World Premier International Research Center Initiative (WPI)
FY2016 WPI Project Progress Report (Post-Interim Evaluation)

Host Institution	University of Tsukuba	Host Institution Head	Kyosuke Nagata
Research Center	International Institute for Integrative Sleep Medicine (IIIS)	Center Director	Masashi Yanagisawa

Common instructions:
* Unless otherwise specified, prepare this report from the timeline of 31 March 2017.
* So as to base this fiscal year's follow-up review on the document "Post-interim evaluation revised center project," please prepare this report from the perspective of the revised project.
* Use yen (¥) when writing monetary amounts in the report. If an exchange rate is used to calculate the yen amount, give the rate.

Summary of State of WPI Center Project Progress (write within **2 pages**)

1. Conducting research of the highest world level

Sleep is a behavior that everyone experiences daily, but the very fundamental mechanisms of sleep are still unknown today. While sleep remains as a black box, its medical and social importance is very clear. Lack of sound sleep not only causes a reduction in higher brain functions including memory and decision making, but also increases the risk of mood disorders such as depression as well as metabolic syndrome, etc. Economic loss caused by sleep disorders in Japan is estimated as ¥3.5 trillion/year. To solve the issues of sleep disorders, we set out our major objectives as follows.

1. To elucidate the fundamental mechanisms of sleep/wake regulation
2. To elucidate molecular pathogenesis of sleep disorders and related diseases
3. To develop treatments for sleep disorders

To address the 1st objective, 8 PIs are dissecting neuronal and molecular mechanisms and elucidating operating principles of neural networks regulating sleep/wake. We also use a completely unbiased genetic approach in order to identify new genes involved in the regulation of sleep/wake. As for the 2nd objective, we study molecular pathogenesis of various sleep disorders using genetically engineered mouse models. To achieve the 3rd objective, we develop new drug candidates as well as early interventions of sleep disorders, including sleep-enhancing supplements based on natural products and functional bedding products.

Implementation of the translational research is our challenge to establish "sleep science." We aim to translate achievements in basic biology/pharmaceutical science into experimental medicine and/or clinical research. To enforce the translational research, our major efforts have been dedicated to increase and expand collaborations/research alliances.

To implement and encourage broad use of new treatments of sleep disorders we develop, alliances with health industries are essential. We thus intensively secure intellectual property rights and seek opportunities of collaboration and licensing to companies.

2. Advancing fusion of various research fields

To achieve 3 objectives, there is a need for wide-ranging sleep research, covering a scope from basic biology such as neuroscience to pharmaceutical science and further to experimental medicine to create the new interdisciplinary research domain, "sleep science." To foster the interdisciplinary research under the Center Director's leadership, the team has been organized by PIs with sufficient expertise in 3 research fields. To reinforce research capabilities of basic biology, T. Sakurai was invited from Kanazawa University and appointed as Vice Center Director. A clinical sleep lab was newly established to introduce state-of-the-art equipment for sleep and metabolism studies. To strengthen pharmaceutical science, we have commenced collaboration with pharmaceutical companies. The internal collaboration among laboratories in IIIS is also crucial to fuse 3 research fields and becoming much more active after the completion of the new research building.

3. Globalization of the institution

The PIs at overseas satellites visited IIIS quite often and actively participated in events such as the Site Visit, WPI-IIIS Symposium, WPI-IIIS Seminar, etc. In FY2016 we hosted 32 WPI-IIIS Seminars, for which 13 foreign speakers (47%) were invited. The 5th IIIS Symposium was held on December 12, 2016 in Tokyo as a joint meeting with 32nd Wako Workshop, inviting 5 international

and 6 domestic speakers. The joint meeting with industry gathered 200 audiences not only from academia but also from pharmaceutical/chemical companies to expand our networks. In FY2016 we accepted 8 visiting foreign research fellows and 7 international students for short- or mid-term training. After the completion of our new research building, requests to visit IIIS are increasing and we accepted visits about 20 times from overseas and overseas universities in FY 2016.

4. Implementing organizational reforms

The basic concepts of the organization and the operation of IIIS involve creating a new style of research center by learning from the merits and virtues in the organization of "departments" in major US universities. In addition to the strong leadership of the "Department Head," other characteristics including the appointment of independent PIs regardless of their age and career stage, and a flexible and dynamic allocation of the floor space to each lab, have been perfectly implicated in IIIS.

The joint appointment system was introduced to University of Tsukuba to let the Center Director occupy concurrent posts at University of Tsukuba and University of Texas Southwestern Medical Center in March 2014. Following to this 1st case, the number of the cross-appointment increased rapidly and there are 16 cases in the University now.

Our collaboration with a global pharmaceutical company was the 1st large collaboration with a foreign company for the University. Currently 9 collaborations with foreign companies are underway, and our initiative was the important trigger of promoting the international collaboration.

5. Efforts to secure the Center's future development over the mid- to long-term

At the end of the first half of WPI project, the research organization and composition of PIs are being reviewed and reconsidered in the course of advancing the research strategy based on the objectives. In accordance with "Action required and recommendations" in the interim evaluation by Program Committee, we continue and even strengthen the collaborations with outside clinical/human research teams, while we expand Satoh Lab working on human physiology as partners of the outside teams in the collaborations.

An important element to be considered for the revision of the organization is organizational diversity, especially in terms of the gender of PIs. In FY2016 we have secured the appointment of a female PI, S. Honjoh, starting September 2017. We continue exploring possibilities of female PI appointment including the potential promotion of an assistant professor.

In terms of organizational rejuvenation, the reappointment of 2 elder PIs has been carefully considered. We decided to limit extension of the employment contract of one PI to September 2017, due to the limited prospect of his studies. On the other hand, since the leadership and expertise in medicinal chemistry of another elder PI are indispensable for our pioneering drug discovery in academia, we decided to stipulate, following negotiations with the university management, an extension of the retirement age through the special assignment by the President.

In the recent revision of the Center Plan after the Interim Evaluation, the target numbers of researchers and research support staffs were reduced to 62 and 20, respectively, considering the financial constrains.

The amount of external research funding acquired by the core group of IIIS has grown rapidly. We continue the efforts to secure the same or even higher levels of external research funds.

University of Tsukuba has provided IIIS with various resources as operational supports, and has positioned IIIS as its forefront research organization in the 3rd mid-term plan of the University starting FY2016, as committing itself to maintain IIIS as a permanent organization even after the end of the WPI program. A couple of specific measures, including offering a tenure position to qualified PIs, establishment of a system to return to IIIS licensing revenues of its intellectual property rights, implementation of the future expansion space by inviting a open-innovation drug discovery lab sponsored by pharmaceutical companies, are under consideration.

6. Others

Aggressive outreach activities, conducted at the Super Science High School Annual Research Meeting and other events, resulted in the regular visits by several high schools.

Since the completion of the IIIS building in June 2015, the development of the facility has been continuously moved forward, *e.g.,* a clinical sleep lab with human metabolic chamber, and a server room with upgraded IT infrastructure.

* Please describe clearly and concisely the progress being made by the WPI center project from the viewpoints below.
- In addressing the below-listed 1-6 criteria, please place emphasis on the following:
  (1) Whether research is being carried out at a top world-level (including whether research advances are being made by fusing fields).
  (2) Whether a proactive effort continues to be made to establish itself as a "truly" world premier international research center.
  (3) Whether a steadfast effort is being made to secure the center's future development over the mid- to long-term.
- Please prepare this report within 10-20 pages (excluding the appendices, and including Summary of State of WPI Center Project Progress (within 2 pages)).

1. Conducting research of the highest world level

* Regarding the criteria used when evaluating the world level of center, please note any updated results using your previous evaluation criteria and methods or any improvements you have made to those criteria and methods.

1-1. Background and objectives of sleep research in IIIS

Sleep is a behavior that everyone experiences daily and it takes up as much as one third of one's entire lifetime. However, the very fundamental mechanisms of sleep and its raison d'être remain still unknown today. While sleep has been a black box stubbornly resisting scientists' challenges, its medical and social importance is very clear. Healthy sleep is necessary for maintaining our mind and body fitness; lack of sound sleep not only causes a reduction in higher brain functions including memory and decision making, but also increases the risk of mood disorders such as depression as well as metabolic syndrome, etc.

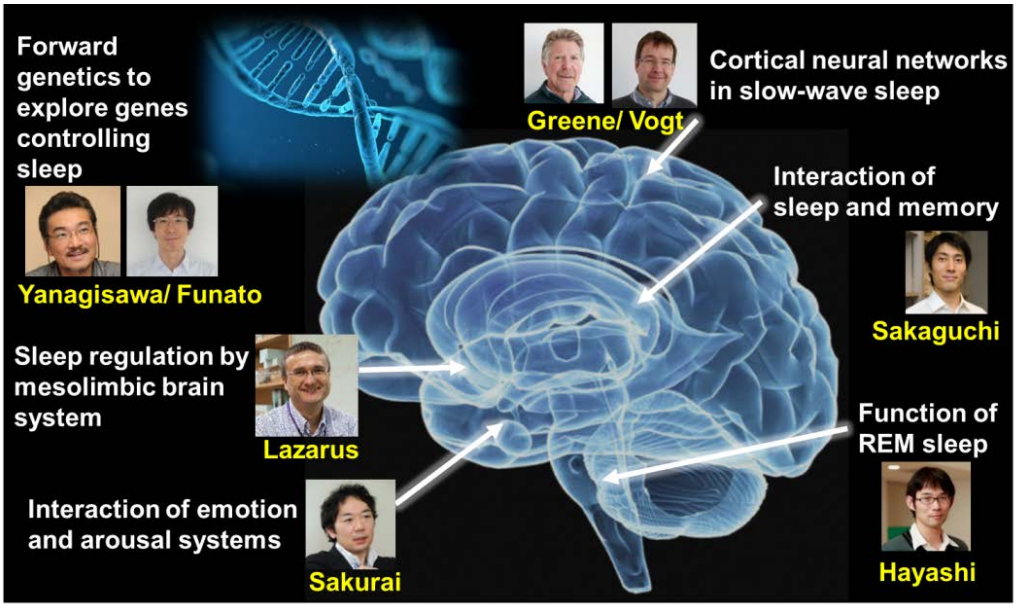
In developed countries, the prevalence rate of sleep disorders is around 15%, with the lifetime prevalence more than 30%. The underlying factors behind this problem include an increase of the elderly population and the increasingly nocturnal lifestyle of today's societies. The deficiencies in healthy sleep cause significant social losses, and are linked to decrease in working efficiency and increase in accidents due to excessive sleepiness, and increased prevalence of mood disorders and metabolic syndromes, and even increased suicide deaths. Domestic economic loss caused by sleep disorders in Japan is estimated as 3.5 trillion yen/year, hence it is the urgent need to solve sleep-related issues.

To solve the issues of sleep disorders, we set out our major objectives as follows.

1. To elucidate the fundamental mechanisms of sleep/wake regulation
2. To elucidate molecular pathogenesis of sleep disorders and related diseases
3. To develop treatments for sleep disorders

1-1-1. Progress and achievements in elucidation of the fundamental mechanisms of sleep/wake regulation

We dissect neuronal and molecular mechanisms of sleep regulation to elucidate operating principles of neural networks regulating sleep/wake as well as sleep-related mental activities such as emotion and memory. At the same time, we use a completely unbiased genetic approach in order to identify new and unexpected genes that are importantly involved in the regulation of sleep/wake.



(1) Forward genetics to explore genes controlling sleep / wake regulation (Yanagisawa / Funato Lab)

As many of IIIS labs successfully utilize optogenetic and chemogenetic approaches, a recent advance in directly manipulating the activity of specific neurons has uncovered the neural circuitries regulating sleep/wakefulness states. However, the molecular and cellular mechanism that determines the propensity of switching between wakefulness, NREM sleep and REM sleep remains unknown. To tackle this issue, we have conducted EEG/EMG-based genetic screening of more than 8,000 randomly mutagenized mice, which led to identify three gene mutations resulting in sleep/wakefulness abnormalities (Funato *et al.*, *Nature 2016*; Kim *et al.*, in preparation). A splice mutation of the *Sik3* gene causes a marked increase of NREM sleep time that characterizes the *Sleepy* mutant pedigree. SIK3 is a member of AMP-activated protein kinase (AMPK) family and is broadly expressed in both excitatory and inhibitory neurons of the forebrain and brain stem. The exon 13 that is skipped in *Sik3* mutant mice encodes a phylogenetically conserved PKA phosphorylation site (S551), suggesting a conserved role of *Sik3* orthologues in sleep-like behaviors. In collaboration with Yu Hayashi of IIIS and Dr. Kazuhiko Kume at Nagoya City University, we showed that the modification of *Sik3* orthologues altered the amount of sleep-like behaviors of roundworms and flies in a direction that is consistent with *Sleepy* mutant mice (Funato *et al.*, *Nature* 2016). To examine the phosphorylation status of SIK3 protein in brain, we inserted a FLAG-HA tag in the wild-type and mutant *Sik3* alleles using the CRISPR method. Phosphoproteomic analyses showed that sleep deprivation increased phosphorylation at T221 that is associated with SIK3 kinase activity (Figure 1a). Furthermore, we showed that mutant SIK3 exhibited altered phosphorylation at multiple sites (Figure 1b). In parallel, a quantitative phosphoproteomic analysis of *Sleepy* mutant brains has been conducted (Wang, Liu *et al.*, in preparation). As there has been a total lack of knowledge about the intracellular signaling that regulates sleep/wakefulness, the identification of SIK3 protein will open new frontiers in sleep research.

As for REM sleep, we found a single amino acid substitution of the leak cation channel NALCN in *Dreamless* mutant mice, which show a drastic reduction in the total amount and mean episode duration of REM sleep (Funato *et al.*, *Nature* 2016). To examine whether altered neuronal activity underlies

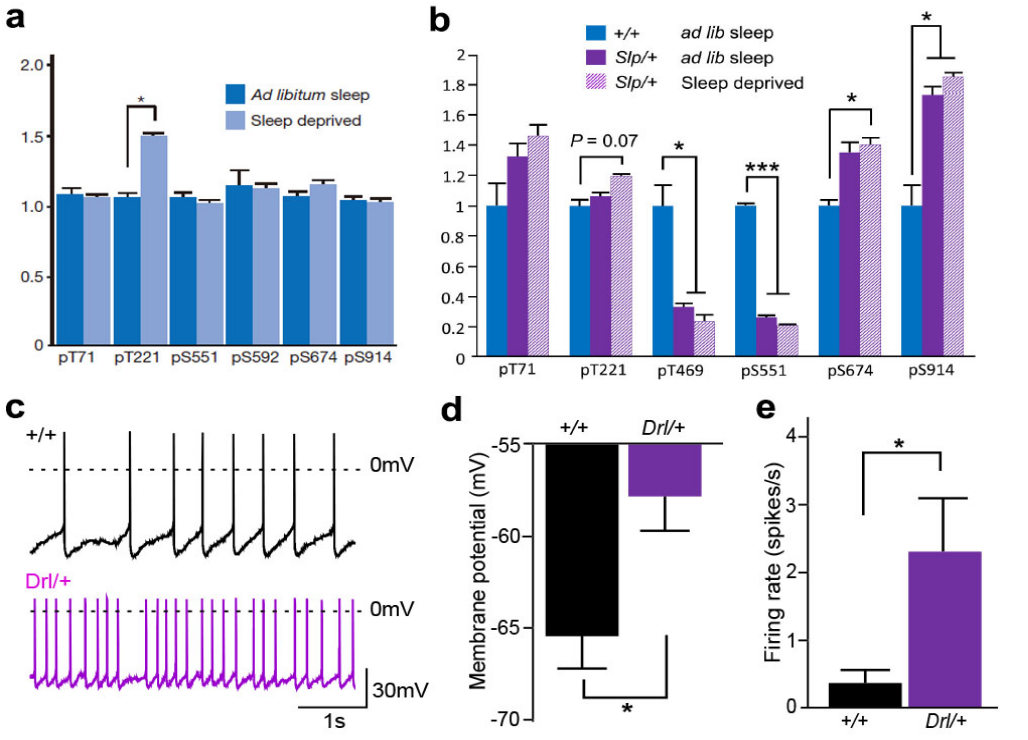


Figure 1. Biochemical and electrophysiological characterization of *Sik3* mutant (*Slp*)and *Nalcn* mutant (*Drl*) mice. (**a**, **b**) Phosphoproteomic analysis of *FLAG-HA-Sik3* knock-in and *FLAG-HA-mutant Sik3* knock-in mice revealed altered phosphorylation status. (**a**) Sleep deprivation increased phosphorylation at T221 that is associated with kinase activity of SIK3. (**b**) Mutant SIK3 that lacks 52 amino acids encompassing S551 showed altered phosphorylation at T221, T469, S674 and S914. (**c**, **d**, **e**) Patch clamp recording of DpMe neurons in brain slices from *Nalcn* mutant and wild-type mice. (**c**) Representative traces of membrane potentials. DpMe neurons of *Nalcn* mutants had shallower membrane potentials (**d**) and higher firing rate (**e**).

