The 3rd KULOS Symposium

Brain Research for Well-Being

Date: **Jan 26, 2024,** 1:30 pm～

Venue: Cascade Room in Burke Museum (University of Washington)

12:00 pm	**Networking Lunch** - Introduction of Kobe University and its Project
1:30 pm	**Opening Remarks** Tamotsu NAKAMURA (Kobe University) Cecilia GIACHELLI (University of Washington)
Session 1	**Role of Kinases in Brain Function** Session Chair : Toru TAKUMI (Kobe University)
1:50 pm	Smita YADAV (University of Washington)
2:20 pm	Yasuhito SHIRAI (Kobe University)
2:50 pm	Kimberly ALDINGER (Seattle Children's Research Institute/University of Washington)
3:10 pm	**Break**
Session 2	**Technology in Brain Function** Session Chair : Ayaka BOTA (Kobe University)
3:30 pm	Nobuhiro NAKAI (Kobe University)
4:00 pm	Garret STUBER (University of Washington)
4:30 pm	Cindy van VELTHOVEN (Allen Brain Institute)
5:00 pm	**Closing Remarks** John SCOTT (University of Washington) Junko TANAKA (Kobe University)

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For information and registration, visit

https://www.office.kobe-u.ac.jp/ipiep/events/20240126_en.html

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KOBE UNIVERSITY

Center for Medical Transformation

Mechanisms Underlying TAOK1 Kinase Dysfunction in Neurodevelopmental Disorders

Dr. Smita YADAV

University of Washington

TAOK1 encodes for a serine-threonine protein kinase and is strongly associated with both neurodevelopmental delay and autism spectrum disorder. The molecular function of this evolutionarily conserved kinase, and how TAOK1 mutations lead to neuropathology is unknown. We have found that TAOK1 is highly expressed in both cortical and hippocampal neurons in the mammalian brain. TAOK1 kinase binds and deforms the plasma membrane in an activity dependent fashion. Using domain dissection and biochemical assays we mapped the minimal domain required for plasma membrane association, and show that the C-terminal helical coiled coil bundle can directly bind phospholipids enriched in the plasma membrane. Expression of the membrane binding domain is necessary and sufficient to bind PM and induce filopodial protrusions in neurons. We characterized four autism-associated TAOK1 mutations and found that these point mutations render TAOK1 catalytically dead, lead to aberrant membrane association and tubulation. Exogenous expression of the kinase domain alone is sufficient to rescue the localization and phenotype of these gain of function TAOK1 autism mutations. Finally, using proteomics we have identified critical residues in the helical bundle that are phosphorylated by TAOK1 to autoregulate its plasma membrane association. This work defines the molecular function of a plasma membrane tubulating kinase and reveals the molecular mechanisms underlying TAOK1 dysfunction in neurodevelopmental disorders.

Dr. Smita YADAV

Biography:
Dr. Smita Yadav is an Associate Professor in the Department of Pharmacology at the University of Washington, and her research is focused on elucidating how mutations in protein kinases lead to abnormal brain development. Her laboratory utilizes proteomics, biochemistry, stem cell technology and brain organoids to understand neuropathology caused by kinase dysfunction.

Research keyword:
Protein Kinases, Phosphorylation, Autism, Neurodevelopmental Disorders, Stem Cells

The role of protein kinase C in impairments of memory, emotion, and coordinated movement associated with aging.

Yasuhito Shirai, Ph.D

Graduate School of Agricultural Science, Kobe University

Aging has become a serious issue recently. Specifically, it is predicted that by 2065, approximately one in four Japanese individuals will be 75 or older. Medical costs are consequently expected to rise, and issues such as locomotive disorders (locomotive syndrome) and dementia are projected to become increasingly severe in near future. Aging often coincides with a combination of disorders affecting memory, movement, and emotion. Improvement of these motor, memory, and emotional disorders is necessary if we hope to build a healthy and long-lived society. Our research found that knockout (KO) mice that lack the DGKgamma lipid-metabolizing enzyme exhibit memory, motor and emotional deficits as a result of aging. By using these aged model mice, we discovered that the memory, motor, and emotional deficits were caused by an increase in the activity of PKCgamma in specific regions of the brain. We also found an increased activity of PKCgamma in the brains of SAM mice, a well-known mouse model for human aging. More surprisingly, the memory, emotional, and motor deficits were ameliorated after two weeks of oral administration of a certain flavonoid, along with normalization of PKCgamma activity. These findings suggest that a relatively short-term intake of functional food targeting on PKCgamma can improve the memory, emotional, and motor impairments associated with aging.

