The 7th Annual
IIIS Symposium

~ Solving the mystery of sleep ~

Date : **Thursday, December 20, 2018**

Venue : **Tokyo Conference Center Shinagawa**

The 7th Annual IIIS Symposium

~ Solving the mystery of sleep ~

December 20, 2018

Tokyo Conference Center Shinagawa

Tokyo, Japan

Organizer

Masashi Yanagisawa

International Institute for Integrative Sleep Medicine (WPI-IIIS)
University of Tsukuba

IIIS
INTERNATIONAL INSTITUTE FOR INTEGRATIVE SLEEP MEDICINE

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科研費
KAKENHI

WILLDYNAMICS

Time Table

Opening				
10:00 - 10:15	Welcome	**Masashi Yanagisawa**	Director, WPI-IIIS, University of Tsukuba	
	Opening Address 1	**Akira Ukawa**	WPI Program Director	
	Opening Address 2	**Tadatoshi Kaneko**	Director of Office for Basic Research Programs, Basic Research Promotion Division (MEXT)	
Session 1 | Chair: Yo Oishi				
10:15 - 10:45	Neurochemincal mechanisms of post-training processing in perceptual learning	**Takeo Watanabe**	Brown University	Page. 4
10:45 - 11:15	Genetic and circuit analysis of empathy behaviors in the mouse	**Hee-Sup Shin**	Center for Cognition and Sociality, Institute for Basic Science	Page. 5
11:15 - 11:45	The interaction between sleep and aging mediated by DMH neurons	**Akiko Satoh**	National Center for Geriatrics and Gerontology	Page. 6
11:45 - 12:15	Break & Lunch preparation			
WILLDYNAMICS Luncheon Session | Chair: Takeshi Sakurai				
12:15 - 12:45	Motivated behavior regulated by the ventral striatum	**Kenji Tanaka**	Keio University	Page. 7
12:45 - 13:15	How do mice detect and escape from their predator?	**Peng Cao**	National Institute of Biological Sciences, Beijing	Page. 8
Poster Session & Tea Break | Chair: Michael Lazarus				
13:15 - 14:15	Data Blitz and Poster Presentation			
Session 2 | Chair: Kaspar Vogt				
14:15 - 14:45	Multiscale understanding of synaptic pathology of psychiatric disorders	**Akiko Hayashi-Takagi**	Gunma University	Page. 9
14:45 - 15:15	Balancing brain plasticity/stability	**Takao Hensch**	Harvard Medical School / Harvard University / WPI-IRCN, The University of Tokyo	Page. 10
15:15 - 15:45	Neural ensemble dynamics during REM sleep and P-waves in mice	**Tomomi Tsunematsu**	Tohoku University	Page. 11
15:45 - 16:00	Break / Photo			
MSD Afternoon Seminar | Chair: Masashi Yanagisawa				
16:00 - 16:30	Neural circuitry of sleepiness and cataplexy in narcolepsy	**Thomas E. Scammell**	Beth Israel Deaconess Medical Center / Harvard Medical School	Page. 13
16:30 - 17:00	Identification of neurons regulating REM/non-REM sleep and insights to the mechanisms of REM sleep behavior disorder	**Yu Hayashi**	WPI-IIIS, University of Tsukuba	Page. 14
17:00 - 17:30	Neuron-glia metabolic coupling : role in neuronal plasticity, neuroprotection and regulation across the sleep-wake cycle	**Pierre J. Magistretti**	King Abdullah University of Science and Technology / École Polytechnique Fédérale de Lausanne / Département de Psychiatrie, UNIL-CHUV, Site de Cery	Page. 15
17:30	Closing			
18:00 - 20:00	Reception			

Information

Precautions

1. No outlets are available nearby audience seats
2. No smoking in symposium venues: please smoke at the designated area on each floor
3. Wireless LAN is available in the foyer.