REMS abnormality of *Nalcn* mutant mice, we performed slice patch recording of the deep mesencephalic nucleus (DpMe) responsible for the termination of REMS, which have been identified by Yu Hayashi, IIIS. DpMe neurons of *Nalcn* mutant mice exhibited more deporalized membrane potentials and higher firing frequency, which is consistent with the short REMS episode duration and short REMS time.

(2) Interaction between the emotion and arousal systems (Sakurai/Sakaguchi Lab)

Orexin neurons are activated in response to emotionally salient cues with both positive and negative valence (Sakurai, *Nat Rev Neurosci*, 2014). To reveal the mechanisms by which orexin neurons are regulated by salient cues and/or contexts, we identified neurons that make monosynaptic inputs to orexin neurons using a recombinant rabies virus-mediated trans-synaptic retrograde tracing in mice. We identified positive cells in the many brain regions implicated in emotion, reward system, and sleep. By combination of the cell type-specific tracing the relationship between input and output (cTRIO) analysis and anterograde tracing we found many GABAergic neurons in the POA, including the VLPO, which send projections to orexin neurons receive monosynaptic projections by neurons in the central nucleus of the amygdalanucleus accumbens (NAcCeA) and BST (Saito *et al.*, unpublished) (Figure 2). VLPO neurons that make direct synaptic input to orexin neurons and histamine neurons were inhibited by noradrenalin (NA) and 5HT.

We also found that optogenetic activation of BST GABAergic neurons during NREM sleep made immediate transition from NREM sleep to wakefulness, while stimulation during REM sleep did not show any effects (Kodani *et al.*, unpublished). This transition was not affected by dual orexin receptor antagonists DORA 22. However, chemogenetic excitation of BNSTGABA neurons evoked a sustained wakefulness state, but this arousal effect was markedly attenuated by DORA 22. These observations suggest that BNSTGABA neurons play an important role in transition from NREM sleep to wakefulness without the function of orexin neurons, but prolonged excitation of these cells mobilizes the orexin system to sustain wakefulness.

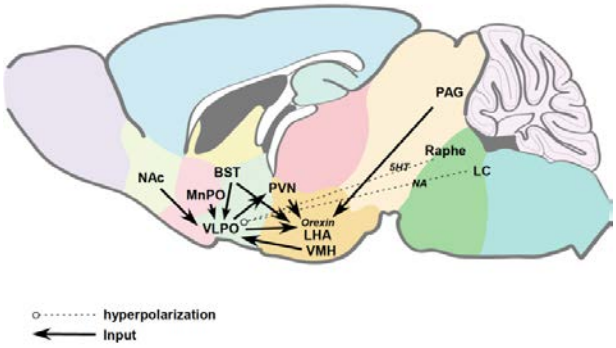


Figure 2. Neuronal circuits that regulate hypothalamic arousal system.

We also examined the function of orexinergic projections in the regulation of emotion-related behavior. We previously found that targeted restoration of orexin receptor expression in noradrenergic neurons of the locus coeruleus (LC) and in serotonergic neurons of the dorsal raphe (DR) in OX1R-/-;OX2R-/- mice, which display a severe narcoleptic phenotype, differentially inhibited fragmentation of wakefulness and cataplexy, respectively (Hasegawa *et al.*, *J Clin Invest*, 2014). We further found that optogenetic excitation of DR-5HT→lateral amygdala (LA) pathway almost completely inhibited cataplexy, which was induced by chocolate feeding in the mice (Hasegawa *et al.* PNAS, in press). We also examined roles of the orexin neurons→LC-NA neurons →lateral amygdala (LA) pathway in the fear-related behavioral responses (Soya *et al.*, *J Neurosci*, 2013). After fear conditioning in the particular context, optogenetic stimulation of orexinergic fibers in the LC, or LC-NA fibers in the LA induced an apparent freezing behavior even in the in alternative context which did not induce freezing when the stimulation was not applied (Soya *et al.*, unpublished) (Figure 3). Pharmacogenetic or optogenetic inhibition of LC-NA neurons reduced the freezing in the fearful context. These results suggest that orexin neurons activate the amygdala projecting-LC-NA neurons to modulate fear-related behavior. These observations suggest that the extended amygdala regulates orexin neurons and monoaminergic systems,

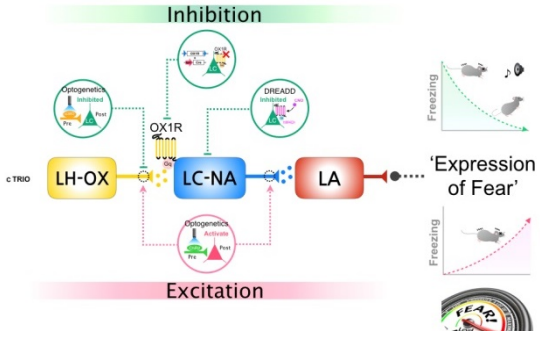


Figure 3. The LH→LC→LA circuit that regulates fear expression.

and arousal systems in turn influences amygdala function to modulate emotion-related behavior as well as arousal.

(3) The causal role of the mesolimbic brain system in the control of sleep and wakefulness (Lazarus Lab)

Sleep regulation is conceptualized by the popular "two-process" model that posits homeostatic and circadian drives control sleep. Sleep/wake behaviour, however, is also influenced by cognitive and emotional factors (Lazarus *et al.*, *Trends Neurosci*, 2012; Lazarus *et al.*, *Curr Opin Neurobiol*, 2013). The arousal effect of caffeine depends on adenosine A_{2A} receptors (A_{2A}R)-positive inhibitory medium spiny neurons in the nucleus accumbens (Lazarus *et al.*, *J Neurosci*, 2011), a major component of the mesolimbic brain system that is involved in the dopaminergic control of motor function and motivational behavior. However, a NAc role in the regulation of sleep was not known. The lab found that chemogenetic and optogenetic stimulation of indirect pathway neurons in the core region of the NAc strongly induced slow-wave sleep via the ventral pallidum (VP) in the basal forebrain. Their findings reveal a prominent contribution of this indirect pathway to sleep control associated with motivation (Oishi *et al., Nat Commun*, in revision).

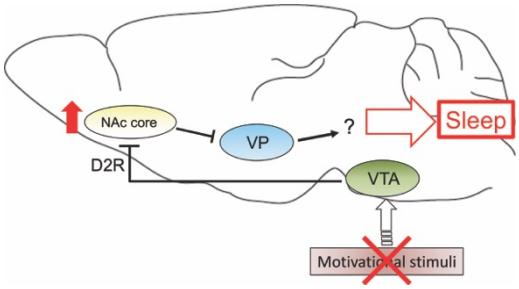


Figure 4. Novel brain circuit for sleep control by motivated behavior. In the absence of motivational stimuli, NAc neurons induce sleep by depressing wake-promoting VP neurons in the basal forebrain.

This interpretation is consistent with other work in the lab showing that chemogenetic activation of ventral midbrain dopaminergic neurons, also known as ventral tegmental area (VTA) dopamine neurons, strongly consolidates wakefulness through dopamine D2 receptors (D2R), but not dopamine D1 receptors, suggesting a D2R-dependent arousal system in the midbrain (Oishi *et al.*, *Brain Struct Funct*, 2017). Interestingly, their findings also indicate that chemogenetic inhibition of VTA dopamine neurons does not affect wakefulness under baseline conditions, suggesting that VTA dopamine neurons do not always function to induce wakefulness. Consolidated wakefulness evoked by the VTA may occur in response to cognitive and emotional stimuli so that animals react appropriately to environmental changes. The NAc is a plausible candidate structure mediating VTA-evoked wakefulness as the NAc is strongly innervated by VTA dopamine neurons and expresses D2R. This novel mesolimbic brain circuit may explain the tendency to fall asleep in the absence of motivating stimuli, i.e., when bored. The tonic sleep drive by neurons in the NAc core may be inhibited by ongoing cognitive and emotional stimuli, but in the absence of such stimuli, i.e. under low dopamine conditions, may allow the brain to fall asleep by depressing firing of arousal circuits in the basal forebrain (Figure 4).

(4) The causal link between REM sleep, medial prefrontal cortex and the desire for sugary and fatty foods (Lazarus Lab)

Human sleep proceeds in cycles that consist of 4 stages, i.e, light sleep, sleep with occasional bursts of rapid waves, deep sleep and rapid eye movement (REM) sleep. A greater amount of deep sleep is prevalent earlier in the night, while the proportion of REM sleep increases in the two cycles prior to natural awakening. REM sleep is a unique phase of sleep in mammals that is closely associated with dreaming and characterized by random eye movement and almost complete paralysis of the body. It is not well understood what role REM sleep loss plays in affecting areas of the brain that control the desire to consume unhealthy foods. The prefrontal cortex (PFC) plays a role in judging the palatability of foods through taste, smell and texture. Moreover, persons who are obese tend to have increased activity in the PFC when exposed to high calorie foods. However, the precise role of the PFC in mediating

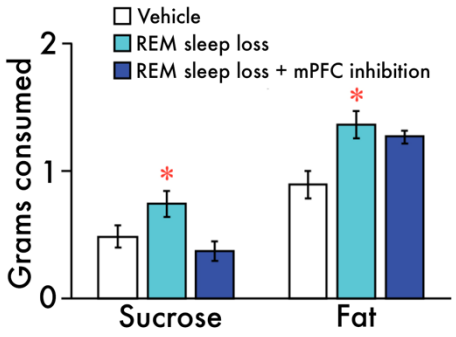


Figure 5. Chemogenetic inhibition of medial prefrontal cortex (mPFC) neurons reverses the effect of REM sleep loss on highly- palatable-foods consumption.

reward responses to highly palatable foods (HPF) after REM sleep deprivation is unclear.

The lab selectively reduced REM sleep in mice over a 25–48 hr period and chemogenetically inhibited the medial PFC (mPFC) by using an altered glutamate-gated and ivermectin-gated chloride channel that facilitated neuronal inhibition through hyperpolarizing infected neurons (McEown *et al.*, *eLIFE*, 2016). HPF consumption was measured while the mPFC was inactivated and REM sleep loss was induced. They found that REM sleep loss increased HPF consumption compared to control animals (Figure 5). However, mPFC inactivation reversed the effect of REM sleep loss on sucrose consumption without affecting fat consumption. Their findings provide, for the first time, a causal link between REM sleep, mPFC function and HPF consumption. In other words, the medial prefrontal cortex may play a direct role in controlling our desire to consume weight promoting foods, high in sucrose content, when we are lacking sleep, especially REM sleep.

(5) Cortical neural network function in wake vs slow-wave sleep (Greene/Vogt Lab)

Slow wave activity during slow wave sleep (SWS-SWA) is a critical indicator of both sleep need buildup and resolution consistent with a role in sleep function (Bjorness *et al.*, *J Neurosci*, 2016). We are employing *in-vivo* multi-electrode tetrode recordings and, in collaboration with Yanagisawa lab, functional imaging using sensors for calcium concentration (Jaafari *et al.*, *Adv Exp Med Biol*, 2015; Willadt *et al.*, *Front Cell Neurosci*, 2014).

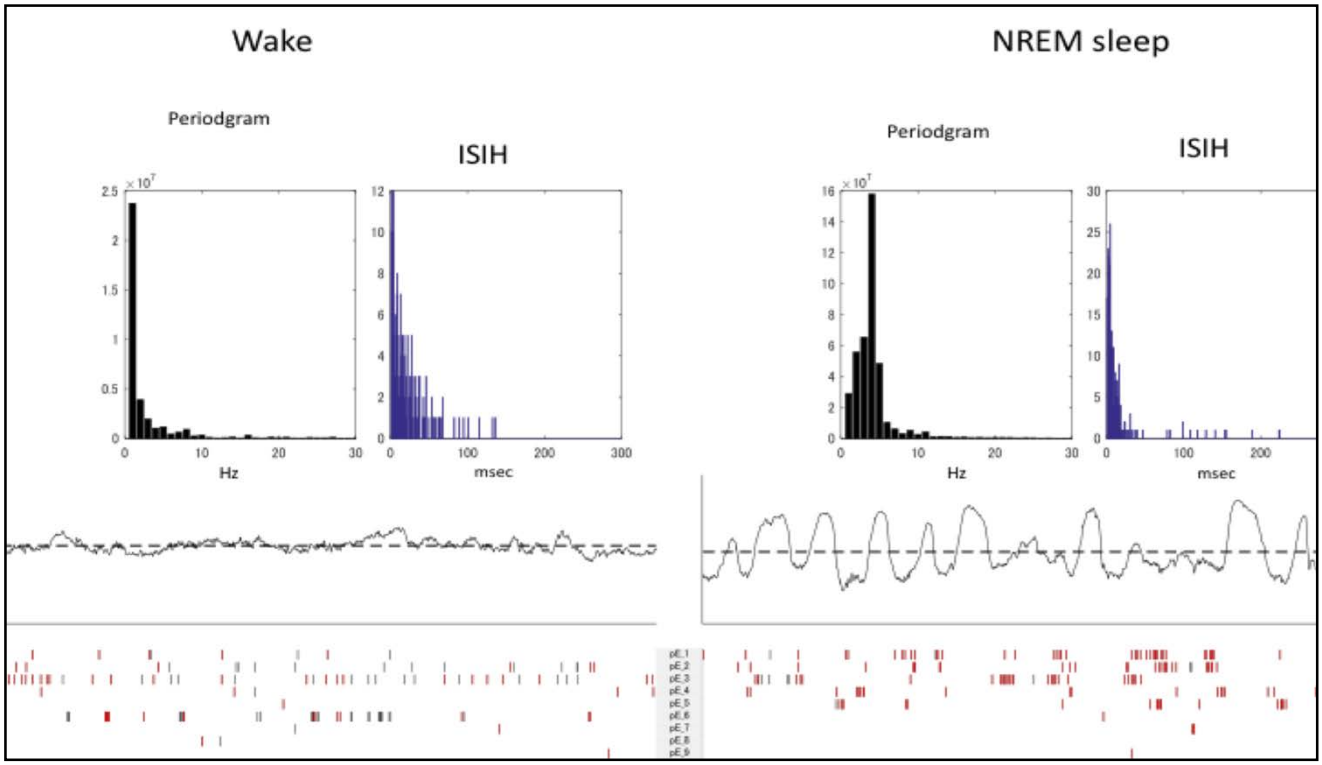


Figure 6. Top panels are FFT periodgram showing that low power during wake and 4 hz delta power peak during SWS. ISIH of all spikes shows that during nrem sleep indicate the burst-like distribution. The middle panels are the local field potentials showing prominent up/down states during SWS. Bottom panels show single unit activity taken simultaneously from 10 different units, n conjunction with the local field shown in the middle panel.

The use of tetrode recordings enables the analysis of identified single unit activity of ~4 single units across sleep states. This has already provided a novel understanding of single unit firing patterns during SWS-SWA compared to waking. Our preliminary recordings provided by Dr. Kaoru Ohyama, indicate that during up-states of SWA, the firing frequency, integrated over the entire up-state, is similar to that of waking but the neurons tend to fire in short burst like patterns throughout the up-state plateau.

We have also begun to employ a novel analytic approach to understanding network function that indicates dramatic shifts in network functional organization for ~4 single units recorded at the same time, from a low entropy wake state to a high entropy SWS state.

(6) Interaction of sleep and memory (Sakurai/Sakaguchi Lab)

We have aimed at applying basic knowledge of fear memory processing during sleep to establish new therapeutic strategies for PTSD. During this fiscal year, we have identified a critical time period where fear memory can be manipulated after learning (Fujinaka *et al.*, *Mol Brain*, 2016). Intriguingly, during this time period, it has been shown that memory can be manipulated during sleep by re-presenting stimuli such as sounds that were given during the original learning of that memory. These 'conditioned stimuli' may therefore reactivate the memory during sleep affecting the memory processing.

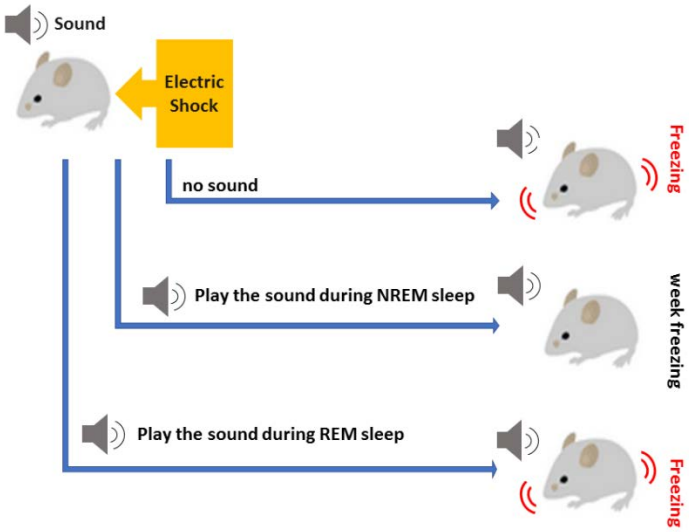


Figure 7. Mice established a fear memory by associating a sound with receiving a foot shock. This sound was then re-played during either NREM sleep, REM sleep or not at all. If mice had the sound replayed during NREM sleep they showed significantly weaker freezing than the other two groups and therefore an impairment of that memory.