Yasuhito Shirai

Biography:
Dean, Graduate School of Agricultural Science, Kobe University (2023-present)
Vice Dean, Graduate School of Agricultural Science, Kobe University (2022-present)
Director of Americas Division, Institute of Promoting Partnership (2021-present)
Professor of Graduate School of Agricultural Science, Kobe University (2010-present)
Visiting scholar, Department of Chemistry, University of California, San Diego (2000-2001)

Research keyword:
PKC, DGK, aging, diabetic disfunction, functional food

Expanding the role of MAST kinases in brain development and epilepsy: identification of de novo pathogenic variants in MAST4

Kimberly ALDINGER

Seattle Children's Research Institute/University of Washington

The MAST family of microtubule-associated serine-threonine kinases has been implicated in neurodevelopmental disorders, including developmental brain abnormalities (MAST1) and epilepsy (MAST3). Through an international collaboration, we identified 7 individuals with de novo heterozygous variants in MAST4, including a recurrent missense variant associated with a consistent brain malformation in two unrelated patients. All MAST4 patients presented with developmental delay and vision abnormalities. Neuroimaging findings included periventricular leukomalacia, cerebellar atrophy, polymicrogyria, and mega corpus callosum. A developmental and epileptic encephalopathy was diagnosed in 4 individuals. Temporal and spatial gene expression analyses of the developing human brain show that MAST4 is prominently expressed in excitatory cells of the developing thalamus. Our investigations into the molecular functions through which MAST4 variants could impact cellular functions demonstrate one variant abolishes MAST4 microtubule binding and mislocalizes to the nucleus, potentially due to formation of an alpha helix that could stabilize the protein. Further investigation is ongoing to decipher how MAST4 mutations impact brain development and function.

Kimberly ALDINGER

Biography:
Dr. Aldinger is an Assistant Professor in the departments of pediatrics and neurology at the University of Washington and a Principal Investigator at Seattle Children's Research Institute. She has over 20 years of research experience using neuroscience and genomics tools to study identify genetic changes that cause neurodevelopmental disorders and the impact of these changes to brain development and function. She is also a rare disease advocate, raising awareness and aiding treatment development for rare genetic epilepsy.

Research keyword:
rare disease

VR-based real-time imaging of cortical networks in voluntary behavior

NAKAI Nobuhiro

Department of Physiology and Cell Biology, Graduate School of Medicine, Kobe University

The cerebral cortex plays a critical role in integrating sensory information from both the external environment and the body, and in generating appropriate behavioral responses. Complex information processing within the cerebral cortex is achieved through the cooperative activity of various functional areas. However, the overall implications of this process for brain network activity remain elusive. To analyze the expansive network activity of the cerebral cortex during voluntary behavior in mice, we designed an experimental platform that integrates wide-field calcium imaging with virtual reality (VR). This system enabled us to visualize the cooperative activity between cortical areas as a functional network. In this discussion, I would like to explore how network patterns are rapidly reorganized in response to shifts in behavioral states. Locomotion induces a swift decoupling of sensory regions and an increased coupling between motor regions, leading to a more distinct modular network organization compared to the rest state. Using a mouse model of autism spectrum disorder (ASD), I unveiled specific abnormalities in the cortical network during the start and stop phases of locomotion indicative of ASD. Looking towards future research directions, the potential of using the VR system to study brain functional network dynamics associated with social behavior, and the possibility of predicting behavior using brain information via machine learning, are topics that warrant further exploration.

NAKAI Nobuhiro, Ph.D. (email: nnakai@med.kobe-u.ac.jp)

Biography:
I am a project assistant professor at Kobe University. I obtained a Ph.D. in biostudies from Kyoto University in 2017. From 2013 to 2019, I worked in Dr. TAKUMI Toru's laboratory at the RIKEN Brain Science Institute and joined Kobe University together with the laboratory when it moved here in 2020.