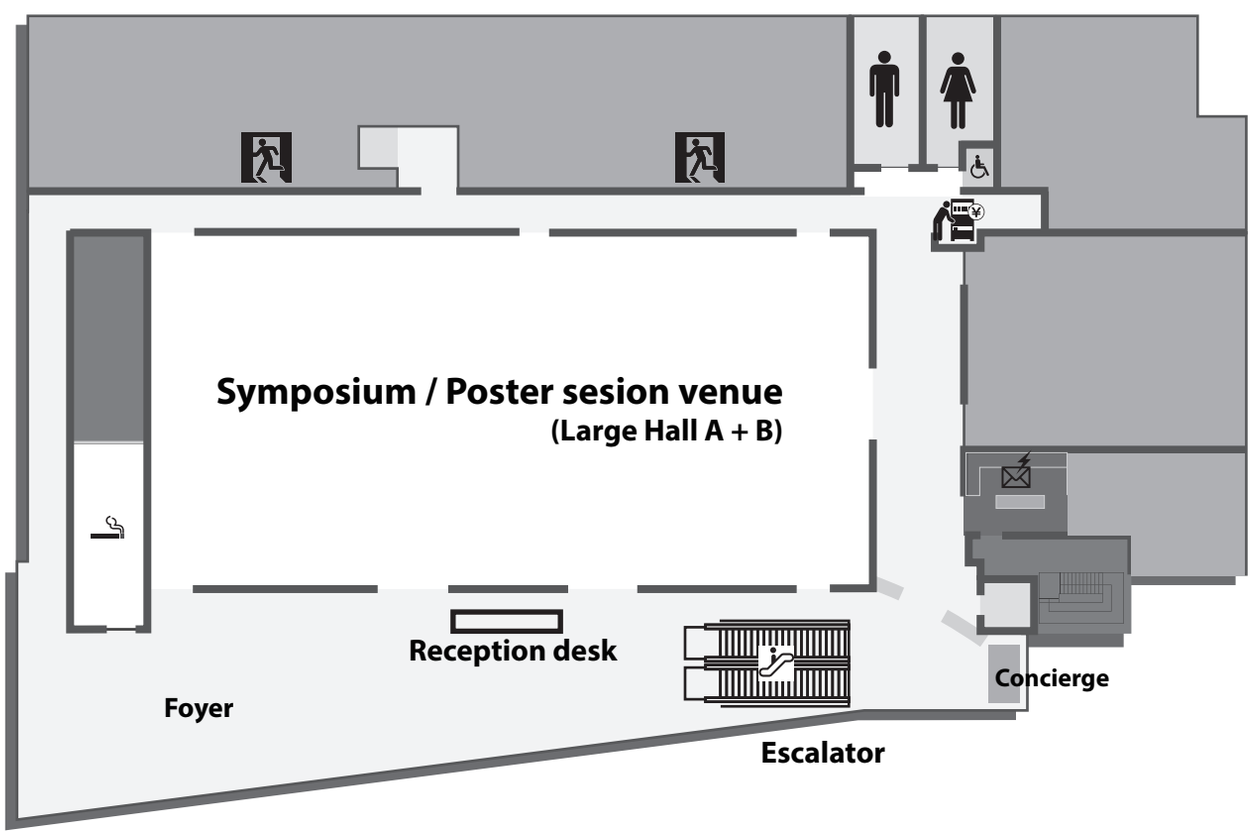
Lunch

Free lunch will be provided for pre-registered participants.

Reception

18:00 - 20:00 at **Foyer** on 5th floor
For MSD afternoon seminar attendees.