To test this idea, a simple training protocol was used where mice were given a mild electric foot shock paired with a sound. By repeating the pairing of the shock and sound, mice eventually associated the sound alone, with receiving the unpleasant sensation. Mice were then allowed to sleep where they were split into groups with the sound being replayed during either NREM sleep, REM sleep, or not at all. The next day, the sound was played again. We identified that mice who previously received the sound during NREM sleep showed less freezing than either of the other two groups (Fig.7; Purple *et al.*, *Sci Rep*, 2017).

This research confirms previous findings showing that using auditory stimuli only seems to have an effect when replayed specifically during NREM sleep. Further, it has previously been shown, using different learning conditions to the current one, that stimuli during NREM sleep can enhance fear memory. Therefore, whether the memories are enhanced or impaired is very dependent upon how the memories are originally learnt. This finding could prove critical when applying this technique to relieve pathological fear memories such as those acquired in post-traumatic stress.

(7) Elucidation of the function of REM sleep (Hayashi Lab)

The function of REM sleep is one of the largest mysteries in neuroscience. To address the roles of REM sleep, we have been aiming to establish mouse models in which REM sleep can be manipulated. On FY2015, we identified neurons in the brainstem pons that strongly inhibit REM sleep. DREADD-activation of these neurons allowed manipulation of REM sleep for several hours, and as a result, it was revealed that REM sleep has a role to increase slow wave activity in the subsequent non-REM sleep (Hayashi *et al.*, *Science*, 2015). Slow wave activity is crucial for promoting neural plasticity. Thus, to reveal the roles of REM sleep at the individual level, we next aimed to establish mice in which REM sleep can be increased for a long time span (several days~months). First, we succeeded in identifying a group of neurons in the brainstem medulla that strongly promote REM sleep. DREADD-activation of these neurons largely increased REM sleep in the subsequent hours (Kashiwagi *et al.*, unpublished). Next, we constructed a viral vector in which neural activity can be increased chronically by expression of the bacteria-derived sodium channel "NaChBac" (Fig. 8A). Expression of NaChBac in REM promoting neurons resulted in a large increase in the amount of REM sleep. Moreover, this effect lasted for at least 6 weeks (Fig. 8B). The overall sleep architecture seemed fairly intact, and thus we believe this mouse is extremely useful for addressing the function of REM sleep. We are currently trying to address how neural plasticity is affected in this mouse. In addition, we are crossing this mouse with mouse models of

various neurological diseases to examine if increasing REM sleep can improve any of the diseases, including Alzheimer's disease and depression.

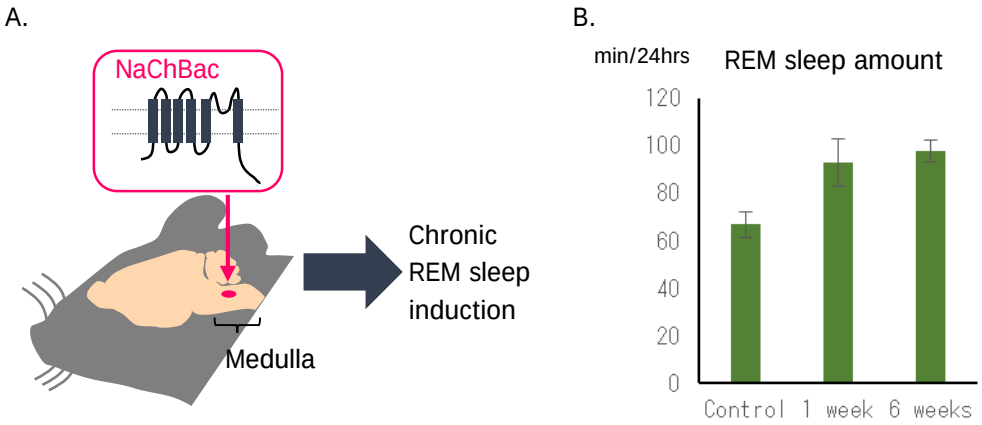


Figure 8. Success in increasing REM sleep for a long time span by expression of NaChBac in identified REM sleep-inducing brain area (Kashiwagi *et al.*, unpublished).

1-1-2. Progress and achievements in elucidation of molecular pathogenesis of sleep disorders and related diseases

Using genetically engineered mouse models, we study pathogenesis of various sleep disorders and related mental disorders including fear/anxiety disorders, in order to elucidate neuronal/molecular mechanisms and to find new drug targets.

(8) Establishment of a REM sleep behavior disorder (RBD) model — translational research using the orexin antagonist (Yanagisawa/Funato Lab)

REM sleep behavior disorder (RBD) is a REM parasomnia, which is characterized by defective REM atonia and accompanied by a considerably high probability for developing α-synuclein disorders later. To study the neuronal mechanisms and find new drug targets, a good genetic model of RBD would be highly useful. Based on our hypothesis that disrupted glycinergic system underlies RBD symptoms, we have systematically examined the glycine receptor (*Glra1*) gene-modified mice using the Cre-loxP system. We then succeeded in developing RBD model mice (*Glra1*$^{flox/flox}$*;ChAT-Cre*$^{Cre/wt}$), which displayed gross body and limb movements including jerking, kicking, punching and chewing during REM sleep. These RBD phenotypes were ameliorated by

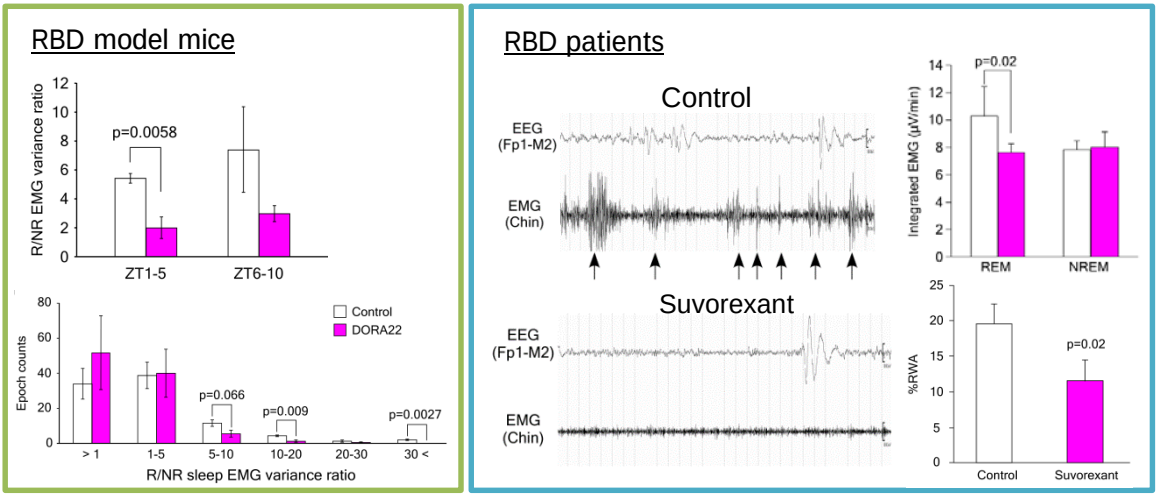


Figure 9. Orexin receptor antagonists rescue the RBD phenotype in our novel mouse model and human patients. (Left panels) Normalized average score of REM sleep EMG variance in RBD model mice after DORA22 (magenta) and vehicle (white) injection. (Right panels) Typical EMG and EEG traces, integrated EMG score, and % score of REM without atonia (RWA) in RBD patients; control (white) and suvorexant (magenta) in crossover studies.

clonazepam, a benzodiazepine often used clinically to treat RBD symptoms, further validating the model. Surprisingly, the dual orexin receptor antagonist DORA22 was also highly effective (Figure 9). Then, we immediately began collaborating with one of major sleep clinics in Tokyo to examine the clinical benefit of orexin receptor antagonists. In human studies, we found that suvorexant caused a significant reduction of motor activity during REM sleep in 78% of RBD patients. Thus, this is the first report to show that blocking orexin pathway could be a promising way to treat RBD (Hondo *et al.,* in preparation). Also, our RBD model mice would serve as a platform for screening novel drugs for treating RBD.

(9) Genetic and biochemical studies to understand the molecular basis of sleep, fear and relevant diseases (Liu, Yanagisawa/Funato Lab)

To understand the molecular basis of sleep drive, Sleep-wake homeostasis is maintained by generating a sleep need that accumulates during wakefulness and dissipates through sleep. We performed quantitative phosphoproteomic studies of whole mouse brains from behavioral (sleep-deprivation) and genetic (*Sleepy* mutant) models of sleep/wake perturbation. Our studies showed that sleep and waking drove opposite remodeling of brain phosphoproteome. *Sleepy* (*Sik3*$^{Slp/+}$) mice, due to a gain-of-function mutation of SIK3 kinase, exhibited constitutively higher sleep need and phosphoproteome imbalance mimicking sleep-deprived mice. Our results expose an unexplored phosphoproteome landscape of sleep-wake homeostasis and revealed novel insight into the molecular basis of homeostatic sleep drive. Taken together, our studies will identify specific molecular targets and animal models to advance treatments for sleep disorders, promoting resilience of neurological health and optimizing human aptitude and performance.

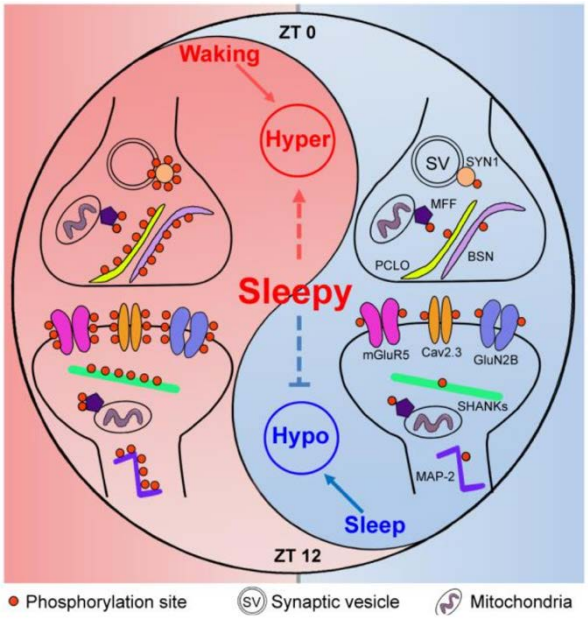


Figure 10. Concept of sleep-wake homeostasis driven by brain phosphoproteomes.

Furthermore, millions of people worldwide are afflicted by fear/anxiety disorders, including general anxiety disorders, general and specific phobia, obsessive compulsive disorders (OCD), and post-traumatic stress disorders (PTSD). There are few effective treatments for these devastating brain diseases because their genetic bases are unknown and there is a scarcity of good animal models for therapeutics development. We conducted, in collaboration with Drs. Yanagisawa/Funato lab, a dominant fear screen of ENU-mutagenized mice to identify heritable fearless and fearful mutant strains. In particular, we established a putative "fearful" mutant pedigree, named "*Popcorn*", that exhibited repetitive jumping up to 2,000 times/20 minutes in our fear assay. We identified the causative mutation for *Popcorn* in the intron of a previously uncharacterized gene by classical genetic intercross, positional mapping, and exome sequencing. We hypothesize that the "fearful" (e.g. *Popcorn*) mice may be genetically predisposed to anxiety disorders, PTSD, and depression, in a manner similar to the well- established "Onco(gene)mice" models that will develop cancer with age. Our studies may usher in a new era of molecular investigations into the fundamental principles of emotions and facilitate the studies and therapeutics development for human anxiety disorders that affect millions of people worldwide.

1-1-3. Progress and achievements in development of treatments for sleep disorders

We are developing new drug-candidate compounds modulating sleep/wake that are different from existing sleep-inducing agents or psychostimulants in their mechanism of action. We also develop methods for prevention and early intervention of sleep disorders and related diseases. This includes behavioral modifications to specific aspects of lifestyle, such as sleep, diet, exercise, and stress-coping. It is likely that these new drugs and intervention programs are not only effective for sleep disorders, but also for mood disorders and metabolic diseases. We will utilize such associations in order to elucidate the molecular mechanisms behind the association.

(10) Design and synthesis of orexin agonists (Nagase and Yanagisawa/Funato Lab)

The non-peptidic small molecules showing agonist activity for orexin receptors, especially for OX2R, have been expected as a chemotherapeutic agent for narcolepsy. Nagase's group have discovered the potent OX2R selective agonist YNT-185 (EC_{50} = 28 nM; selectivity ratio to OX1R over 100 times), and confirmed its significant anti-narcoleptic effects in murine narcoleptic model. However, YNT-185 was still remained to improve its lower blood-brain barrier (BBB) permeability. In 2015, we obtained a potent selective OX2R agonist YNT-1114 (EC_{50} = 31 nM) through the lead optimization processes for improvement of physicochemical properties. The *in vitro* BBB permeability assay by our collaborator indicated that YNT-1114 showed a good Pgp character and its *in vivo* pharmacological effects weren't observed obvious improvement from YNT-185.

In 2016, to obtain the preclinical candidate with improved ADMET properties, we focused on the discovery of more potent agonist and the scaffold hopping for satisfactory physicochemical properties. We synthesized > 600 compounds and evaluated their agonist activities on orexin receptors, and finally identified the most potent and selective OX2R agonist YNT-1757, which shows an activity (EC_{50} = 0.6 nM) in the same order of magnitude as that of endogenous orexin (EC_{50} = 0.3 nM) with moderate physicochemical properties. The structure hopping of YNT-1757 aiming at reduction of molecular weight (MW = 626.8) afforded YNT-1687 (EC_{50} = 59 nM, MW = 522.7) with desirable physicochemical properties. The evaluation of their in vivo efficacies is undergoing.

(11) Identification of somnogenic natural compounds and elucidation of their mechanisms (Urade Lab)

We are focusing on the identification of sleep promoting substances from foods or traditional medicines as well as elucidating their molecular mechanisms of action. In the past fiscal year, on the screening side of our research, we identified two new natural compounds exhibiting the ability to increase non-REM sleep in mice: triethylene glycol, an active component of Ashwagandha (*Withania somnifera*) leaves (Kaushik *et al.*, *PLoS One*, 2017) and Japanese sake yeast (*Saccharomyces cerevisiae* sake) (Nakamura *et al.*, *J Sleep Res*, 2016).

We also extended our research on 3 previously identified molecules regulating sleep to understand their mechanisms of action and found out that saffron and crocin exhibited a neuroprotective activity (Soeda *et al.*, *Adv Neurobiol*, 2016), while zinc-rich food was able to improve sleep quality in healthy human subjects (Saito *et al.*, *Mol Nutr Food Res*, 2016). Finally, we developed a new antagonistic monoclonal antibody against an extracellular domain of mouse DP2 (CRTH2/GPR44) receptors for prostaglandin D2 (PGD2) (Nagata N *et al.*, *PLoS One*, 2017). PGD2 is a major regulator of sleep and we expect this new tool will help us to understand better the molecular mechanisms of PGD2 induced sleep.

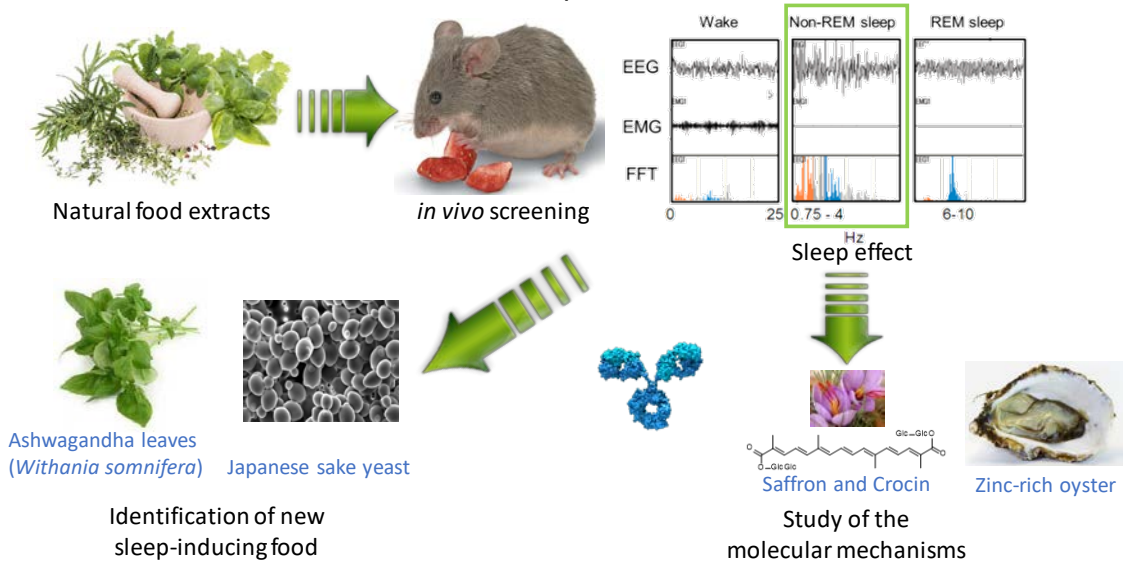


Figure 11. Screening for somnogenic natural compounds from foods and study of their molecular mechanisms of action.