Research keywords:
Cortical functional network, calcium imaging, VR, mouse behavior, machine learning

Neural Circuits for Motivation and Reward

Dr. Garret STUBER

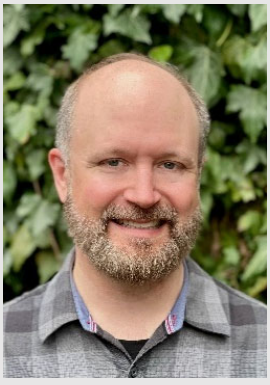
Professor – University of Washington

Center for the Neurobiology of Addiction, Pain, and Emotion (NAPE)

Department of Anesthesiology and Pain Medicine

Department of Pharmacology

In the quest to thrive within a dynamic and often unpredictable environment, animals are tasked with the continual adaptation of their behaviors to effectively procure essential resources while evading potentially perilous situations. This delicate balance of attraction and aversion is orchestrated by intricate neural circuitry, which is dynamically influenced by both environmental stimuli and internal physiological states to elicit appropriate behavioral responses. The research conducted in my laboratory is focused on unraveling the complex neural circuits that govern both reward-seeking and aversion-driven behaviors. Employing cutting-edge methodologies—optogenetics, calcium imaging, and single-cell sequencing—our goal is to elucidate the nuanced functional interactions among molecularly distinct neuronal populations. These interactions are pivotal for the genesis of these critical behavioral states. Through this approach, we aim to construct a comprehensive map of the neural circuitry underpinning diverse motivational behaviors, shedding light on the multifaceted networks that drive decision-making processes in response to both positive and negative stimuli. A deep understanding of these neural networks and their interplay is not just an academic pursuit; it holds profound implications for the field of medicine, particularly in understanding and potentially mitigating complex neurological and neuropsychiatric conditions. Insights gleaned from our research could significantly advance our knowledge of disorders such as addiction, chronic pain, and emotional disturbances. By decoding the neural substrates of motivation and behavioral regulation, we pave the way for novel therapeutic strategies and interventions, potentially transforming the landscape of treatment for these pervasive and challenging conditions.



Dr. Garret STUBER

Biography:
Professor of Anesthesiology and Pain Medicine, University of Washington (2018-)
Professor of Pharmacology, University of Washington (2018-)
Associate Professor, Department Psychiatry, Department of Cell Biology and Physiology, Neuroscience Center of North Carolina, Chapel Hill (2015-2018)
Assistant Professor, Department Psychiatry, Department of Cell Biology and Physiology, Neuroscience Center of North Carolina, Chapel Hill (2010-2015)

Research keyword:
neurocircuits, motivation, reward, behavior, mouse

Understanding Cell Type Diversity in the Brain

Cindy van VELTHOVEN

Allen Institute for Brain Science

The mammalian brain is composed of millions to billions of cells that are organized into numerous cell types with specific spatial distribution patterns and structural and functional properties. An essential step towards understanding brain function is to obtain a parts list, i.e., a catalog of cell types, of the brain. We recently created a comprehensive and high-resolution transcriptomic and spatial cell type atlas for the whole adult mouse brain. This cell type atlas combines two single-cell-level, whole-brain-scale datasets: a single cell RNA-sequencing dataset of ~4.0 million cells passing QC, and a spatially resolved transcriptomic dataset of ~4.3 million cells using MERFISH. The atlas is hierarchically organized into four nested levels of classification: 34 classes, 338 subclasses, 1,201 supertypes and 5,322 clusters. We systematically analyzed the neuronal, non-neuronal, and immature neuronal cell types across the brain and identified a high degree of correspondence between transcriptomic identity and spatial specificity for each cell type. The results reveal unique features of cell type organization in different brain regions, the extraordinary diversity and heterogeneity in neurotransmitter and neuropeptide (co-)expression patterns in different cell types across the brain, and the combinatorial transcription factor code that defines cell types across all parts of the brain. With the completion of this benchmark reference atlas, we are now starting to explore what cell type characteristics we can use to gain genetic access and develop new cell type targeting tools, how these cell types arise from common progenitors during development, and which cell types are susceptible to processes like aging. Finally, we can integrate all these data from mouse to define the cell type landscape over the life span of a mouse as well integrate with data from other species to answer questions about evolution and cell type specification.

Cindy van VELTHOVEN

Biography:
Cindy van Velthoven is an Associate Investigator at the Allen Institute for Brain Science where she is part of a large effort to define cell types in the developing and adult mouse brain. Here she develops and applies computational tools to identify cell types in various mouse brain regions and characterize changes in gene regulation associated with development or experimental perturbations.
Prior to joining the Allen Institute, she completed her postdoctoral training in the lab of Tom Rando at Stanford University where she studied post-transcriptional mechanisms involved in regulating stem cell quiescence. She used various transcriptional and translational profiling techniques to probe the earliest activation changes in quiescent stem cells in vivo. Cindy received her Ph.D. in neuroscience from Utrecht University, The Netherlands, where she examined the use of stem cells to repair the neonatal brain after ischemic injury.

Research keyword:
Single cell genomics