**Plenary Session Speech (III)**

# Systems neuroscience of functional recovery after brain and spinal cord injury

Speaker: Tadashi Isa (伊佐正)

Vice Dean and Professor of Department of Neuroscience,
Chair of the Human Brain Research Centre,
Deputy Director of Institute for the Advanced Study of Human Biology (WPI-ASHBi), Kyoto University, Japan
Ph.D., University of Tokyo, Japan
M.D., University of Tokyo, Japan

Location: 生物醫學科學研究所 B1B會議室
Institute of Biomedical Sciences (IBMS) B1B

Time: Sept. 13 9:00-9:45

## Abstract

Impairment of sensory, motor and cognitive functions are the causes of long-lasting devastating suffer for the patients with neuronal injuries. Therefore, development of effective therapeutic strategies is waited, however for that, understanding the recovery mechanism is crucial. The functional recovery after neuronal injuries are considered to be a kind of motor learning, and we need to understand the mechanism in the framework of systems neuroscience. In this talk, I will summarize our recent achievements on two recovery models using macaque monkeys. One is the recovery of dexterous hand movements after partial spinal cord injury. In this case, after the transection of the corticospinal tract (CST), the precision grip of the hand is impaired but substantial recovery is observed through intensive rehabilitative trainings. Here, interneurons in the spinal cord take over the function of the direct connection of CST to hand motoneurons. At the cortical level, the bilateral motor and premotor cortices contribute to recovery with different time sequences, and furthermore, the limbic structure such as the nucleus accumbens also contribute by facilitating the motor cortical activity. Thus, large-scaled networks are involved in the recovery. Another model is the blindsight after injury of the primary visual cortex. Here, the areas like superior colliculus, pulvinar and parietal cortex, which are not essential for the control of simple eye movements become critical for the recovery. Thus, the mechanism how the areas which are not essential in the intact state are recruited to the recovery will be argued.

## Selected recent publications:

1. Kinoshita M, Kato R, Isa K, Kobayashi K, Kobayashi K, Onoe H, Isa T (2019) Dissecting the circuit for blindsight to reveal the critical role of the pulvinar and superior colliculus. Nature Communications, 10:135

2. Tohyama T, Kinoshita M, Kobayashi K, Isa K, Watanabe D, Kobayashi K, Liu M, Isa T (2017) Contribution of propriospinal neurons to recovery of hand dexterity after corticospinal tract lesions in monkeys. Proceedings of National Academy of Science USA: 114:604-609

3. Sawada M, Kato K, Kunieda T, Mikuni N, Miyamoto S, Onoe H, Isa T, Nishimura Y (2015) Function of nucleus accumbens in motor control during recovery after spinal cord injury. Science, 350: 98-101

4. Kinoshita M, Matsui R, Kato S, Hasegawa T, Kasahara H, Isa K, Watakabe A, Yamamori T, Nishimura Y, Alstermark B., Watanabe D, Kobayashi K, Isa T (2012) Genetic dissection of the circuit for hand dexterity in primates. Nature, 487: 235-238

5. Nishimura Y, Onoe T, Morichika Y, Perfiliev S, Tsukada H, Isa T (2007) Time-dependent central compensatory mechanism of finger dexterity after spinal-cord injury. Science, 318: 1150-1155

**Plenary Session Speech (III)**

# Targeting Peripheral Neuropathy and Chronic Pain with Natural Killer Cells

Speaker: Seog Bae Oh (吳碩培)

Professor Department of Neurobiology and Physiology
School of Dentistry, Seoul National University, Republic of Korea

Ph.D., Seoul National University, Republic of Korea
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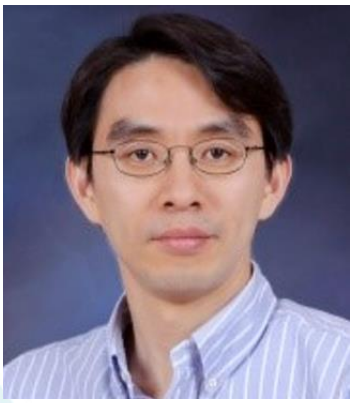
Location: 生物醫學科學研究所 B1C會議室
Institute of Biomedical Sciences (IBMS) B1C

Time: Sept. 13 9:00-9:45



## Abstract

Peripheral neurons are readily capable of regeneration after nerve damage, which is unlike neurons in the central nervous system. The immune response to peripheral nerve injury contributes to the adaptive mechanisms of axonal regeneration, but it may also trigger maladaptive changes which lead to incomplete functional recovery such as neuropathic pain. Understanding the roles of immune cell populations in these processes is therefore likely to help the resolution of pain after nerve injury.