(12) Relation between energy metabolism and sleep in human (Satoh Lab)

Human sleep is generally consolidated into a single prolonged period, and its metabolic consequence is to impose an extended period of fasting. Changes in sleep stage and homeostatic sleep drive following sleep onset may affect sleeping metabolic rate through cross talk between the mechanisms controlling energy metabolism and sleep. We measured the metabolic rate using whole room indirect calorimetry during sleep and demonstrated that energy expenditure differed significantly between sleep stages: wake after sleep onset (WASO) > stage 2, slow wave sleep (SWS), and REM; stage 1 > stage 2 and SWS; and REM > SWS. Similarly, carbohydrate oxidation differed significantly between sleep stages: WASO > stage 2 and SWS; and stage 1 > SWS. Energy expenditure and carbohydrate oxidation decreased during the first half of sleep followed by an increase during the second half of sleep. These results identified characteristic phenotypes in energy expenditure and carbohydrate oxidation indicating that sleeping metabolic rate differs between sleep stages.

1-2. Challenges to implement translational research bridging from basic biology/pharmaceutical science to experimental medicine

Implementation of the translational research is our challenge to establish “sleep science” (or to create the new interdisciplinary research domain). We aim to translate achievements in basic biology/pharmaceutical science into experimental medicine and/or clinical research. To enforce the translational research, our major efforts have been dedicated to increase and expand collaboration/research alliances with outside groups including groups in University of Tsukuba, the satellites, external research institutions, and even research groups in industries.

(1) Pre-clinical study of a CNS drug by a global pharmaceutical company

The purpose of the collaborative research with the company is to develop a CNS drug. IIIS is responsible for chemical structure optimization and evaluation of pharmacological activities, while the company evaluate brain penetrance (PgP activity, P_{app}), pharmacokinetics ([CSF]/[plasma], Fu%, $T_{1/2}$, AUC), cardiac ion channel activity, off-target activities (Pan labs) of selected compounds. At the end of the 2-year term collaboration, IIIS is supposed to supply one or two optimized lead candidates for the detail pre-clinical characterization. A researcher in the company strongly supports this collaboration project as satellite PI. This is a real translational research bridging from basic research to clinical development in collaboration with the company.

(2) Study of effects of the orexin antagonist on physical and cognitive functions (with Faculty of Health and Sport Science, University of Tsukuba)

The purpose of this study is to investigate effects of Suvorexant, a novel orexin receptor antagonist, on physical and cognitive functions after nocturnal forced-awakening condition in healthy male subjects. This is a randomized, double-blind, placebo-controlled and crossover PSG study to compare effects of the orexin antagonist with a $GABA_A$ agonist with similar PK profile, Brotizolam. On each trial, subjects receive one of the three treatments 15 min before bedtime. Ninety min after the administration, at the timing corresponding to T_{max} of Suvorexant and Brotizolam, they are forcibly awoken. Four-way choice reaction time (reaction ability), body sway with eyes opened and closed (static balance), Purdue pegboard test (dexterity), timed up and go test (agility and dynamic balance) and Stroop color-word test (executive function) are conducted before the administration and immediately after awakening. So far we have already conducted these experiments on 16 out of 30 subjects.

(3) Exploring the somnogenic target of thalidomide (with Tokyo Medical University)

Thalidomide was marketed as a safe non-barbiturate sedative and hypnotic in the late 1950's, but withdrawn from the market due to severe teratogenicity in humans. Chance discovery of immunomodulatory and antineoplastic effects led to its reintroduction for the treatment of leprosy and multiple myeloma. Cereblon, a component of the ubiquitin ligase pathway, was recently identified as the target for thalidomide's teratogenic and antineoplastic activities. However, mechanisms for the somnogenic action of thalidomide remain unknown. We studied synaptic transmission in the cortex to identify factors contributing to its sedative effect, and found that thalidomide depressed excitatory synapses, but did not affect inhibitory synaptic transmission. In

order to examine whether cereblon also mediates sleep-inducing effects of thalidomide, we generated gene knock-in mice possessing a thalidomide-resistant mutant allele of cereblon, and confirmed that cereblon-dependent ubiquitination was resistant to thalidomide in these mice. We then found that these mice are equally sensitive to thalidomide's somnogenic effects as compared with wild-type controls. Moreover, depression of cortical excitatory transmission was indistinguishable between wild-type and cereblon mutant mice. We thus postulate depression of excitatory synaptic transmission as a compelling mechanism for the sedative and hypnotic action of thalidomide. Moreover, our results indicate that thalidomide's teratogenic and somnogenic effects could be dissociable, and point to a strategy for discovering new sleep inducing drugs.

(4) Screening of true short sleeper individuals and families for human genetic studies (with Akita University Graduate School of Medicine)

Using a questionnaire, we recruited 12 candidates of short sleeper from 700 students in Akita University. All subjects are in good conditions without any medical problems and take no medicine influencing their sleep. We asked them to keep sleep diary for 8-19 days, and selected 7 subjects whose average full-sleep time is less than 5.5 hours. Further, we measured their sleep conditions for 8-14 days by using Actigraphy as well as sleep diary, and identified 6 subjects showing their average full-sleep times less than 5 hours. In addition, we are measuring the real sleeping time by using 2 channel PSG (EEG and EOG). Interestingly two cases among them were found to have a family history of short sleeper phenotype. In one of these families, the mother of the proband was also identified as short sleeper, the father had a normal sleeping time and the younger sister had long sleeping time. We now prepare for a study of human molecular genetics.

(5) Participation in a cohort study in terms of sleep studies (with Graduate School of Medicine Kyoto University)

In collaboration with Dr. Fumihiko Matsuda at Kyoto University, who coordinates the Nagahama cohort study with actigraphy-based sleep data from ~7,000 people, Sato/Tokuyama lab is; (i) looking at human SNPs within the genes identified in Yanagisawa's mouse forward genetic analysis, including the SIK3 (Sleepy) and NALCN (Dreamless) genes; (ii) conducting GWAS studies on daily sleep amounts and other sleep parameters in this population; (iii) ascertaining individuals with extreme sleep phenotype, such as "true short sleepers," especially familial cases.

(6) Development of algorithms and software for fully-automated sleep/wakefulness stages analyses from EEG and EMG data (with Center for Computational Science, University of Tsukuba)

We developed machine learning algorithms and software, named MASC, to automatically and accurately classify sleep/wakefulness stages of mice using EEG and EMG signals. We found several drawbacks of the algorithm named exFASTER, which we developed last fiscal year. MASC is designed based on the analysis of the drawbacks and features the following three approaches: (1) MASC makes the best of essential features that fully represent properties of the sleep/wakefulness stages, (2) MASC takes temporal state transition patterns into consideration, and (3) MASC employs the novel validation phase for classification results with low confidences to further improve the classification accuracy. MASC successfully achieved more than 95% accuracy, which is higher than the accuracy of exFASTER, in the stage classification of mouse EEG and EMG datasets. We are planning to proceed to fully-automated human sleep/wakefulness staging based on this study.

(7) Study of the effect of body-pressure dispersion of a mattress on sleep (with Nishikawa Sangyo Co.)

We study effects of body-pressure dispersion of a mattress on sleep. With 11 healthy young male individuals, we conducted a randomized crossover study of mattresses showing different body-pressure dispersions by means of polysomnography. A mattress commonly used in the medical institution and the nursing homes was used as the control, and a mattress designed for higher body-pressure dispersion (a functional mattress) was used for the intervention. In the crossover study, the episode duration of slow wave sleep was found significantly longer with the functional mattress than that with the control ($p = 0.013$). According to the OSA questionnaire answered after trials overnight, Factor IV (recovery from fatigue) was significantly better with the intervention than the control ($p = 0.028$). The prolonged slow wave sleep induced by the higher body-pressure dispersion may contribute to the better recovery from the fatigue in the sleep.

(8) A large-scale epidemiological survey for sleep on occupational fields (with High Energy Accelerator Research Organization, and MEDIROM Inc.)

While total sleep time decreases with age, labor environments as well as genetic variations have been also shown to exhibit large influences on sleep habits and needs from person to person. To study the environmental and genetic influences on sleep duration, we have planned a large-scale epidemiological survey for sleep on occupational fields. Not only a questionnaire but also the one week actigraphy records in each participant are used to estimate the real sleep duration in the general public. Since September 2016, more than one hundred have participated in this survey so far.

1-3. Challenges to contribute to innovation of drugs and early intervention of sleep disorders

We aim at contributing to solve the issues of sleep disorders, and the development of drugs and early intervention of sleep disorders is one of our major objectives, as discussed in 1-1. To implement and encourage broad use of new treatments we develop, alliances with health industries are essential. We thus intensively secure intellectual property rights of our research achievements and seek opportunities of collaborations and licensing to companies.

1-3-1. Patent applications in FY2016

We filed 4 patent applications as listed in the following table in FY2016. These inventions are all commensurate with developing new drugs of sleep and sleep-related disorders. Since the inauguration of IIIS in December 2012, 14 patent applications have been filed.

No.	Title of invention	Inventor	Date	Application number
1	Morphinane derivatives and their pharmaceutical use	Nagase H, Yamamoto N, Irukayama Y, Saito T, Nagumo Y.	Aug 8, 2016	Patent application 2016-155477
2	Morphinane derivatives	Nagase H, Fujii H, Saitoh A, Nakata E, Hirose M, Ooi S, Hayashida K	Aug 9, 2016	Patent application 2016-156049
3	Morphinane derivatives and their pharmaceutical use against diseases related with opioid δ agonist	Nagase H, Fujii H, Saitoh A, Nakata E, Hirose M, Ooi S, Hayashida K	Sep 16, 2016	Patent application 2016-203925
4	Morphinane derivatives	Nagase H, Yamamoto N	Feb 10, 2017	Patent application 2017-023444

1-3-2. Joint research with companies

(1) A global pharmaceutical company

Science FY2015, we started the joint research project targeting a CNS drug with a global pharmaceutical company. The ultimate goal is to deliver groundbreaking eradicative medicine to patients suffering from a CNS disease.

(2) Sumitomo Dainippon Pharma Co., Ltd.

From FY2016, we started exploratory research of treatment for REM sleep behavior disorder (RBD) using our original RBD model mouse with Sumitomo Dainippon Pharma. We screened and evaluated compounds of Sumitomo Dainippon Pharma using this model, which has been validated with the orexin antagonist as described in 1-1-2. As a result, we successfully found several drugs with different drug targets, which ameliorated the RBD phenotype. In 2016, we investigated in detail one of them, which caused a significant reduction of motor activity during REM sleep. This effect was not seen on EMG of other sleep stages in RBD model mice. Moreover, the effect of the drug was not seen on the amount of sleep/wakefulness and EMG power of sleep/wakefulness when the same examination was done in the wildtype mice (Ishibashi *et al.*, in prep.; patent application, in prep.). Our results demonstrate that the RBD model mouse is a valuable resource to find new drugs and drug targets of RBD symptom.

(3) Nippon Chemiphar Co., Ltd.

During the course of the screening of orexin receptor ligand, we discovered that nalfurafine, a kappa opioid agonist showed antagonistic activity for OX1R (IC_{50} = 415 nM) and the "Hit to Lead" study of nalfurafine led to a selective OX1R antagonist YNT-1336 (IC_{50} = 1.4 nM). Intraperitoneal administration of YNT-1336 dihydrosulfate salt in morphine-dependent mice significantly attenuated the expression of naloxone-precipitated morphine withdrawal. These results suggested that the morphinan skeletons which is promised to penetrate BBB and grateful ADMET properties can be useful not only for opioid receptors but also the other important receptors [No. pub]. We are starting collaboration with Nippon Chemiphar for optimization of YNT-1336.

(4) Lion Corporation

Y. Urade has continued the collaboration with Lion since his previous position at Osaka Bioscience Institute. The collaboration resulted in Lion's marketed product, the sleep-aiding supplement "Gussumin," which is made from Japanese sake yeast (Saccharomyces cerevisiae sake). The continued collaboration revealed that the orally available active ingredients of the supplement promote non-rapid eye movement sleep via adenosine A_{2A} receptor.

(5) Nishikawa Sangyo Co., Ltd.

In FY2015 we started the joint research with Nishikawa on the "effect of body-pressure dispersion of a mattress on sleep." Although experiences on a daily basis reaffirm the significant impact of bedding on sleep, given the lack of scientific research and validation, we aim to objectively evaluate the effect of body-pressure dispersion of a mattress on sleep. The first study with 11 young healthy male subjects has given an interesting result as shown in 1-2., and we plan to expand it to include both male and female elder subjects.

1-4. Self-assessments of our global standing using criteria proposed in the Center Plan

In the Center Plan, we proposed three criteria to be used for evaluating our global standing, 1) number of citations of published papers, 2) positions and scientific accomplishments of the alumni (as the long-term criteria), and 3) acquisition of competitive research funding. We would like to add another criterion, i.e., contribution to scientific community as editors and/or reviewers of scientific journals. The self-assessments with the criteria are as follows.

1-4-1. Number of citations of published papers, and contribution as reviewers and editors

Papers published by IIIS members are highly cited. The number of citations in 2016 (calendar year) drastically increased to over 350 times, 3-fold increase since establishment of IIIS. Those published in high impact journals (with impact factors > 10) in 2016, such as *Nature* (and its related journals), *Cell Metab*, *PNAS*, *J Clin Invest*, etc will also be highly cited in the following years. Those activities largely contribute to improving the visibility of IIIS.

PIs in the core group of IIIS actively contribute to scientific community through serving as editors and/or reviewers of scientific journals as shown in the following table. Five PIs are appointed as editors of 9 journals and all PIs serve as reviews of many journals including *Cell*, *Nature*, *J Neuroscience*, *PNAS*, *PLoS ONE*, *J Biol Chem*, *Sleep*, etc. The average number of reviewing in FY2016 reaches more than 11/person in FY2016.

#	PI	Reviewer		Editor
		Journal	Times	Journal
1	Yanagisawa	*Cell*, *Nature Neuroscience*, *Journal of Neuroscience*, *Annals of Neurology*, *Proceedings of the National Academy of Sciences*	8	—
2	Funato	*Nutrients*, *Journal of Neurochemistry*, *Cellular and Molecular Neurobiology*, *PLoS ONE*	4	—
3	Sakurai	*Journal of Neuroscience*, *Nature Reviews Disease Primers*	4	*Journal of Neuroscience*

4	Greene	*Proceedings of the National Academy of Sciences*, *Journal of Neuroscience*, *Neuropharmacology*, *eLife*, *Scientific Reports*, *Journal of Clinical Investigation*, *Cerebral Cortex*, *Journal of Neurodevelopmental Disorders*, *Current Opinion in Neurobiology*, *Biological Psychiatry*, *Neuropsychopharmacology*, *ENeuro*, *Biochemical Pharmacology*	30	*Hippocampus*, *Scientific Reports*, *Neurobiology of Sleep and Circadian Rhythms*, *Neuropharmacology*, *Current Molecular Pharmacology*
5	Liu	*Molecular Cell*, *Journal of Biological Chemistry*, *Proceedings of the National Academy of Sciences*, *RNA*, *Nucleic Acids Research*, *PLoS ONE*	39	*Journal of Biological Chemistry*
6	Nagase	*Bioorganic & Medicinal Chemistry Letters*, *Bioorganic & Medicinal Chemistry*, *ACS Chemical Neuroscience*, *MedChemComm*	6	*Current Topic in Medicinal Chemistry*
7	Sakaguchi	*Stem Cell Reports*, *Scientific Reports*	7	—
8	Lazarus	*Scientific Reports*, *Sleep*, *Journal of Neuroscience*, *Journal of Visualized Experiments*, *Molecular Nutrition & Food Research*, *Acta Pharmacologica Sinica*	9	*Frontiers in Neuroanatomy*
9	Hayashi	*Journal of Neuroscience*, *Neuroscience Research*	11	*Neuroscience Research*
10	Vogt	*Sleep*, *Frontiers in Neural Circuits*, *Scientific Reports*, *Journal of Neuroscience*	6	—
		Total	124	

1-4-2. Career tracks of ex-IIIS members (faculties, postdocs and students)

Only 4 years have passed since the establishment, there are not many alumni yet. Ex-IIIS members (faculties and researchers) acquired positions in the University of Tokyo (3 people), promoted to a professor position at Daiichi University of Pharmacy, or obtained a postdoc position in the University of Illinois Chicago after finishing Ph.D. at IIIS. Achievements and experiences at IIIS seem to positively influence the career paths of researchers, and number of the acquired positions outside IIIS is gradually increasing.

