB-CeA synaptic transmission via the neuropeptide CGRP, contributing to widespread

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tactile sensitization, a typical symptom of chronic pain patients. Hirohide Takebayashi (Niigata University, Japan) explained neuroanatomical mechanisms for neural and non-neural phenotypes of genetic dystonia mice with a dystonin mutation. He showed that the disruption of distinct dystonin isoforms underlies the abnormality in the movement, skin, and heart, and that the defective sensory feedback circuit is responsible for their dystonia-like movements.

Session 7, 'Brain-Periphery Communications in Ageing,' started with a remarkable presentation by Shin-ichiro Imai (Washington University, USA; Institute of Biomedical Research and Innovation, Japan). He emphasized the importance of the inter-tissue communication between the hypothalamus and adipose tissue through the secretion of extracellular nicotinamide phosphoribosyltransferase (eNAMPT) in mammalian ageing/longevity control. He also presented the most recent findings from the first human clinical trial on nicotinamide mononucleotide (NMN), a key NAD+ intermediate and a product of the NAMPT reaction. The importance of the hypothalamic function was further emphasized in the next presentation by Dongsheng Cai (Albert Einstein College of Medicine, USA). He -showed that hypothalamic neural stem/progenitor cells (htNSCs) are important in producing exosomes that contain many microRNA species and convey significant anti-ageing effects in mice. Interestingly, his lab employed an htNSC subclone to derive- neurospheres which are able to mimic pancreatic islets, secreting microRNA-rich exosomes as well as multiple peptides, and when peripherally implanted in vivo, these spheres can lead to enhanced survival and an amelioration of hyperglycemia in mouse models of streptozotocin-induced severe diabetes. Tony Wyss-Coray (Stanford University, USA) revealed the power of blood to modulate ageing. He conducted a plasma proteome labelling experiment and found a number of plasma proteins whose uptake was correlated or anti-correlated to endothelial transcription. He showed that with age, brains reduced the uptake of plasma proteins, most likely due to "specific" and "non-specific" changes (increases in caveolin-driven uptake and decreases in clathrin-driven uptake). He also showed that selective loss of matrix pericytes contributed to changes in plasma protein uptake in Alzheimer's disease. Presentations in this session firmly demonstrated the importance of brain-periphery communications in mammalian ageing and gave critical insights into the development of anti-ageing interventions.

Session 8, entitled 'Immune Control of Brain Pathology,' started with ground-breaking discoveries by Jonathan Kipnis (Washington University, USA) on brain-draining lymphatics, its functions, and the relevance to neurological disorders. He discovered that meningeal myeloid cells sample brain interstitial fluids for antigen presentation for immune cells and that the lymphatics drain brain molecules and cells to cervical lymph nodes, work that contributes to antibody-based therapeutics of Alzheimer's disease. He also identified a new entry route of meningeal myeloid cells that migrate directly from the skull bone marrow through dural channels surrounding blood vessels. Sidonia Fagarasan (RIKEN IMS, Kyoto University, Japan) elucidated an unexpected systemic metabolic effect of sustained activation of adaptive immunity. She discovered that the deletion of the inhibitory receptor PD-1 induces serum depletion of some amino acids, particularly tryptophan, due to their accumulation in activated T cells, leading to brain monoamine deficiency and anxiety and fear responses. She also introduced a novel immunoregulatory role of the local metabolic shift in the lymph node for adaptive immune responses. Lastly, Akihiko Yoshimura (Keio University, Japan) presented his phenomenal discoveries on innate and adaptive immunity not only for the progression of brain ischemia-reperfusion injury but also for neurological repair. He demonstrated that extracellular damage-associated molecular patterns (DAMPs) activate infiltrated macrophages through a TLR2/TLR4-dependent mechanism but are cleared by macrophages through type A scavenger receptors. During the chronic phase, regulatory T cells accumulate in the brain, regulate astrocyte activation, and reduce neural damages by Amphiregulin.

This three-day symposium attracted 463 participants, who enjoyed these excellent presentations and discussions. ■

公益財団法人
上原記念生命科学財団
The Uehara Memorial Foundation

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