Floor Map (5th floor) | Tokyo Conference Center Shinagawa



Neurochemincal mechanisms of post-training processing in perceptual learning

Takeo Watanabe

Brown University, USA

ABSTRACT

After encoding of learning, its state changes through several different stages. We examined post-training stages of visual perceptual learning (VPL; Watanabe et al, *Nature*, 2001 & 2003; Tsushima et al, 2006, *Science*; Shibata et al, 2011, *Science*). Particularly, we have addressed the questions of how VPL is stabilized after training and also how consolidated VPL is re-stabilized after reactivation. Inspired by a series of work by Dr. Takao Hensch and his colleagues on a animal visual critical period (Morishita & Hensch, 2008, *Curr Opin Neurobiol*), we measured the concentration of glutamate, an excitatory neurotransmitter, divided by the concentration of GABA, an inhibitory neurotransmitter (E/I ratio) in human visual areas using magnetic resonance spectroscopy at different post-encoding stages of VPL. First, we examined overlearning that refers to a learning state resulting from continuous training after the saturation of performance increases. We found that overlearned VPL interfered with subsequent learning of a new task (anterograde interference). In this case, overlearning was accompanied with rapid and abrupt decrease in E/I ratios from higher to lower than baselines. Second, we found that if training was terminated before the saturation of performance increase, VPL of the trained task was interfered with by subsequent training on a new task (retrograde interference) and that an E/I ratio was higher 30 min after the training than baselines and then decreased to the baselines 3.5 hours later (Shibata et al, 2017, *Nat Neurosci*). Third, after encoding and consolidation of learning of a task, performance of a handful of trials of the task made a VPL state subject to retrograde interference (reactivation) and E/I ratio changes after the reactivation were highly similar to those after encoding. This suggests similar aspects of mechanisms between the states after encoding and reactivation of VPL (Bang et al, 2018, *Nat Hum Behav*).

Genetic and circuit analysis of empathy behaviors in the mouse

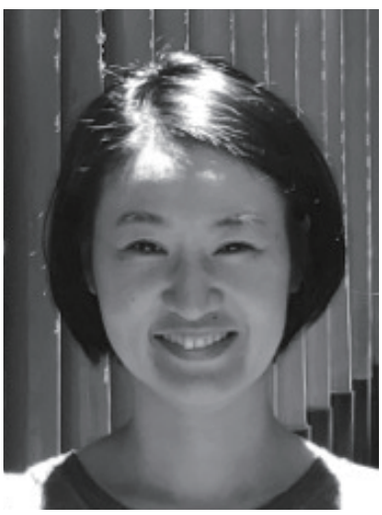
Hee-Sup Shin

Center for Cognition and Sociality, Institute for Basic Science, Korea

ABSTRACT

Unraveling neural mechanisms underlying social behaviors is one of the major subjects in neuroscience. Diverse tools recently developed for doing experiments in rodents allow multidisciplinary studies on such subjects from molecules to systems. Empathy, the capacity to recognize and share emotions with others, is crucial for our social interaction and mental well-being. This ability is conserved from rodents to humans, and the anterior cingulate cortex (ACC) is known to be integral in the acquisition of observational fear, a rodent model of empathic fear. Despite the fundamental importance of genetic factors underlying individual variability in empathy-related behaviors, molecular and cellular mechanisms in the ACC that control observational fear (OF) remain to be determined. Through examining several mutant strains for OF behavior as well as through behavior-driven forward genetic analyses, we found several gene mutations that influence OF behavior in the mouse. One of them, a missense mutation in *Nrxn3*, causes an increase in observational fear. Using a combination of tools we find evidence that *Nrxn3* is an essential molecule for inhibitory synaptic transmission in SST-positive neurons, and uncover a novel role of SST interneurons in the ACC in gating the top-down computation for the expression of socially incited fear.

The interaction between sleep and aging mediated by DMH neurons



Akiko Satoh

National Center for Geriatrics and Gerontology, Japan

ABSTRACT

Aging has significant impacts on sleep, resulting in increases in sleep fragmentation and sleep onset latency, and a decrease in sleep quality in mammals. We have recently found that diet restriction (DR), a dietary regimen well-known to delay the aging process and to extend lifespan in a wide variety of organisms including mammals, can dramatically attenuate some of age-associated sleep alterations. For example, DR significantly reduces the level of age-associated sleep fragmentation. Therefore, DR may delay the aging process and extend lifespan by critically altering sleep control in aged animals.