1-4-3. Securing competitive research funding

External funds acquired by IIIS core researchers, except for the Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST) project, have drastically increased as ¥1,520,000 in FY2012, ¥63,840,000 in FY2013 (42-fold increase), ¥177,930,000 in FY2014 (2.8-fold increase), and ¥282,070,000 in FY2015 (1.6-fold increase). In FY2016, the total amount of external funds acquired by IIIS core researchers reached ¥610,920,000. That was beyond ¥451,920,000 of the annual budget of the FIRST project in FY2012 and corresponded to 2.2-fold increase over the preceding year. The mean value of external funding per faculty in IIIS core group was ¥26,560,000, which is about 3.3 and 1.4 times higher than the averages of University of Tsukuba (¥8,000,000) and University of Tokyo (¥19,560,000) in the latest statistics, respectively. IIIS would be assessed becoming to a world-top level institute on this aspect as well. We continue the efforts to secure the same or even higher levels of external research funds after FY2016 as describing 5-2-1.

2. Advancing fusion of various research fields

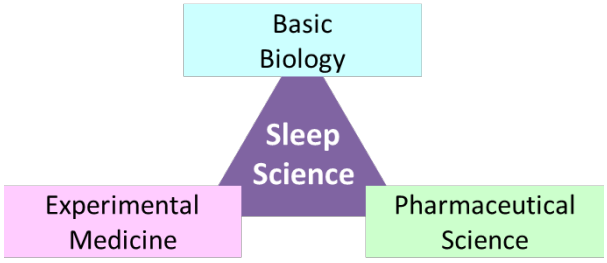
2-1. Interdisciplinary research domain to be created

The research objectives we aim to achieve are: 1) Elucidating the fundamental mechanisms of sleep/wake regulation, 2) Elucidating molecular pathogenesis of sleep disorders and related diseases, and 3) Developing treatments for sleep disorders, as shown 1-1. To achieve these objectives, there is a need for wide-ranging sleep research, covering a scope from basic biology such as neuroscience and molecular genetics to pharmaceutical science and further to experimental medicine, as shown in the right scheme. It is the new interdisciplinary research domain, “sleep science,” we aim to create by fusing 3 research fields.

2-2. Undertakings towards creating the new interdisciplinary research domain

A crucial driving force to create “sleep science” remains the leadership of the Center Director, who discovered orexin, *i.e.,* the hypothalamic neuropeptide functioning as an effector molecule to maintain arousal state, and is known as a pioneer of neuroscience of sleep. To foster the

interdisciplinary research under his leadership, the team of IIIS has been organized by PIs with sufficient expertise and achievements in 3 research fields, basic biology, pharmaceutical science and experimental medicine.



In FY2016, to reinforce research capabilities of the team, especially in basic biology such as neuroscience, T. Sakurai was invited from Kanazawa University and appointed as Vice Center Director as of April 1, 2016. His full-time appointment improved not only the research capabilities, but also the operational management of IIIS and the guidance for young researchers and graduate students.

Further, to enhance studies of experimental medicine and human physiology, M. Satoh's lab founded by the special collaborative research with Ibaraki Prefecture in 2015 was expanded as an endowed laboratory with the funds from Seven Dreamers Laboratory Inc. as of April 1, 2016. Along with the expansion of Satoh Lab, K. Tokuyama in Faculty of Health and Sport Sciences, University of Tsukuba, who was appointed as Collaborative PI in FY2015, was positioned as a joint PI for Satoh Lab on April 1, 2016. To provide Satoh Lab with state-of-the-art equipment for sleep and metabolism studies, a clinical sleep lab was newly established on the east side of the 3rd floor of the new research building in March 2017. A human metabolic chamber and a bed for clinical research are being installed in the lab.

To strengthen pharmaceutical science in the team, we have commenced collaboration with the global pharmaceutical company and appointed the leader of the collaboration on the company side, as a Satellite PI in the beginning of FY2016. It is very difficult for academic institutions to conduct studies necessary for the pre-clinical development, *i.e.*, pharmacokinetics, pharmacodynamics and toxicology due to large resources specific for them. To fulfil the missing functions in the pharmaceutical science in IIIS and complete the framework of sleep science, the collaboration with pharmaceutical companies is essential. Unfortunately, the leader left the company in August 2016, and a successor has taken over the leader of the collaboration.

2-3. Collaborative research among laboratories

Collaborative research among laboratories in IIIS is thus crucial to fuse 3 research fields and establish "sleep science." The internal collaborations are becoming more active recently, most likely due to the completion of the new research building, which makes the physical distance of the scientists closer than before. As a result, the number of articles by collaborative research drastically increased in FY2015 - 16. The Nature paper published by Funato *et al.* in 2016 is a good example of the successful internal collaborations, *i.e.,* the collaboration between Yanagisawa/Funato, Liu, Hayashi, S. Takahashi and J. Takahashi Labs. Cross-sectional research activities are expected to further develop in the future. Examples are listed below.

#	Article information	Labs involved
1	Irukayama-Tomobe Y *et al.* (in press) *Proc Natl Acad Sci* USA	Yanagisawa/Funato, Nagase, Sakurai, Greene/Vogt
2	Ogawa Y *et al.* (in press) *J Comp Neurol*	Liu, Yanagisawa/Funato, Vogt
3	Oishi Y *et al.* (2017) *Brain Struct Funct* doi: 10.1007/s00429-017-1365-7.	Lazarus, Yanagisawa/Funato
4	Kaushik MK *et al.* (2017) *PLoS ONE* **12**: e0172508.	Urade, Yanagiswa/Funato
5	Zhang BJ *et al.* (2017) *Neuroscience* doi: 10.1016/j.neuroscience.2016.09.053.	Urade, Lazarus
6	Ogawa Y *et al.* (2016) *eLife* doi: 10.7554/eLife.21055.	Yanagisawa/Funato, Hayashi
7	McEown K *et al.* (2016) *eLife* e20269.	Urade, Lazarus
8	Funato *et al.* (2016) *Nature* **539**: 378-383.	Yanagisawa/Funato, Liu, Hayashi, Takahashi S, Takahashi J
9	Deguchi Y *et al.* (2016) *Cell Rep* **17**: 2405-2417.	Urade, Lazarus
10	Okamoto K *et al.* (2016) *PLoS One* **11**: e0164716.	Yanagisawa/Funato, Sakurai
11	Chen L *et al.* (2016) *Neuropsychopharmacology* **41**: 2133-2146.	Urade, Lazarus
12	Hossain MS *et al.* (2016) *Sci Rep* doi:10.1038/srep32453	Yanagisawa/Funato, Takahashi J

13	Tsuneki H *et al*. (2016) *Endocrinology* **157**: 4146-4157.	Yanagisawa/Funato, Sakurai
14	Motoike T *et al*. (2016) *Proc Natl Acad Sci* USA **113**: 6023-6028.	Yanagisawa/Funato, Sakurai
15	Bjorness TE *et al*. (2016) *J Neurosci* **36**: 3709-3721.	Yanagisawa/Funato, Greene/Vogt
16	Fujinaka A *et al*. (2016) *Mol Brain* doi: 10.1186/s13041-015-0184-0.	Sakurai, Sakaguchi, Lazarus
17	Tsuneki H *et al*. (2015) *Endocrinology* **157**: 195-206.	Yanagisawa/Funato, Sakurai
18	Oishi Y *et al*. (2016) *J Vis Exp* **107**: e53678.	Urade, Lazarus
19	Nagahara T *et al*. (2015) *J Med Chem* **58**: 7931-7937.	Nagase, Yanagisawa/Funato
20	Cherasse Y *et al*. (2015) *Mol Nutr Food Res* **59**: 2087-2093.	Urade, Lazarus
21	Lee IT *et al*. (2015) *Neuron* **85**: 1086-1102.	Yanagisawa/Funato, Takahashi J
22	Kaushik MK *et al*. (2014) *Exp Neurol* **253**: 82-90.	Urade, Lazarus
23	Wang Z *et al*. (2014) *J Biol Chem* **289**: 31950-31959.	Yanagisawa/Funato, Liu
24	Kaneko K *et al* (2014) *Am J Physiol Regul Integr Comp Physiol* **306**: R265-272.	Urade, Lazarus
25	Soya *et al*. (2013) *J Neurosci* **33**:14549-14557.	Yanagisawa/Funato, Sakurai
26	Lazarus *et al*. (2013) *Curr Opin Neurobiol* **23**: 780-785.	Urade, Lazarus
27	Suzuki A *et al*. (2013) *Proc Natl Acad Sci* USA **110**: 10288-10293.	Yanagisawa/Funato, Greene/Vogt

3. Globalization of the institution

* Describe what's been accomplished or recognized in the efforts to raise the center's international recognition as a genuine top world-level research institute, along with innovative efforts proactively being taken in accordance with the development stage of the center, including the following points, for example:
- Efforts being developed based on the analysis of number and state of world-leading, frontline researchers; number and state of visiting researchers; exchanges with overseas entities
- Proactive efforts to raise the level of the center's international recognition
- Efforts to make the center into one that attracts excellent young researchers from around the world (such as efforts fostering young researchers and contributing to advancing their career paths)

3-1. Efforts to improve international recognition of the Center

3-1-1. State of top world-level researchers visiting and residing at the Center

The PIs at overseas satellites actively participate in research activities at IIIS. Q. Liu stayed in IIIS for 129 days during 5 visits to Japan in FY2016, and initiatively attended WPI-IIIS events, such as the Site Visit and WPI-IIIS Symposium. On the other hand, R. Greene stayed at IIIS for 28 days in 2 visits to Japan in FY2016, and gave us a lecture at the 85th WPI-IIIS seminar (held on August 3, 2016) and attended WPI-IIIS Site Visit and the International Symposium as well. They actively contribute to the management of IIIS by participating in the PI meeting every month, even when absent from the institute, via Skype from UTSW. Moreover, Joseph Takahashi, another Satellite PI in UTSW, visited IIIS to attend the Site Visit and meetings concerning the joint research and to give a lecture at WPI-IIIS seminar (held on August 9, 2016).

On matters of particular note, 5 outstanding foreign researchers were invited to WPI-IIIS Symposium (held on December 12, 2016 at Tokyo Conference Center) from abroad in order to introduce the latest achievements in sleep research and relevant fields to researchers in Tokyo/Tsukuba community. Additionally, we hosted 32 WPI-IIIS Seminar in FY2016, where we invited domestic and international researchers in sleep/neuroscience fields almost every other week; 13 speakers from overseas gave us lectures and the ratio of foreign researchers were 47% of the total seminar speakers in FY2016. Consequently, 108 seminars have been conducted since the inauguration in December 2012. Another thing especially worth mentioning is that the successor of the collaboration leader of the pharmaceutical company who was a WPI-IIIS Seminar speaker on January 25th has been requested to join IIIS as a satellite PI from the next fiscal year and will visit IIIS frequently. Refer to Appendix 5.

3-1-2. Hosting international meetings

IIIS has held international meetings every year since the establishment in 2012. In FY2016, we held the international symposium "The 5th IIIS Symposium / 32nd Wako Workshop" in Tokyo on December 12, 2016. As a new trial, this symposium was held in collaboration with a company, Wako Pure Chemical Industries. We invited 5 international and 6 domestic speakers, and about 200 people participated in and enjoyed active scientific discussions.

Wako Pure Chemical Industries Co., Ltd. has held workshops more than 30 times so far, but it was the first time for them to hold an international workshop in English, giving a great ripple effect in the industry as well. In addition, the joint meeting with the industry brought about a change of audience. Gathering people not only from academia but also from pharmaceutical/chemical companies, the meeting largely contributed to create novel networks and improve domestic/international visibility of IIIS.

Furthermore, the joint meeting had another good aspect: we succeeded in reducing the cost for holding the symposium. We were able to save WPI subsidies a lot and allocate the fund to other things in IIIS.

3-2. Efforts to attract young researchers to the Center

3-2-1. Employment and training of young researchers from abroad

To recruit female PIs and young researchers including postdoctoral fellows, IIIS actively engages in international open recruitment by placing job advertisements on websites such as the homepage of IIIS and jREC-IN jobsite. The total number of applications for postdoctoral fellow positions in FY2016 was 29, where 100% of the applicants were foreign researchers. As for Jr. PI, we had 9 applicants, whose 67% were foreign researchers. In addition to posting job advertisements, we have employed some brilliant researchers through the continuous efforts in international recruitment through networks of PIs. We regularly invite speakers from outside for the IIIS Seminar series and make use of the opportunity to look for Junior PI candidates in particular.

In FY2016, we employed no foreign scientists but succeeded in recruiting a female PI and a potential candidate of female PI for the appointment in FY2017. They are young talented Japanese researchers having studied abroad for a few years. We have offered a junior PI position to Dr. Sakiko Honjoh, who currently works in Tononi/Cirelli Lab at the University of Wisconsin-Madison, and she has accepted the offer. She plans to start in September 2017. We have recruited also Dr. Arisa Hirano from University of California San Francisco to Sakurai Lab starting April 2017. Her appointment to junior PI is under consideration.

On the other hand, we have accepted quite a few visiting foreign research fellows from overseas in FY2016, as shown in the following table. Most of them stayed at IIIS for sufficient time (6 months-2 years) to obtain skills and knowledge of sleep research, to advance their career paths.

Name of Visitors	Country	Instructor	Duration
Kristopher McEown	Canada	Lazarus	Nov 28, 2014～Nov 27, 2016
Hanan Bouaouda	Morocco	Lazarus	Apr 24, 2015～Apr 23, 2016
Linzi Conner	UK	Hayashi	Jul 22, 2015～Jul 14, 2016
Deependra Kumar	India	Sakaguchi	Oct 1, 2015～Sep 30, 2017
Ying Ho	Taiwan	Lazarus	Jul 11, 2016～Jul 29, 2016
Sunir Kumar Vimal	India	Urade	Jan 11, 2017～Jan 10, 2018
Zhenkang Chen	China	Liu	Mar 1, 2017～Aug 31, 2017
Ying Liu	China	Liu	Mar 1, 2017～Aug 31, 2017

3-2-2. Admission of foreign students

We have accepted 7 international students (4 graduates and 3 undergraduates) in FY2016 through various systems to accept foreign students to University of Tsukuba, as shown in the following Table. We accepted 2 students from France and Taiwan through the Tsukuba Short-term Study Program (TSSP), which allows even short-term trainees to use the student dormitory at a nominal fee and yet requires no entrance and tuition fees. As described in the WPI Self-Evaluation Report for Interim Evaluation, the bylaw for TSSP was revised in March 2016, according to our request to the Vice President in charge of student affairs, to extend a period of stay from 3 month to 1 year. We plan to accept more students as interns/trainees under this revised program in following fiscal year to hold a workshop of skills/experimental methods of sleep research.

In addition, we invited 2 students from University of Bordeaux under the Campus–In-Campus (CiC) initiative, which is aimed to enable sharing of educational and research resources and to contribute to the mutual enhancement of research and education capacities between University of Tsukuba and University of Bordeaux. On the other hand, 3 graduate students were approved for Research Assistants to be supported with monthly wages in FY2016. Taking advantage of these

acceptance systems, we will broaden up opportunities for training of foreign students.

Name	Status	Country	Instructor	Duration	Program
Matthieu Suire	Undergraduate	France	Lazarus	Jul 11, 2016～Aug 21, 2016	TSSP
Yen-Ling Sung	Undergraduate	Taiwan	Sakaguchi	Nov 1, 2016～Dec 2, 2016	TSSP
Solal Chauquet	Undergraduate	France	Lazarus	Jan 9, 2017～Jun 9, 2017	CiC
Thibault Bittar	Graduate	France	Urade	Jan 9, 2017～Jun 9, 2017	CiC
Sarowar Hossain	Graduate	Bangladesh	Yanagisawa	Apr 1, 2016～Feb 28, 2017	RA
Tingting Lou	Graduate	China	Liu	Oct 1, 2016～Dec 31, 2016	RA
Insung Park	Graduate	Korea	Satoh	Jan 1, 2017～Mar 31, 2017	RA

3-3. Other initiatives

After the completion of our new research building, requests to visit IIIS greatly increased. In FY2016, we accepted visits about 20 times from overseas and overseas universities, research institutes, companies and high schools, and more than 230 visitors enjoyed the tours. This is probably due to the improvement of visibility both in Japan and abroad, outcome of outreach activities and the influence of high reputation by personal communications.

An official neuroscience coursework was approved and opened by University of Tsukuba. This coursework was originally started voluntarily by the junior PI, Vogt and a graduate student, but it was highly evaluated because of its prominent quality. The faculty members in IIIS have high level of education and requested to give lectures from the host institute. All of those lectures are conducted in English, influencing the educational system of the university in which most of lectures are conducted in Japanese. Also, those educational experiences contribute to improving mentoring skills of PIs and other faculties.

4. Implementing organizational reforms

* If innovated system reforms generated by the center have had a ripple effect on other departments of the host institutions or on other research institutions, clearly describe in what ways.