We investigated the response and functional consequences of Natural Killer (NK) cells, a cytotoxic peripheral immune cells, in the context of peripheral nerve injury from the adult mouse. Our study revealed cytotoxic NK cells can trigger the specific degeneration of damaged primary afferent axons that are still intact in the injured axons. We have identified that RAE1, an activating ligand of NK cells, is specifically upregulated by the damaged peripheral nerve and NK cells are infiltrated into the injured peripheral nerve by extravasation. The physical contact mediated by RAE1 and NKG2D, activating receptors of NK cells, between injured sensory axons and NK cells leads to the degeneration of the injured sensory axons. NK cell function correlates loss of sensation due to degeneration of injured afferents and lowered levels of mechanical hypersensitivity after axonal reinnervation. We propose that NK cell-mediated neurodegeneration may complement Wallerian degeneration which occurs after peripheral nerve injury. This discovery further provides new insight into non-neuronal mechanisms of damaged axon clearance and suggests that targeting NK cells may have a therapeutic potential to treat chronic pain patients with peripheral neuropathy.

## Selected recent publications:

1. Kim YH, Back SK, Davies AJ, Jeong H, Jo HJ, Chung G, Na HS, Bae YC, Kim SJ, Kim JS, Jung SJ, **Oh SB** (2012) TRPV1 in GABAergic interneurons mediates neuropathic mechanical allodynia and disinhibition of the nociceptive circuitry in the spinal cord. *Neuron* 2012 74(4):640-7

2. Jeong H, Na YJ, Lee K, Kim YH, Lee Y, Kang M, Jiang BC, Yeom YI, Wu LJ, Gao YJ, Kim J, **Oh SB** (2016) High-resolution transcriptome analysis reveals neuropathic pain gene- expression signatures in spinal microglia following nerve injury. *Pain* 157(4):964-76

3. Won J, Vang H, Kim JH, Lee PR, Kang Y, **Oh SB** (2018) TRPM7 mediates mechanosensitivity in adult rat odontoblasts. *J Dent Res* 2018 97(9):1039-1046

4. Davies AJ, Kim D, Park J, Lee JY, Vang H, Pickering AE, **Oh SB** (2019) Hedonic drinking engages a supra-spinal inhibition of thermal nociception in adult rats. *Pain* 160(5):1059-1069

5. Davies AJ, Kim HW, Gonzalez-Cano R, Choi J, Back SK, Roh SE, Johnson E, Gabriac M, Kim MS, Lee J, Lee JE, Kim YS, Bae YC, Kim SJ, Lee KM, Na HS, Riva P, Latremoliere A, Rinaldi S, Ugolini S, Costigan M, **Oh SB** (2019) Natural killer cells degenerate intact sensory afferents following nerve injury. *Cell* 176(4):716-728

**Plenary Session Speech (III)**

# Taiwan brain bank: current progress and future perspectives

Speaker: Sung-Tsang Hsieh (謝松蒼 )

Professor, Department of Anatomy and Cell Biology, Attending physician, Department of Neurology, National Taiwan University Hospital, Taiwan

Ph.D., Johns Hopkins University, USA
M.P.H., Harvard University, USA
M.D., National Taiwan University, Taiwan

Location:跨領域大樓
Interdisciplinary Research Building for Science and Technology (IRB)

Time: Sept. 13 9:00-9:45

## Abstract

Although brain bank is a mature concept and has been operated in most countries for decades, it is still at its infancy in Taiwan for several obstacles: public awareness, law regulations, infrastructure etc. Nevertheless the necessity for brain bank to facilitate neuroscience researches in Taiwan has been proposed since 1990s. Indeed there have been voices to set up brain bank emerging from various groups: scientific communities, medical researchers, and patient groups etc. This is particularly urgent as Taiwan became an “aged” society with neurodegenerative disease (Alzheimer disease, Parkinson disease etc) and rare diseases (spinocerebellar atrophy, motor neuron disease, and familial mayloid polyneuropathy etc) emerging as medical and socioeconomic burden. Since 2017, under the auspices of Society for Neurological Rare Disorders-Taiwan and guided by National Health Research Institutes (NHRI), Taiwan Brain Bank task force was formed to tackle the above difficulties, in particular, the cadaver dissection law which prohibited immediate processing of brain tissues. Responding the combined efforts from patient groups and medical experts, in 2019 Ministry of Health and Welfare announced that brain bank can be established following the regulation of biobank regulations in Taiwan. Currently we are preparing all documents for establishing the first brain bank in Taiwan. In the meantime, we sent neuropathologist to practice brain bank and started collecting brain tissues, conducting brain pathology examinations and research. Our long-term goal is to establish Taiwan Brain Bank consortium and provide high-quality brain tissues to researcher in Taiwan and worldwide.