To further elucidate mechanisms by which DR ameliorates age-associated sleep alterations, we focus on the gene called PR-domain containing factor 13 (PRDM13). PRDM13 is a SIRT1 downstream gene and is exclusively expressed in the dorsomedial hypothalamus (DMH). The DMH has been shown to control age-associated physiological changes and longevity through SIRT1. Mice with knockdown of *Prdm13* in the DMH display reduced NREM delta power. In addition, DMH-specific *Prdm13*-knockdown mice display defect in sleep homeostasis, but not in circadian clock. As well as *Prdm13*-knockdown mice, DMH-specific *Sirt1*-knockdown mice also display reduced NREM delta power. These findings suggest that the DMH contributes to modulate quality of sleep through maintaining sleep homeostasis by the SIRT1/PRDM13 axis during the aging process. In this talk, I will discuss about a role of DMH neurons on age-associated sleep alterations. I will also propose how poor sleep quality promotes the age-associated pathophysiology in peripheral organs/tissues and ultimately affects longevity.

Motivated behavior regulated by the ventral striatum

Kenji Tanaka

Keio University, Japan

ABSTRACT

The assessment of motivation is highly subjective, owing to the variety of psychological conception of motivation. To improve the objectivity of motivation, it has been proposed that the level of motivation is addressed by the quantitative consequences of the goal-directed behavior. The goal-directed behavior comprises of action selection, action initiation, and action sustainment to pursue the goal. Each domain is regulated by the cortico-striatal circuit and the ventral striatum is known to be a key node of this behavior. Recent animal studies demonstrated that the ventromedial part of the striatum controls the action selection, and the ventrolateral striatum regulates action initiation. However, little is known about how the ventral striatum is involved in the action sustainment. We will talk about the neural substrate mediating action sustainment and will discuss the involvement of the ventral striatum in the goal-directed action sustainment.

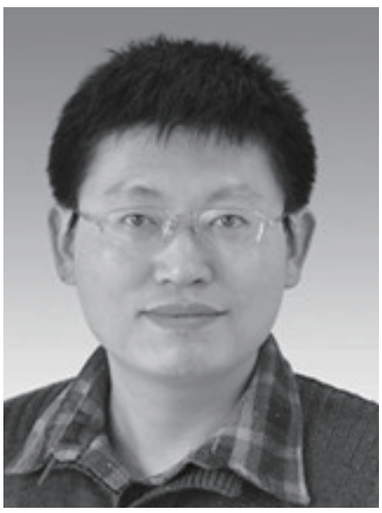
Ref:

1. Tsutsui-Kimura et al., Distinct roles of ventromedial versus ventrolateral striatal medium spiny neurons in reward-oriented behavior. **Current Biology**, 27(19):3042-3048, 2017
2. Natsubori et al., Ventrolateral Striatal Medium Spiny Neurons Positively Regulate Food-Incentive, Goal-Directed Behavior Independently of D1 and D2 Selectivity. **J Neurosci**. 37(10):2723-2733, 2017
3. Tsutsui-Kimura et al., Dysfunction of ventrolateral striatal dopamine receptor type 2-expressing medium spiny neurons impairs instrumental motivation. **Nat Commun** 8: 14304, 2017

WILLDYNAMICS Luncheon Session

12:45 - 13:15

How do mice detect and escape from their predator?



Peng Cao

National Institute of Biological Sciences, Beijing, China

ABSTRACT

The innate defensive behaviors in response to environmental threats play a fundamental role in survival. However, little is known about the neural circuits specifically processing threat-relevant sensory information in the mammalian brain. We identified parvalbumin-positive (PV+) excitatory projection neurons in mouse superior colliculus (SC) as a key neuronal subtype for detecting looming visual objects. These neurons, distributed predominantly in the retinal-recipient layers of the SC, are both necessary and sufficient to trigger dimorphic defensive behaviors, i.e. escape and freezing. Two distinct groups of SC PV+ neurons form divergent pathways to transmit threat-relevant visual signals to neurons in the parabigeminal nucleus (PBGN) and lateral posterior thalamic nucleus (LPTN). Activations of PV+ SC-PBGN and SC-LPTN pathways mimic the dimorphic defensive behaviors. Bilateral inactivation of either nucleus results in the defensive behavior dominated by the other nucleus. Together, these data suggest that the SC PV+ neurons, as a key neuronal subtype to detect looming visual objects, orchestrates dimorphic defensive behaviors with two mutually competitive tectofugal pathways that may operate in a "winner-take-all" process.