4-1. Concept of organization/operation to be learned from “departments” in major US universities

The basic concept of the organization and the operation of IIIS involves creating a new style of research center at University of Tsukuba by learning from the merits and virtues in the organization of “departments” in major U.S. universities. We could implement the WPI’s mission and mandate aiming at “system reform” by selectively learning from the merits of department organizations in the U.S. academia. The strong leadership of the “Department Head” of a U.S. university would be the first feature we should pick up, and we thus assigned similar authority to the Center Director, Masashi Yanagisawa, who had served as a professor/principal investigator for 20 years at University of Texas Southwestern Medical Center (UTSW), one of the best biomedical campuses in the U.S. Other characteristics of this “department-style” organizational operation we would like to adopt include:

- Flexible and timely appointment of principal investigators (PIs) at the discretion of the Department Head within the budget limitation,
- Appointment of independent principal investigators regardless of their age and career stage with a necessary startup package,
- A flexible and dynamic allocation of the floor space for each laboratory considering the laboratory’s scale of funding, number of personnel and facility requirements, and
- Sharing of large facilities and capital equipment among laboratories.

Indeed, all of these characteristics are perfectly realized in the organization and operation of IIIS. There are four young PIs in the core group of IIIS. One of them has been PI since his appointment as an assistant professor in 2012 and promoted to an associate professor in 2015. The labs and offices in the new research building are designed as open labs and open offices, respectively, which enable the flexible and dynamic allocation of the floor space. The basic concept of the organization and the operation surely motivates young scientists and contributes to free interaction and open communication throughout IIIS, and hence vitalizes the whole research activities of IIIS.

Likewise, concerning the administration department, it is the basic concept to construct a support organization that allows researchers to focus on their research without being hampered by many administrative and miscellaneous tasks. To this end, we recruited Ph.D. scientists that have experiences of drug discovery and/or liaison officer in industries for three key positions in the administration, *i.e.*, Administrative Director, the leader of Research Planning, and the leader of Outreach Activity, to act as an interface between researchers (the Center Director and PIs) and the administrative staffs without scientific background in the administration as well as the university headquarters. This pre-empts the University Research Administrator (URA) system, the development of which has been focused on recently by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and which constitutes one of the IIIS characteristics.

4-2. System reforms and their ripple effect within the Host Institution

4-2-1. Integration of joint appointment system

The joint appointment system was introduced to University of Tsukuba in March 2014, for the purpose of enabling the Center Director to occupy concurrent posts at University of Tsukuba and UTSW. University of Tsukuba made the tenure appointment of Yanagisawa as of April 1, 2014. Subsequently, Liu was also employed from FY2014 under the joint appointment system, demonstrating, in University of Tsukuba, IIIS take the initiative in implementing the cross-appointment with outside research institutions and offer the model cases. Following to our cases, the number of the cross-appointment increased rapidly and there are 16 cases in the University now.

4-2-2. Enhancement of international collaborative research with foreign companies

IIIS started the collaborative research with the global pharmaceutical company in FY2015, and that was the first large international collaboration with foreign company for University of Tsukuba. We still continue this collaboration and have started the negotiation for extension.

In University of Tsukuba, 9 collaborations with foreign companies are underway now, and their research funding amounts to ¥211,990,742 in total, including ¥118,420,000 of our contribution. There was a huge increase in FY2015, and we believe that our initiative of the collaboration was the important turning point of the promotion of international collaborations with industries for University of Tsukuba.

5. Efforts to secure the center's future development over the mid- to long-term

* Please address the following items, which are essential to mid- to long-term center development:
- Future Prospects with regard to the research plan, research organization and PI composition; prospects for the fostering and securing of next-generation researchers
- Prospects for securing resources such as permanent positions and revenues; plan and/or implementation for defining the center's role and/or positioning the center within the host institution's institutional structure
- Measures to sustain the center as a world premier international research center after program funding ends (including measures of support by the host institution)

5-1. Prospects of advancing the Center's operation and project

5-1-1. Revision of composition of PIs toward the second-half of WPI project

At the end of the first half of WPI project, the research organization and composition of PIs are being reviewed and reconsidered in the course of advancing the research strategy based on the objectives outlined in 1-1.

In accordance with "Action required and recommendations" in the interim evaluation of IIIS by Program Committee, we continue and even strengthen the collaborations with outside clinical/human research teams to translate the animal studies into human, while we expand Satoh Lab working on human physiology as partners of the outside teams in the collaboration. As a part of this effort, recruitment for the open position of the satellite PI at Ibaraki Prefectural Medical Center of Psychiatry, who takes responsibility for clinical study as well as medical care work under the special joint research project with Ibaraki Prefecture, shall be made urgently.

An important element to be considered for the revision of the organization is organizational diversity, especially in terms of the gender of PIs, and we intend to appoint multiple female PIs in the core group. As the first step, after careful selection and following negotiation with several

candidates during FY2016, we have secured the appointment of Dr. Sakiko Honjoh starting September 2017, as mentioned in 3-2-1. We continue exploring possibilities of female appointment including the potential promotion of Dr. A. Hirano.

Organizational rejuvenation should be also considered to keep productivity towards achieving the objectives. Especially, the reappointment of 2 elder PIs, Y. Urade (63 years old) and H. Nagase (69 years old) has been carefully considered.

Urade actively screened for somnogenic substances from foods and natural products at his previous position in Osaka Bioscience Institute. After moving to IIIS, in collaboration with food and chemical companies, he continued the development of sleep-enhancing supplements based on the somnogenic substances and succeeded in bringing 3 products to market. He has also identified active ingredients in the natural substances and studied their mechanisms of somnogenic activities. It should be praised that Urade Lab has attained one of our objectives, to develop early intervention of sleep disorders, and achieved a degree of success in social implementation of research achievements. However, future prospects of his study are rather limited due to lack of a wider scope to extend the routine approach and translational capabilities in his Lab. We had carefully discussed this issue for more than one year and decided to limit the extension of his employment contract to September 2017.

On the other hand, Nagase actively pursues the drug discovery of orexin 2 receptor agonists and leads the collaboration with the pharmaceutical company, which is crucial to achieve the objective, the development of new treatments for sleep disorders. However, he is supposed to reach the retirement age of 70 in FY2017. Since his leadership and expertise in medicinal chemistry are essential for a success of the collaboration and hence indispensable for our pioneering drug discovery in academia, we decided to stipulate, following negotiations with the university management, an extension of the retirement age through the special assignment by the President, enabling to secure his employment and continuation of Nagase Lab by the end of the WPI program.

5-1-2. Revision of the target size of the core group

In the recent revision of the Center Plan after the Interim Evaluation, the target number of researchers including PIs was reduced from 115 to 62. The target number of research support staffs was also reduced from 40 to 20. As of March 31, 2016, in the core group of IIIS, there are 56 researchers including PIs, 14 research support staffs, and 19 administrative staffs including secretaries. In FY2016 the personnel expenses occupied 70% of the WPI subsidy, and there was no much room to increase researchers and research support staffs. We thus decided to change the target numbers.

5-1-3. Mentorship of graduate students

One of unique characteristics of IIIS is the association of many graduate students. In University of Tsukuba, the faculty organizations and the graduate schools are separated, and all faculties that would like to give lectures and to serve as official dissertation advisors have to be qualified by and registered in the graduate schools. All PIs in the core group have been qualified for mentoring graduate students and now accept 50 students from 4 graduate schools.

Since we expect further increases in the number of graduate students in future, we would like to offer them better supports in terms of scientific mentoring as well as mental care and financial support to be a good model of the top world-level research institute.

5-2. Future prospects of IIIS

5-2-1. Prospect for securing competitive research funding

The amount of external research funding that the IIIS core group acquired in FY2016 reached ¥611 million by great efforts of all the researchers and the research strategy/management team including the URA. We acquired the long-term research grants, e.g., JST CREST for FY2016-2021, Grant-in-Aid for Scientific Research on Innovative Areas for FY2016-2020, AMED Strategic Research Program for Brain Science for FY2016-2020, MEXT Regional Innovation Ecosystem Support Program for FY2016-2020, which would provide IIIS with a stable financial foundation. We will continue the efforts to secure the same or even higher levels of external research funds, and will start new collaboration from FY2017 with companies such as Suntory Holdings Ltd., Nippon Chemiphar Co., Ltd., etc. We will continuously apply for other large-scale research grants, such as Grant-in-Aid for Specially Promoted Research at JSPS, Model R&D Project in Alliance for

Knowledge Integration/Application among Industry, Academia and Government at MAFF, Cyclic Innovation for Clinical Empowerment at AMED, etc. The continuation of joint research with the pharmaceutical company is under negotiation.

5-2-2. Positioning of IIIS in the mid-term plan of University of Tsukuba

During the third mid-term plan of University of Tsukuba starting from FY2016, the university aims to develop a globally unrivaled frontier research of 2 objectives, *i.e.,* research to deeply seek truth and research for application contributing to society, in wide-ranging disciplines and research fields. To realize this objective, the university will make a plan of reorganization/restructuring/ merger of all research centers and implement it during the period of the 3rd mid-term plan. IIIS is positioned as a pioneering model of the forefront research organization the mid-term plan targets.

5-2-3. Support by the Host Institution

University of Tsukuba has provided IIIS with various resources as operational and financial supports. The provided supports are equal to or greater than the supports planned in the Center Plan proposed in the application for the WPI program as following;

1) University of Tsukuba established the Organization for the Support and Development of Strategic Initiatives (formed by the President and Vice-presidents), and IIIS receives ¥10 million for management expenses as the support from the Organization every year.
2) The Department of Research Promotion, as a counterpart in the university headquarters to IIIS, supports various office procedures including the applications for competitive funding.
3) The University supported ¥1.8 billion for the costs of new research building, facilities, equipment, exterior, landscaping including a parking lot and moving from temporary labs distributed among 4 places in the University campus.
4) The University supports most of the personnel cost of Vice Center Director, Sakurai.
5) The University delegates 3 university personnel to the administrative positions, including Vice-Administrative Director, in the key areas of general affairs and accounting. Since July, 2015, a URA has been also assigned to the Research Strategy and Management team.
6) IIIS rents for ¥70 million/year a part of the new research building (2,000 m^2) that was expanded by the university funds, while the University bore ¥84 million of utility costs of IIIS building in FY2016.

5-3. Measures to sustain the center as a World Premier International Research Center after program funding ends

In the application for WPI program, University of Tsukuba committed itself to maintain IIIS as a permanent organization of the university even after the end of the program implementation period. The University President and Vice President for Research have been confirming this commitment at every program committee meeting.

5-3-1. Tenure positions of PIs

In the third mid-term plan of University of Tsukuba, it will set out a strategic framework of research resources over the entire university and plans to reallocate it, based on evaluation of research activities/achievements. Tenure positions will also be subjected to the reallocation. The President, University of Tsukuba, Dr. Nagata has committed himself to offer a tenure position to the PI that produces sufficient research achievements in IIIS by using the planned reallocation system, so that IIIS will survive as a World premier international research center beyond the end of the WPI program implementation period. As specific measures, the Vice President for Research and Vice President for Personnel Affairs are discussing how to qualify PI to be offered a tenure position at the end of the program.

5-3-2. Establishment of IIIS-TLO

We are considering a system whereby license revenues of the intellectual property rights created by IIIS could be directly used to offset partially the costs of operating the Center, as one of potential measures to ensure the continuous operation of IIIS after the completion of the WPI program. One of options of the specific method for implementing this idea is to establish a

company to manage the IP rights and promote licensing them to industries (tentative name: IIIS-TLO). Actually, we started discussion with a few companies on the conditions of the licensing in FY2016. We now discuss feasibility of this method with the university administration including the consulting lawyer.

5-3-3. Implementation of the future expansion space (the south side of the 4th floor of IIIS Building)

In the next few years, we aim at implementation of the future expansion space in IIIS building, located on the south side of the 4th floor. We will be attracting open-innovation drug discovery lab sponsored by pharmaceutical companies, or hosting a research group of the JST Basic Research programs such as ERATO to the future expansion space, as a part of our efforts to obtain major research funds or grants.

6. Others

* In addition to the above 1-5 evaluation items, only if there is anything else that deserves mention regarding the center project's progress, please note it.

6-1. Characteristic outreach activities

Aggressive outreach activities, conducted at the Super Science High School (SSH) Annual Research Meeting and other events mainly targeting high school students, resulted in the regular visits by several high schools. Facing the advanced research activities at IIIS, many students decided to aim for basic research in the future. Additionally, a school in Kyushu was attracted with our sleep studies after the visit, and started their own sleep studies using sleep surveys and actigraphs for the entire school, introducing a nap time after lunch every day. We believe that our activities have huge ripple effects even on young generations. Some of those students visiting IIIS wish to enter our university, and we expect that they could greatly contribute to expand the base of science.

6-2. Further facility development

Since the completion of the IIIS building in June 2015, the development of the facility has been continuously moved forward.

The human metabolic chamber with the most advanced O_2/CO_2 analysis system, a bed and an organic EL lighting system is being installed to the clinical sleep lab on the 3 floor of which interior finish work was completed in March, 2017.

During the same period, we also made a major upgrade of our IT infrastructure, including servers, firewalls, and network switches, which were centralized in a newly dedicated room. The series of equipment offer building databases, storing experiment data, and hosting websites, as well as accessing Internet and Intranet, for free to all the members, enabling us to accelerate our collaborative research within IIIS and also allowing better and secure IT services.

As continuous collaboration with the School of Art in the university, another artwork has newly been placed on the pathway to the main entrance of the building and it attracts people's attention.

7. Center's response to the site-visit report

* Transcribe each item from the "Actions required and recommendations" section and note how the center has responded to them. However, if you have already provided this information, please indicate where in the report.

1. *Although genes involved in sleep are identified, details of their signal transduction pathways remain to be elucidated. Further identification of molecular targets will facilitate development of sleep-related drugs. The PIs in IIIS are quite familiar with physiological studies, but not so familiar with intracellular signal transduction. Because they continue the forward genetic studies to understand how sleep and fear are controlled at the molecular levels, they will need the help of groups familiar with intracellular signal transduction after identifying the causal genes to dissect their functions.*

Our discovery of *Sleepy* and *Dreamless* mutants was published on Nature this fiscal year, and it covers some characterizations of the gene products. Anchoring this milestone paper as a starting

point, we will further explore the intracellular signal transduction pathways underlying sleep/wake regulation and challenge to solve the entire neural network regulating sleep.

2. *For identification of human genes in sleep disorders by cohort studies, collaboration and advice by clinicians and epidemiologists are needed. IIIS should keep collaborating with clinical and human research teams to translate animal studies into humans.*

Many collaborative human studies are ongoing, as described in 1-2., and we will continue those efforts to translate animal studies into humans. Also we are implementing the human physiology lab in our building and Sato/Tokuyama Lab is setting up the suite for human sleep studies, as shown in 2-2. and 6-2.

3. *In addition to the initial established satellite PIs, additional senior satellite PIs have been included. Even in satellite PIs, three keywords of "young", "female", and "non-Japanese" may be important in addition to their scientific level.*

We have recruited 2 female satellite PIs, C. Green in University of Texas Southwestern Medical Center, and Y. Dan in University of California Berkeley. We continue to look for young, female, and non-Japanese researchers qualified for satellite PIs.

4. *Female PIs should definitely be recruited because the ratio of female researchers is more than 40% in FY2015. We do not understand why the final goals of the female ratios are set lower than they were in FY2015 (Appendix 5-2). Because IIIS has identified a good candidate female PIs, we hope that the candidate will join the institute soon.*

As descried in 3-2-1. and 5-1-1., we have decided to recruit a female researcher as a junior PI in the core group. Furthermore, one female faculty member newly hired in IIIS from April 2017 may be promoted to junior PI position in the near future. We would recruit even more female researchers as PIs, subjected to availability of good candidates. The final goal stated in the Appendix of the previous year report simply reflected the initial plan in the WPI application, and we have changed it in the revised version of the proposal.

5. *The addition of a foreign national to the administrative staff should be considered when positions become vacant due to staff turnover.*

We understand the importance of non-Japanese staff member in the administration office. However, many of those administrative works include communication with the university management and administration in the headquarters and prominent ability of speaking Japanese is also important. It is not an easy task to find out fully bilingual foreign nationals, although we continue to seek a foreign national candidate.

6. *Young IIIS researchers should be encouraged to present their work at international scientific meetings to enhance the global impact of IIIS.*

Although it was not clearly mentioned in the director's presentation at the site visit, young (non-PI) faculties, researchers, students have been actively presenting their works at international conferences. IIIS will keep encouraging young scientists to join international meetings to enhance global visibility.

7. *IIIS should create more clear mentorship programs, and delineate better exit or promotion pathways for the various investigators. This was lacking.*

All junior PIs are paired up with senior PIs for direct mentoring. This system is not one-on-one basis and all PIs are closely, reciprocally interacting. Takeshi Sakurai officially joined IIIS as a full-time Vice Director, and this would enhance the mentorship more.

World Premier International Research Center Initiative (WPI)
Appendix 1 FY2016 List of Center's Research Results and Main Awards

A. Refereed Papers

- List only the Center's papers published in 2016. (Note: The list should be for the calendar year, not the fiscal year.)

(1) WPI papers

List papers whose author(s) can be identified as affiliated with the WPI program (e.g., that state the name of his/her WPI center) (Not including papers whose acknowledgements contain the names of persons affiliated with the WPI program.)