## Selected recent publications:

1. Chao CC, Hsueh HW, Kan HW, Liao CH, Jiang HH, Chiang H, Lin WM, Yeh TY, Lin YH, Cheng YY, Hsieh ST* (2019) Skin nerve pathology: biomarkers of premanifest and manifest amyloid neuropathy. Ann Neurol 85:560-573

2. Hsieh YL, Kan HW, Chiang H, Lee YC, Hsieh ST* (2018) Distinct TrkA and Ret modulated negative and positive neuropathic behaviors in a mouse model of resiniferatoxin-induced small fiber neuropathy. Exp Neurol 300:87-99

3. Kan HW, Hsieh JH, Chien HF, Lin YH, Yeh TY, Chao CC, Hsieh ST* (2018) CD40-mediated HIF-1a expression underlying microangiopathy in diabetic nerve pathology. Dis Models Mech 11:4

4. Kan HW, Chiang H, Lin WM, Yu IS, Lin SW, Hsieh ST* (2018) Sensory nerve degeneration in a mouse model mimicking early manifestations of familial amyloid polyneuropathy due to transthyretin Ala97Ser. Neuropathol Appl Neurobiol 44:673-686

5. Tseng TJ, Yang ML, Hsieh YL, Ko MH, Hsieh ST* (2018) Nerve decompression improves spinal synaptic plasticity of opioid receptors for pain relief. Neurotox Res 33:362-376

**Plenary Session Speech (III)**

# Nutritional neuroscience as mainstream of psychiatry: How omega-3 fatty acids interface mind and body?

Speaker: Kuan-Pin Su (蘇冠賓 )

Professor of Psychiatry and Neural Science; Director of Mind-Body Interface Laboratory (MBI-Lab); Deputy Superintendent of An-Nan Hospital, China Medical University, China Medical University & Hospital, Taiwan

Ph.D., Institute of Psychiatry, King's College London, UK
M.D., Kaohsiung Medical College, Taiwan

Location: 分子生物研究所
Institute of Molecular biology (IMB)

Time: Sept. 13 9:00-9:45

## Abstract

Clinicians and researchers are facing the huge challenge of developing new treatment for mental disorders despite of the advance of neurosciences. Current psychiatric practice is dominated by the use of pharmacological and psychological therapies; however, the limited therapeutic effects of monoamine-based antidepressant therapy, for example, imply that the monoamine hypothesis is insufficient to approach the aetiology of major depressive disorder (MDD). Accumulating evidence has shown the relationship between diet quality (and potential nutritional deficiencies) and mental health, and for the judicious application of nutrient-based supplements to address deficiencies, or as mono- or augmentation therapies. On behalf of the International Society of Nutritional Psychiatry Research (ISNPR), we recently published a statement in the Lancet Psychiatry and World Psychiatry and treatment Guideline in the Psychosomatics and Psychotherapy that nutritional medicine is regarded as a mainstream in psychiatry.

Several lines of evidence support the efficacy of the omega-3 polyunsaturated fatty acids (n-3 PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as preventive and treatment strategies in MDD. The key proposed biological antidepressant mechanisms of n-3 PUFAs include: (1) neurotransmitter regulation, (2) anti-inflammatory and anti-oxidative effects, (3) neuroplasticity effects, and (4) impact on the arachidonic acid cascade. Although DHA is the major n-3 PUFA in the brain, EPA seems to be the most active n-3 PUFA regarding antidepressant effects. Recent studies have established that EPA enters the brain, but is rapidly metabolised following entry. Therefore, the homeostatic mechanisms of EPA and the cell signalling of its derivatives (e.g. resolvins and endocannabionids) may play important roles in EPA's antidepressant effects.

## Selected recent publications:

1. Chang JP, Su KP* (2020) Nutrition and immunology in mental health: Precision medicine and integrative approaches to address unmet clinical needs in psychiatric treatments. Brain Behav Immun 85:1-3.

2. Chang JP, Chang SS, Yang HT, Chen HT, Chien YC, Yang B, Su H, Su KP* (2020) Omega-3 polyunsaturated fatty acids (n-3 PUFAs) in cardiovascular diseases comorbid major depressive disorder (MDD)- Results from a randomized controlled trial. Brain Behav Immun 85:14-20.

3. Guu TW, Mischoulon D, Sarris J, Hibbeln J, McNamara RK, ……, Marx W, Su KP* (2019) International Society for Nutritional Psychiatry Research (ISNPR) practice guidelines for omega-3 fatty acids in the treatment of major depressive disorder. Psychother Psychosom 88: 263-273 [Editor's Choice].

4. Yang B, Lin L, Bazinet RP, Chien YC, Chang JPC, Satyanarayanan SK, Su HX, Su KP* (2019) Clinical efficacy and biological regulations of omega-3 PUFA-derived endocannabinoids in major depressive disorder. Psychother Psychosom 88:215-224.

5. Satyanarayanan SK, Shih YH, Wen YR, Mahalakshmi P, Lin YW, Su HX, Gałecki P, Su KP* (2020) miR-200a-3p modulates gene expression in comorbid pain and depression: Molecular implication for central sensitization. Brain Behav Immun 82: 230-238.