Multiscale understanding of synaptic pathology of psychiatric disorders

Akiko Hayashi-Takagi

Gunma University, Japan

ABSTRACT

Various lines of evidence have suggested that synaptopathy is involved in schizophrenia. However, it is unknown whether synaptopathy is an underlying mechanism of disease or a secondary consequence. Thus, we performed a longitudinal *in vivo* 2-photon imaging analysis of the brain of a schizophrenia model (DISC1 knockdown mice) and found that this model exhibited a decrease in the density of dendritic spines, where the majority of excitatory synapses are formed. Furthermore, we found a significantly greater number of large dendritic spines in the model mice. The presence of the large spines in the schizophrenia mice model mirrors findings from another schizophrenia mice model, calcineurin knockout mice. It is well-known that there is a strong correlation between spine head size and its synaptic efficacy, whereby the large spines can generate a larger synaptic current. This led us to hypothesize that large spines can non-linearly affect the dendritic computation, causally resulting in subsequent behavioral alterations. To test this hypothesis, we use a multiscale analysis that consists of an uncaging-evoked single spine EPSC measurement and Ca^{2+} imaging to visualize the synaptic input, dendritic event, action potential, and behavioral manifestations. In addition, with use of *in vivo* optical and *in silico* manipulation of the spines in the model animals, we are now trying to causally examine what kind of synaptic pathology would underlie the pathology of disorders.

Balancing brain plasticity/stability

Takao Hensch

Harvard Medical School, USA /

Harvard University, USA /

WPI-IRCN, The University of Tokyo, Japan

ABSTRACT

Brain function is largely shaped by experience in early life, creating windows of both great opportunity and vulnerability. Our work has focused on the biological basis for such critical periods, identifying both “triggers” and “brakes” on plasticity. Strikingly, the maturation of particular inhibitory circuits is pivotal for the onset timing of these windows. Manipulations of their emergence can either accelerate or delay developmental trajectories regardless of chronological age. Notably, many neurodevelopmental disorders are linked to alterations in excitatory-inhibitory balance, suggesting shifted critical period timing as part of their etiology. Closure of critical periods in turn reflects an active process, rather than a purely passive loss of plasticity factors. Lifting these brakes allows the reopening of plastic windows later in life, but may also underlie instability in disease states. Thus, understanding how brain plasticity and stability are balanced throughout life offers new insight into mental illness and novel therapeutic strategies for recovery of function in adulthood.

Neural ensemble dynamics during REM sleep and P-waves in mice

Tomomi Tsunematsu

Tohoku University, Japan

ABSTRACT

Rapid eye movement (REM) sleep is characterized by hippocampal theta waves and phasic sub-second waves in the brainstem, so-called ponto-geniculo-occipital (PGO) waves in cats or pontine (P) waves in rodents. The sub-second pontine wave during REM sleep was originally described in the 1960s. Hobson and colleagues have proposed that P-waves construct the hallucinoid visual imagery of dreams. However, we still do not know the biological function of P-waves and also occurrence of P-waves in mice. In this study, we investigated the temporal evolution of P-waves and underlying neural ensemble dynamics in the brainstem. First, to examine how P-waves appear during the sleep-wake cycle, bipolar electrodes were implanted into the sublaterodorsal nucleus (SLD) of head-fixed mice. The density of P-waves was typically at ~ 0.8 Hz during REM sleep, consistent with that in cats and rats. Second, to monitor neural ensemble dynamics during P-wave, we inserted a 4-shank silicon probe to cover multiple brainstem nuclei simultaneously. While a rich structure of neural activity was apparent across brainstem nuclei, we found that P-waves during REM sleep were associated with highly synchronous burst firing across nuclei. Next, we also investigated functional interactions between the brainstem and hippocampus during P-wave genesis. While P-waves were seen during both REM and non-REM sleep, the functional connectivity between two structures was changed depending on sleep states. Our findings suggest that P-waves involve in state-dependent coordinated activity across brain regions.