Order of Listing

1. Original articles
2. Review articles
3. Proceedings
4. Other English articles
5. Articles written in other than English

(2) Method of listing paper

- List only referred papers. Divide them into categories (e.g., original articles, reviews, proceedings).
- For each, write the author name(s); year of publication; journal name, volume, page(s), and article title. Any listing order may be used as long as format is the same. (The names of the center researchers do not need to be underlined.)
- If a paper has many authors (say, more than 20), all of their names do not need to be listed.
- If the papers are written in languages other than English, divide them into language categories when listing them.
- Assign a serial number to each paper to be used to identify it throughout the system.

(3) Submission of electronic data

- In addition to the above, for each paper provide a .csv file output from the Web of Science (e.g.) or other database giving the paper's raw data including Document ID. (Note: the Document ID is assigned by paper database.)
- These files do not need to be divided into paper categories.

(4) Use in assessments

- The lists of papers will be used in assessing the state of WPI project's progress in FY 2016.
- They will be used as reference in analyzing the trends and states of research in all the WPI centers, not to evaluate individual researcher performance.
- The special characteristics of each research domain will be considered when conducting assessments.

(5) Additional documents

- After all documents, including these paper listings, showing the state of research progress have been submitted, additional documents may be requested.

WPI papers

(1) Original Articles

1. Funato H, Miyoshi C, Fujiyama T, Kanda T, Sato M, Wang ZQ, Ma J, Nakane S, Tomita J, Ikkyu A, Kakizaki M, Hotta-Hirashima N, Kanno S, Komiya H, Asano F, Honda T, Kim SJ, Harano K, Muramoto H, Yonezawa T, Mizuno S, Miyazaki S, Connor L, Kumar V, Miura I, Suzuki T, Watanabe A, Abe M, Sugiyama F, Takahashi S, Sakimura K, Hayashi Y, Liu QH, Kume K, Wakana S, Takahashi JS, Yanagisawa M (2016) Forward-genetics analysis of sleep in randomly mutagenized mice. *Nature* **539**(7629): 378-383. doi:10.1038/nature20142

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127. Matsuzaka T, Shimano H (2016) Novel role for the CRTC2 in lipid homeostasis. *J. Diabetes Investig*.

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B. Invited Lectures, Plenary Addresses (etc.) at International Conferences and International Research Meetings

- List up to 10 main presentations during FY2016 in order from most recent.
- For each, write the lecturer/presenter's name, presentation title, conference name and date(s)

1) Hiroshi Nagase, "The science and the development of non-addictive opioid receptor agonists", 76th FIP World Congress of Pharmacy and Pharmaceutical Sciences 2016 (Buenos Aires, Argentina), Aug 30, 2016

2) Yu Hayashi, "Why Do We Need Sleep?", 15th Japanese-American Kavli Frontiers of Science Symposium (Irvine, USA), Dec 2-4, 2016

3) Michael Lazarus, "Why do we fall asleep when bored? - The role of the nucleus accumbens in sleep-wake regulation", 23rd Congress of the European Sleep Research Society (Bologna, Italy), Sep 13-17, 2016

4) Yoshihiro Urade, "Orphan Drug Development for Duchenne Muscular Dystrophy by Protein Crystallization in Space", 67th International Astronautical Congress (Guadalajara, Mexico), Sep 27, 2016

5) Joseph Takahashi, Keynote Address, Trainee Professional Development Day, Society for Research on Biological Rhythms (Palm Harbor, Florida), May 21 2016

6) Joseph Takahashi, "Molecular Basis of Circadian Clock", 62nd Annual International Meeting, Radiation Research Society (Big Island, Hawaii), Oct 16, 2016

7) Takeshi Sakurai, "Neural Circuits of Orexin Neurons: Interface of Systems of Emotion, Energy Homeostasis and Arousal", 30th CINP World Congress of Neuropsychopharmacology Satellite Symposium (COEX Convention Center, Korea), Jul 4, 2016

8) Masashi Yanagisawa, "Forward genetic analysis of sleep in mice", The Fourth Kyoto Course and Symposium on Bioinformatics for Next Generation Sequencing with Applications in Human Genetics (Kyoto, Japan), April 1, 2016

9) Masashi Yanagisawa, Invited Speaker, French-Japanese Symposium on Medical and Fine Chemistry (Tama, Japan), May 16, 2016

10) Masashi Yanagisawa, "Towards the mysteries of sleep: forward genetic analysis in mice", The Second Chile-Japan Academic Forum at Patagonia (Patagonia, Chile), Nov 8, 2016

C. Major Awards

- List up to 10 main awards received during FY2016 in order from the most recent.
- For each, write the recipient's name, name of award, and year issued.
- In case of multiple recipients, underline those affiliated with the center.

1) Masashi Yanagisawa, Medal with Purple Ribbon, 2016

2) Masashi Yanagisawa, BodyCap Medical Award for the Best Research Paper on Body Temperature

3) Joseph Takahashi, Peter C. Farrell Prize in Sleep Medicine, 2016

4) Yoshihiro Urade, Hot Topics Award: Japan Society for Bioscience, Biotechnology, and Agrochemistry,

2017

5) Tsuyoshi Saito, Encouragement Award for Young Scientist, University of Tsukuba, 2017

6) Yu Hayashi, Research Encouragement Award, The Japanese Society for Sleep Research, 2016

7) Yu Hayashi, The 26th Tsukuba Encouragement Prize, The Science and Technology Promotion Foundation of Ibaraki, 2016

8) Hiroshi Nagase, Highly Read Article of 2015 Award, *Journal of Medicinal Chemistry*, 2017

World Premier International Research Center Initiative (WPI)
Appendix 2　FY 2016 List of Principal Investigators

NOTE:
・Underline names of principal investigators who belong to an overseas research institution.
・In case of researchers not listed in the latest report, attach “Biographical Sketch of a New Principal Investigator”.

<Results at the end of FY2016>　　Principal Investigators Total: 22

Name (Age)	Affiliation (Position title, department, organization)	Academic degree specialty	Working hours (Total working hours: 100%)				Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
			Work on center project		Others				
			Research activities	Other activities	Research activities	Other activities			
Center director Masashi Yanagisawa (56)*	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Ph.D. Neuroscience, Pharmacology	75%	20%	4%	1%	December 2012	Usually stays at the center	
Takeshi Sakurai (52)*	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Ph.D., Neuroscience	40%	10%	20%	30%	April 2013	Usually stays at the center	
Hiromasa Funato (47)*	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba Associate Professor, Toho University	M.D., Ph.D. Neuroscience	40%	5%	25%	30%	December 2012	Usually stays at the center three times a week	
Yoshihiro Urade (63)*	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D. Biochemistry Neuroscience	45%	5%	45%	5%	October 2013	Usually stays at the center	

<Results at the end of FY2016> Principal Investigators Total: 22

Name (Age)	Affiliation (Position title, department, organization)	Academic degree specialty	Working hours (Total working hours: 100%)				Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
			Work on center project		Others				
			Research activities	Other activities	Research activities	Other activities			
Robert Greene (66)*	Professor, Department of Psychiatry, University of Texas Southwestern Medical Center,	M.D., Ph.D. Neuroscience	10%	0%	70%	20%	December 2013	a) visits center 3X/yr for ~2 weeks /visit b) Skype meeting with lab 1X/week c) attends (by Skype) PI meeting 1X/month d) participates in person with the annual IIIS symposium e) participates in person in annual Site Visit	Collaboration of ongoing research project at UTSW investigating role of adenosine in homeostatic sleep control
Qinghua Liu (45)*	Associate Professor, Department of Biochemistry, University of Texas Southwestern Medical Center	Ph.D. Genetics, Molecular Biology, Biochemistry	33%	2%	60%	5%	April 2013	a) Stays at the center for 3 weeks every 2-3 months, total 3-4.5 months/year; site visit, symposium b) Joins a videoconference from US >2 times a week c) attends (by Skype) PI meeting 1X/month	Accept young scientists to WPI center (10/period)
Hiroshi Nagase (69)*	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D. Medicinal Chemistry, Organic Chemistry	65%	0%	30%	5%	April 2013	Usually stays at the center	
Makoto Satoh (61)	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Ph.D. Sleep Medicine	55%	5%	25%	15%	April 2015	Usually stays at the center	
Ichiyo Matsuzaki (57)*	Professor, Faculty of Medicine, University of Tsukuba	M.D., Ph.D. Occupational Psychiatric Medicine, Space Medicine	5%	5%	60%	30%	March 2013	About 10% of effort. The remaining is allocated for Faculty of Medicine.	

<Results at the end of FY2016> Principal Investigators Total: 22

Name (Age)	Affiliation (Position title, department, organization)	Academic degree specialty	Working hours (Total working hours: 100%)				Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
			Work on center project		Others				
			Research activities	Other activities	Research activities	Other activities			
Hitoshi Shimano (57)*	Professor, Faculty of Medicine, University of Tsukuba	M.D., Ph.D. Endocrinology, Metabolism	10%	5%	55%	30%	March 2013	Usually stays at Faculty of Medicine	
Kumpei Tokuyama (63)	Professor, Faculty of Health and Sport Sciences, University of Tsukuba	Ph.D., Sports Medicine	20%	0%	40%	40%	April 2015	Stays at the center once a week Participates in the annual IIIS symposium Participates in annual Site Visit	
Akiyoshi Fukamizu (57)*	Professor, Tsukuba Advanced Research Alliance, University of Tsukuba	Ph.D., Molecular Biology	1%	1%	50%	48%	March 2013	Usually stays at the satellite center Started the collaboration with Chika Miyoshi (Yanagisawa/Funato Lab.).	
Satoru Takahashi (55)*	Professor, Laboratory Animal Resource Center, Department of Anatomy and Embryology, Faculty of Medicine, University of Tsukuba	M.D., Ph.D. Developmental biology	10%	10%	40%	40%	March 2013	Participates in generation of genetically modified mice by using CRISPR/Cas9 system at Laboratory Animal Resource Center	
Joseph Takahashi (65)*	Professor, Department of Neuroscience, University of Texas Southwestern Medical Center	Ph.D., Neuroscience	5%	0%	75%	20%	December 2012	Usually stays at the satellite center	Collaboration. Available to accept young scientists from WPI for collaborative projects.
Carla Green (54)*	Professor, Department of Neuroscience, University of Texas Southwestern Medical Center	Ph.D. Molecular Biology, Biochemistry, Circadian rhythms	2%	3%	90%	5%	March 2013	Usually stays at the satellite center	

<Results at the end of FY2016> Principal Investigators Total: 22

Name (Age)	Affiliation (Position title, department, organization)	Academic degree specialty	Working hours (Total working hours: 100%)				Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
			Work on center project		Others				
			Research activities	Other activities	Research activities	Other activities			
Yang Dan (49)*	Professor, Department of Molecular and Cell Biology, University of California, Berkeley	Ph.D., Neurobiology	3%	2%	85%	10%	April 2014	Usually stays at the satellite center	
Tetsuo Shimizu (64)*	Professor, Department of Neuropsychiatry, Akita University Graduate School of Medicine	M.D., Ph.D., Psychiatry	10%	5%	20%	65%	April 2013	Joins a video conference from Akita University once a month Participates in the annual IIIS symposium Participates in annual Site Visit	
Hitoshi Okamura (64)*	Professor, Graduate School of Pharmaceutical Sciences, Kyoto University	M.D., Ph.D. Chronobiology	3%	0%	67%	30%	July 2015	Usually stays at the satellite center Participates in annual Site Visit	
Kaspar Vogt (50)	Associate Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Ph.D. Physiology, Pharmacology, Neurobiology	80%	20%	0%	0%	February 2014	Usually stays at the center	
Michael Lazarus (47)	Associate Professor International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D. Neuroscience	95%	5%	0%	0%	April 2013	Usually stays at the center	
Masanori Sakaguchi (40)	Associate Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Ph.D. Neuroscience	95%	5%	0%	0%	January 2013	Usually stays at the center	

<Results at the end of FY2016> Principal Investigators Total: 22

Name (Age)	Affiliation (Position title, department, organization)	Academic degree specialty	Working hours (Total working hours: 100%)				Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
			Work on center project		Others				
			Research activities	Other activities	Research activities	Other activities			
Yu Hayashi (36)	Associate professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D., Neuroscience	70%	10%	10%	10%	April 2013	Usually stays at the center	

World Premier International Research Center Initiative (WPI)

Appendix 3-1 FY2016 Records of Center Activities

1. Researchers and center staffs, satellites, partner institutions

1-1. Number of researchers in the "core" established within the host institution

- Enter the total number of people in the columns below. In the "Researchers" column, put the number and percentage of overseas researchers in the < > brackets and the number and percentage of female researchers in the [ ] brackets.
- In the "Administrative staffs" column, put the number and percentage of bilingual staffs in the ( ) brackets.
- In the "Final Goal" column, enter the currently projected goal and the estimated date for achieving it [OO month, OO year].

	Goal set in the "Post-interim evaluation revised center project"	Results at end of FY 2016	Final goal (Date: March, 2022)
Researchers	62 < 21, 34%> [22, 36%]	56 < 18, 32%> [17, 30%]	62 < 21, 34%> [22, 36%]
Principal investigators	24 < 8, 33%> [4, 17%]	22 < 8, 36%> [2, 9%]	24 < 8, 33%> [4, 17%]
Other researcher	38 < 13, 34%> [18, 47%]	34 < 10, 29%> [15, 44%]	38 < 13, 34%> [18, 47%]
Research support staffs	20	14	20
Graduate students	68	50	68
Administrative staffs	19 (15, 79%)	19 (15, 79%)	19 (15, 79%)
Total	169	139	169

Other matters of special mention

- Enter matters warranting special mention, such as concrete plans for achieving the Center's goals, established schedules for employing main researchers, particularly principal investigators.
- As background to how the Center is working to mobilize/circulate the world's best brains, give good examples, if any, of how career paths are being established for the Center's researchers; that is, from which top-world research institutions do researchers come to the Center and to which research institutions do the Center's researchers go, and how long are their stays at those institutions.

Dr. Sakiko Honjoh, currently a researcher of University of Wisconsin–Madison will be joining the IIIS as a first female Junior PI from September, 2017.

1-2. Satellites and partner institutions

- List the satellite and partner institutions in the table below.
- Indicate newly added and deleted institutions in the "Notes" column.
- If satellite institutions have been established, describe by satellite the Center's achievements in coauthored papers and researcher exchanges in Appendix 4.

<Satellite institutions>

Institution name	Principal Investigator(s), if any	Notes
University of Texas Southwestern Medical Center	Joseph Takahashi, Carla Green, Robby Greene and Qinghua Liu	
Akita University	Tetsuo Shimizu	
University of California, Berkeley	Yang Dan	
Graduate School of Pharmaceutical Sciences, Kyoto University	Hitoshi Okamura	
A global pharmaceutical		

company		

< Partner institutions>

Institution name	Principal Investigator(s), if any	Notes
RIKEN BioResource Center, Tsukuba		
RIKEN Brain Science Institute		
Ibaraki Prefecture/Ibaraki Prefectural Medical Center of Psychiatry		
Center for Genomic Medicine, Kyoto University		
JAXA Space Biomedical Research Office		
Hoshi University		
National Cancer Center Hospital		Newly added in August, 2016
The Jikei University		Newly added in April, 2016

2. Securing competitive research funding

Competitive and other research funding secured in FY2016

Total: 610,918,808 yen

- Describe external funding warranting special mention. Include the name and total amount of each grant.