MSD Afternoon Seminar

MSD Afternoon Seminar | **16:00 - 16:30**

Neural circuitry of sleepiness and cataplexy in narcolepsy

Thomas E. Scammell

Beth Israel Deaconess Medical Center, USA /

Harvard Medical School, USA

ABSTRACT

Narcolepsy is the most common neurological cause of chronic sleepiness and is caused by selective loss of the orexin neurons. Research suggests that this sleepiness is not due to higher homeostatic sleep pressure or weak circadian waking drive, but instead is caused by loss of excitatory signaling from the orexin neurons onto a variety of wake-promoting brain regions. For example, restoration of orexin signaling in the histaminergic neurons of the tuberomammillary nucleus substantially improves the ability of mice to stay awake for long periods, and orexin signaling through other monoaminergic regions is similarly effective. Just which aspects of arousal are mediated by these pathways is now under investigation.

Narcolepsy is also characterized by cataplexy – sudden episode of muscle paralysis usually triggered by strong positive emotions, usually under social circumstances. We found that activation of GABAergic neurons of the central nucleus of the amygdala (CeA) increases cataplexy whereas inhibition reduces cataplexy. The CeA contains a great variety of GABAergic neurons, some mediating responses to positive stimuli and other mediating fear behaviors. We are now finding that CeA neurons responsive to the pro-social hormone oxytocin (OT) can strongly drive cataplexy via specific projections to the brainstem. Defining these pathways helps identify new targets for narcolepsy treatments, and also helps identify specific amygdala population that may influence positive affect of relevance to psychiatric disease.

MSD Afternoon Seminar | **16:30 - 17:00**

Identification of neurons regulating REM/non-REM sleep and insights to the mechanisms of REM sleep behavior disorder

Yu Hayashi

WPI-IIIS, University of Tsukuba, Japan

ABSTRACT

Over the night, our sleep cycles between two distinct states, rapid eye movement (REM) sleep and non-REM sleep. Abnormal balance of the two sleep states is a common and early symptom in various neurological disorders, suggesting that each sleep state plays crucial roles. Little is known, however, about the individual roles and neural substrates of these two states. We applied mouse genetics to functionally dissect neurons in the brainstem and identify neurons involved in regulating REM/non-REM sleep. With this approach, we previously identified glutamatergic and GABAergic neurons in the pontine tegmental area that negatively regulate REM sleep (*). Recently, we further searched for molecular markers in this brain area that allow precise manipulation of neuronal subgroups. In one group of neurons, genetic inhibition led to a drastic decrease in REM sleep, suggesting that these neurons play an essential role in generating REM sleep. Moreover, the mice frequently exhibited aggressive movements during REM sleep, resembling REM sleep behavior disorder (RBD). RBD is a sleep disorder in which patients act out of their dreams and exhibit violent behavior during REM sleep. We expect that these neurons are a key to understanding the neural circuitry of REM/non-REM sleep and that our genetic mouse model provides important implications about the neural mechanisms of RBD.

*Hayashi et al., Science 350, 957-961, 2015

MSD Afternoon Seminar | **17:00 - 17:30**

Neuron-glia metabolic coupling : role in neuronal plasticity, neuroprotection and regulation across the sleep-wake cycle

Pierre J. Magistretti

King Abdullah University of Science and Technology, Saudi Arabia/

École Polytechnique Fédérale de Lausanne, Switzerland/

Département de Psychiatrie, UNIL-CHUV, Site de Cery, Switzerland

ABSTRACT

A tight metabolic coupling between astrocytes and neurons is a key feature of brain energy metabolism (Magistretti and Allaman, Neuron, 2015). Over the years we have described two basic mechanisms of neurometabolic coupling. First the glycogenolytic effect of VIP and of noradrenaline indicating a regulation of brain homeostasis by neurotransmitters acting on astrocytes, as glycogen is exclusively localized in these cells. Second, the glutamate-stimulated aerobic glycolysis in astrocytes. Both the VIP-and noradrenaline-induced glycogenolysis and the glutamate-stimulated aerobic glycolysis result in the release of lactate from astrocytes as an energy substrate for neurons through a process now known as the Astrocyte-Neuron-Lactate Shuttle (ANLS) (Magistretti and Allaman, Neuron, 2015; Magistretti and Allaman, Nature Reviews Neuroscience, 2018).

We have shown that lactate is necessary not only as an energy substrate but is also a signaling molecule for long-term memory consolidation and for maintenance of LTP (Suzuki et al, Cell, 2011).

At the molecular level we have found that L-lactate stimulates the expression of synaptic plasticity-related genes (Yang et al, PNAS, 2014). This effect is mediated by the L-lactate potentiation of NMDA receptor-mediated currents and the ensuing increases in intracellular calcium (Jourdain et al, Scientific Reports, 2018) . These results reveal a novel action of L-lactate as a signaling molecule for neuronal plasticity.

We have also shown that peripheral administration of lactate exerts antidepressant-like effects in three animal models of depression (Carrard et al, Mol.Psy., 2016).

We also investigated the expression of genes associated with the ANLS specifically in astrocytes following sleep deprivation. Quantitative RT-PCR analysis showed that levels of Glut1, α-2-Na/K pump, Glt1, and Ldha mRNAs were significantly increased following Total Sleep Deprivation in astrocytes (Petit et al, Sleep, 2013). These results stress the important role of astrocytes in the maintenance of the neurometabolic coupling across the sleep-wake cycle.

株式会社 S'UIMIN
〒305-8575 茨城県つくば市天王台 1-1-1
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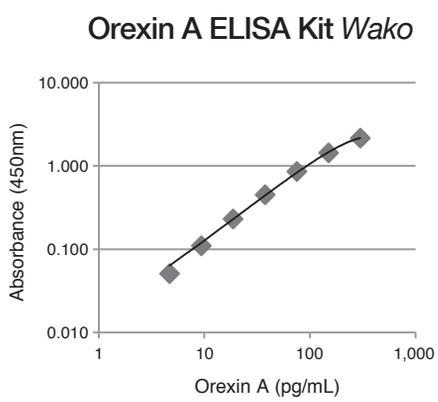

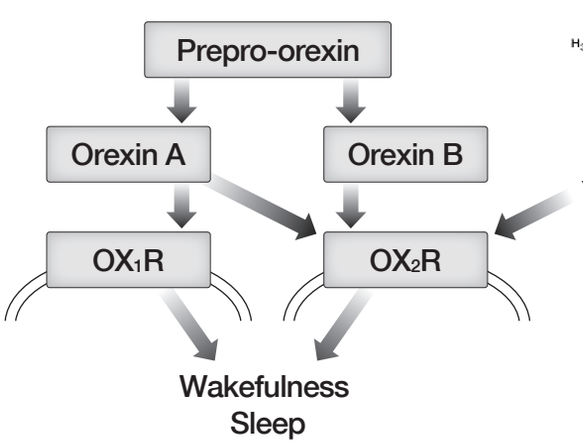

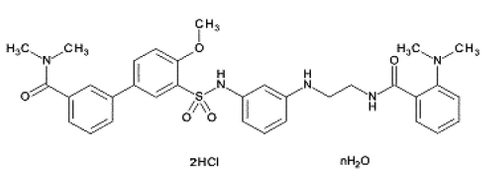

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TEL:029-847-9475　FAX:029-847-7567

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WILLDYNAMICS

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University of Tsukuba
Phone: 029-853-5857 E-mail：wpi-iiis-alliance@ml.cc.tsukuba.ac.jp