Grants and Endowments: 59,264,535 yen
Joint research, etc.: 99,654,940 yen
Commissioned research projects, etc.: 165,028,597 yen
Grants-in-Aid for Scientific Research, etc.: 286,970,736 yen

The acquired large-scale research grants for FY2016
JST CREST: 83,200,000 yen
Grant-in-Aid for Scientific Research on Innovative Areas: 108,979,000 yen
Grant-in-Aid for Scientific Research(S): 39,000,000 yen
AMED Strategic Research Program for Brain Science: 19,800,000 yen
Regional Innovation Ecosystem Program: 30,739,429 yen

3. International research conferences or symposiums held to bring world's leading researchers together

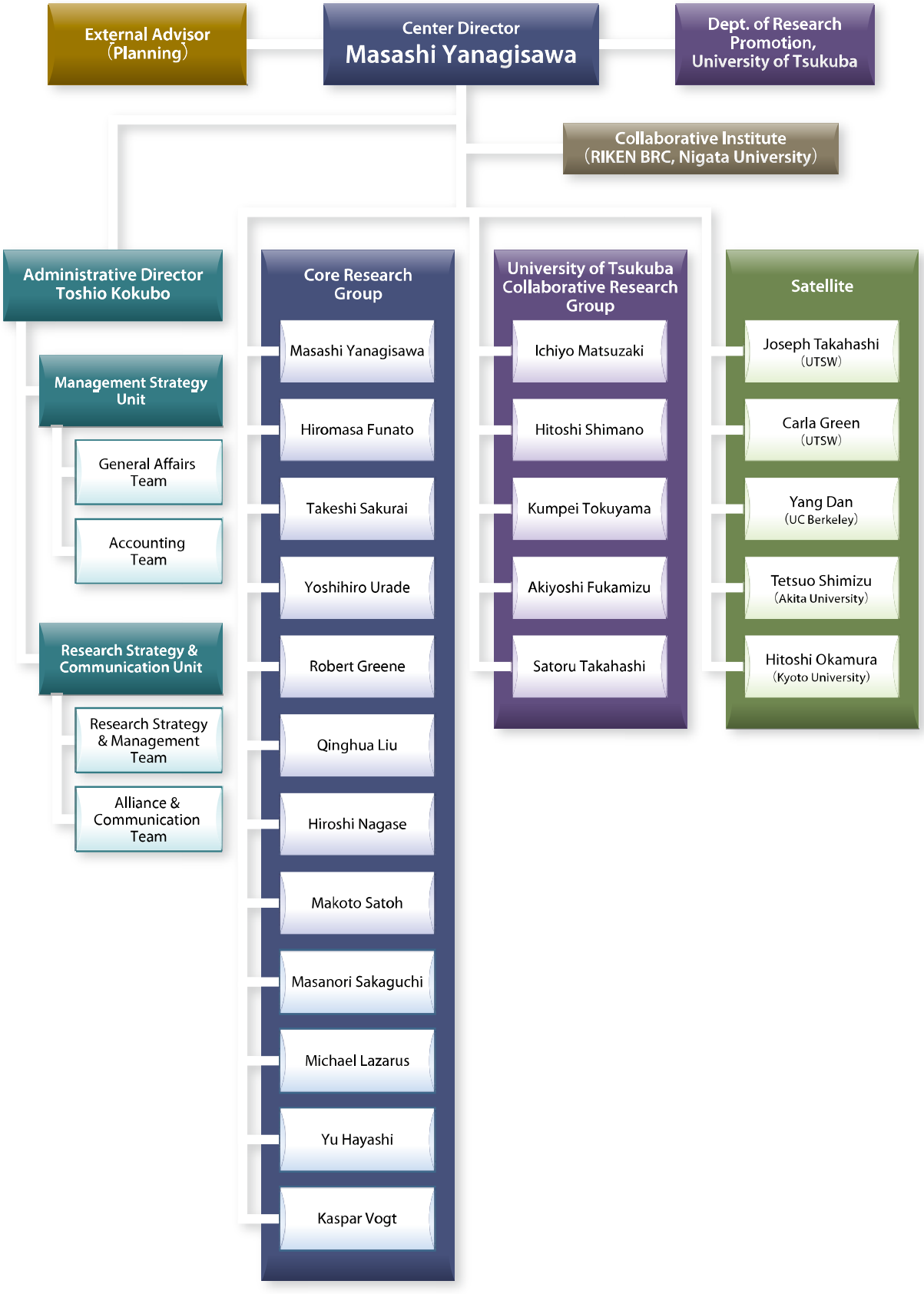
- Indicate the number of international research conferences or symposiums held in FY2016 and give up to three examples of the most representative ones using the table below.

FY 2016: 1 meeting

Major examples (meeting titles and places held)	Number of participants
The 5th Annual IIIS Symposium / The 32nd Wako Workshop	From domestic institutions: 182 From overseas institutions: 7

4. Center's management system

- Please diagram management system in an easily understood manner.
- If any changes have been made in the management system from that in the "Post-interim evaluation revised center project," please describe them. Please describe any changes made in the administrative director, head of host institution, and officer(s) in charge at the host institution (e.g., executive vice president for research)



5. Campus Map

- Please draw a simple map of the campus showing where the main office and principle investigator(s) are located.

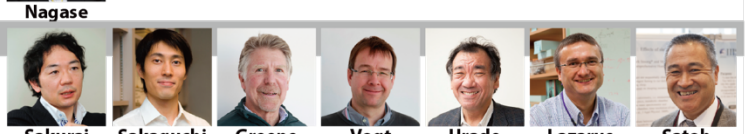
IIIS Building

5/6F Animal Facility (ARC Satellite)

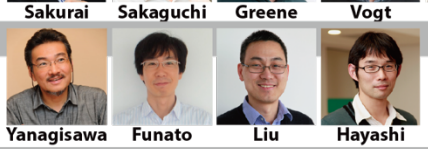
4F + Future Expansion Space


Nagase

3F

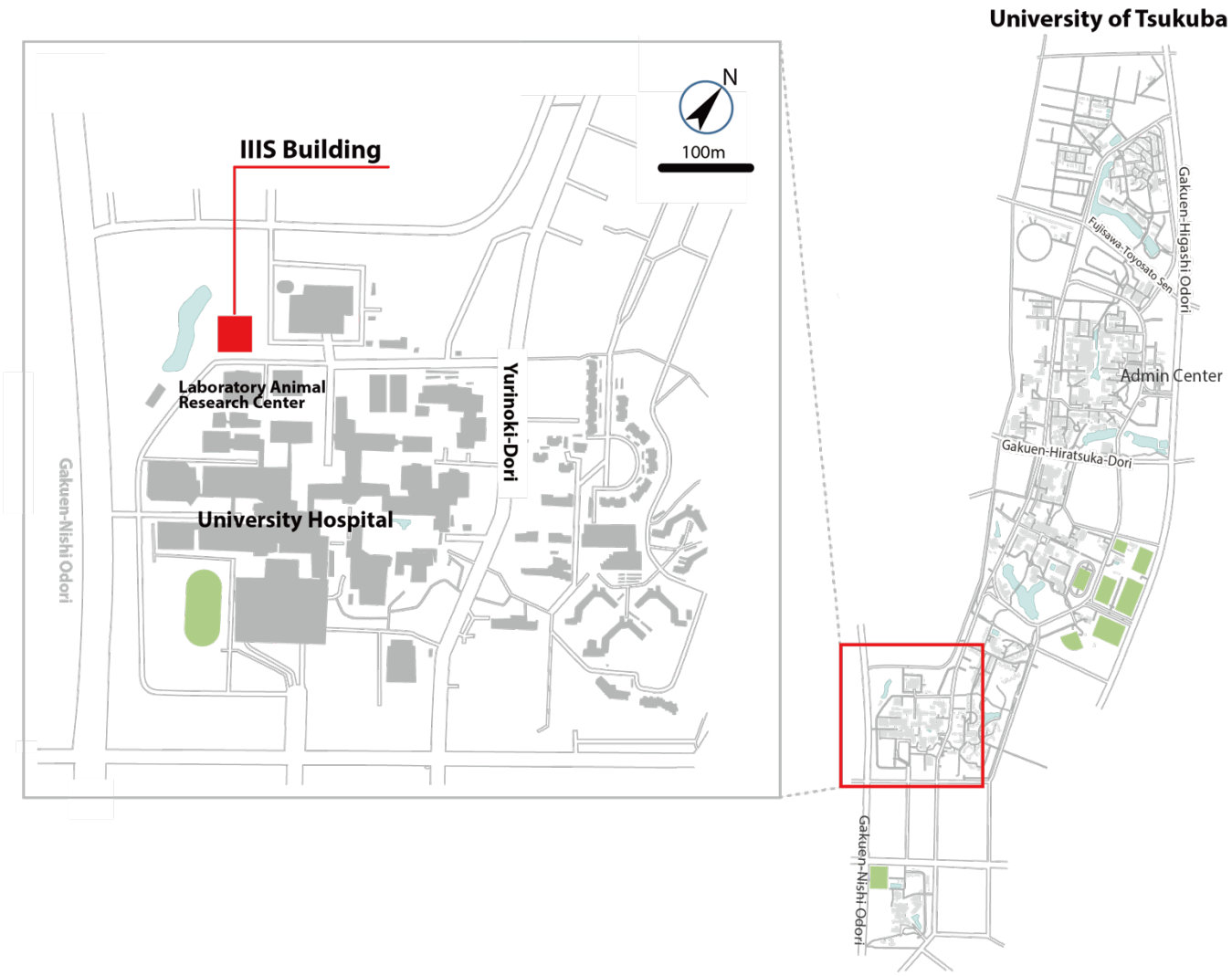

Sakurai Sakaguchi Greene Vogt Urade Lazarus Satoh

2F


Yanagisawa Funato Liu Hayashi

1F Admin Office, Auditorium, Hall, Lounge

Campus Map



World Premier International Research Center Initiative (WPI)

Appendix 3-2 6. Project Expenditures (the exchange rate used: 1USD= 100JPY)

1) Overall project funding

Cost Items	Details	Costs (Ten thousand dollars)
Personnel	Center director and Administrative director	39
	Principal investigators (no. of persons):6	64
	Other researchers (no. of persons):35	233
	Research support staffs (no. of persons):11	37
	Administrative staffs (no. of persons):14	70
	Total	443
Project activities	Gratuities and honoraria paid to invited principal investigators (no. of persons):0	0
	Cost of dispatching scientists (no. of persons):1	4
	Research startup cost (no. of persons):7	7
	Cost of satellite organizations (no. of organizations):2	21
	Cost of international symposiums (no. of symposiums):1	2
	Rental fees for facilities	70
	Cost of consumables	20
	Cost of utilities	80
	Other costs	31
	Total	235
Travel	Domestic travel costs	1
	Overseas travel costs	3
	Travel and accommodations cost for invited scientists (no. of domestic scientists):0 (no. of overseas scientists):1	1
	Travel cost for scientists on secondment (no. of domestic scientists):1 (no. of overseas scientists):0	1
	Total	6
Equipment	Depreciation of buildings	
	Depreciation of equipment	628
	Total	628
Other research projects	Projects supported by other government subsidies, etc.	
	Commissioned research projects, etc.	
	Grants-in-Aid for Scientific Research, etc.	
	Total	0
Total		1312

Costs (Ten thousand dollars)

WPI grant	539
Costs of establishing and maintaining facilities	0
Establishing new facilities	0
Repairing facilities	0
Others	0
Cost of equipment procured	21
Four lab bench with racks for storing chemicals	5
Data server	5
IVC cage for mice	6
Others	6

2) Costs of Satellites and Partner institutions

Cost Items	Details	Costs (Ten thousand dollars)
Personnel	Principal investigators (no. of persons):0	
	Other researchers (no. of persons):5	
	Research support staffs (no. of persons):0	
	Administrative staffs (no. of persons):0	
	Total	21
Project activities		
Travel		
Equipment		
Other research projects		
Total		21

World Premier International Research Center Initiative (WPI)
Appendix4 FY2016 Status of Collaboration with Overseas Satellites

1. Coauthored Papers

- List the refereed papers published in FY2016 that were coauthored between the center's researcher(s) in domestic institution(s) and overseas satellite institution(s). List them by overseas satellite institution in the below blocks.
- Transcribe data in same format as in Appendix 1. Italicize the names of authors affiliated with overseas satellite institutions.
- For reference write the Appendix 1 item number in parentheses after the item number in the blocks below. Let it free, if the paper is published in between Jan.-Mar. 2017 and not described in Appendix 1.

Overseas Satellite 1 (Total: 4 papers)

1) Funato H, Miyoshi C, Fujiyama T, Kanda T, Sato M, Wang ZQ, Ma J, Nakane S, Tomita J, Ikkyu A, Kakizaki M, Hotta-Hirashima N, Kanno S, Komiya H, Asano F, Honda T, Kim SJ, Harano K, Muramoto H, Yonezawa T, Mizuno S, Miyazaki S, Connor L, Kumar V, Miura I, Suzuki T, Watanabe A, Abe M, Sugiyama F, Takahashi S, Sakimura K, Hayashi Y, Liu QH, Kume K, Wakana S, Takahashi JS, Yanagisawa M (2016) Forward-genetics analysis of sleep in randomly mutagenized mice. *Nature* **539**(7629): 378-383. doi:10.1038/nature20142

2) Hossain MS, Asano F, Fujiyama T, Miyoshi C, Sato M, Ikkyu A, Kanno S, Hotta N, Kakizaki M, Honda T, Kim SJ, Komiya H, Miura I, Suzuki T, Kobayashi K, Kaneda H, Kumar V, Takahashi JS, Wakana S, Funato H, Yanagisawa M (2016) Identification of mutations through dominant screening for obesity using C57BL/6 substrains. *Sci Rep* **6**: 34253. doi:10.1038/srep32453

3) Bjorness TE, Dale N, Mettlach G, Sonneborn A, Sahin B, Fienberg AA, Yanagisawa M, Bibb JA, Greene RW (2016) An Adenosine-Mediated Glial-Neuronal Circuit for Homeostatic Sleep. *J. Neurosci.* **36**(13): 3709-3721. doi:10.1523/JNEUROSCI.3906-15.2016

4) Motoike T, Long JM, Tanaka H, Sinton CM, Skach A, Williams SC, Hammer RE, Sakurai T, Yanagisawa M (2016) Mesolimbic neuropeptide W coordinates stress responses under novel environments. *Proc. Natl. Acad. Sci.* U.S.A. **113**(21): 6023-6028. doi:10.1073/pnas.1518658113

Overseas Satellite 2 (Total: 0 paper)

2. Status of Researcher Exchanges

- Using the below tables, indicate the number and length of researcher exchanges in FY2016. Enter by institution and length of exchange.
- Write the number of principal investigator visits in the top of each space and the number of other researchers in the bottom.

Overseas Satellite 1: University of Texas Southwestern Medical Center

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2016	0	0	0	0	0
	0	0	0	0	0

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2016	2	6	1	0	9
	0	0	0	0	0

Overseas Satellite 2: University of California, Berkeley

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2016	0	0	0	0	0
	0	0	0	0	0

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2016	0	0	0	0	0
	0	0	0	0	0

World Premier International Research Center Initiative (WPI)

Appendix 5 FY 2016 Visit Records of World Top-caliber Researchers from Abroad

Researchers Total: 16

#	Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
1	Qinghua Liu	45	Department of Biochemistry, University of Texas Southwestern Medical Center International Institute for Integrative Sleep Medicine University of Tsukuba	Ph.D. Biochemistry Molecular biology	・Member of American Society of Biochemistry & Molecular Biology (2008- Present) ・Member of Editorial Board, Journal of Biological Chemistry (2012-Present) ・Damon Runyon Scholar Award Damon Runyon Cancer Research Foundation, New York (2005-2007) ・W. A. “Tex” Moncrief Jr. Scholar in Biomedical Research UT Southwestern Medical Center, Dallas (2004-2008) ・Alexander Wang Memorial Award for Excellent Biomedical Research Baylor College of Medicine, Houston(2000) ・John J. Trentin Award for Scholastic Excellence Baylor College of Medicine, Houston (1995)	2016 April (26 days) 2016 June (28 days) 2016 July (9 days) 2016 August (22 days) 2016 November (11 days) 2016 December (13 days) 2017 February (18 days) 2017 March (2 days)	Participation in site visit, symposium as principal investigator and short-term stay for joint research
2	Robert W. Greene	66	University of Texas Southwestern Medical Center, Department of Psychiatry University of Tsukuba, International Institute for Integrative Sleep Medicine	M.D, Ph.D. Neuroscience	・Sherry Gold Knopf Crasilneck Chair in Psychiatry, in honor of Mollie and Murray Gold (2007) ・Sherry Knopf Crasilneck Distinguished Chair in Psychiatry (2004) ・Sherry Knopf Crasilneck Chair in Psychiatry, In Honor of Albert Knopf (2001-2004) ・Dept of Veterans Affairs Career Research Enhancement Award (1998) ・Swiss National Science Foundation Fellowship (Fogarty Fellowship)(1984)	2016 July (6 days) 2016 August (10 days) 2016 December (8 days)	Lecture at IIIS seminar, participation in site visit, symposium as principal investigator and short-term stay for joint research
3	Joseph S. Takahashi	65	University of Texas Southwestern Medicinal Center, Molecular Neurobiology and Genetics	Ph.D. Neuroscience	・Peter C. Farrell Prize in Sleep Medicine, Harvard Medical School, Division of Sleep Medicine (2016) ・Outstanding Scientific Achievement Award, Sleep Research Society (2012) ・Eduard Buchner Prize, German Society for Biochemistry and Molecular Biology (2013) ・W. Alden Spencer Award, College of Physicians and Surgeons, Columbia University (2001) ・6th C.U. Ariëns Kappers Award, Netherlands Society for the Advancement of Natural Sciences, Medicine and Surgery (1995) ・Honma Prize in Biological Rhythms Research(1986) ・NSF Presidential Young Investigator Award (1985-1990) ・Searle Scholars Award, The Chicago Community Trust (1985-1988) ・Alfred P. Sloan Research Fellowship in Neuroscience (1983-1985)	2016 August (5 days)	Lecture at IIIS seminar, participation in site visit as principal investigator and short-term stay for joint research
4	Zhijian Chen		Professor of Molecular Biology, UT Southwestern Medical Center, Investigator, Howard Hughes Medical Institute George L. MacGregor Distinguished Chair in Biomedical Science, UT Southwestern Medical Center	Ph.D. Biochemistry	・ Anna Fuller Fellowship (1991 - 1992) ・ Searle Scholar Award (1998 - 2001) ・ Leukemia and Lymphoma Society Scholar (2002 – 2007) ・ Burroughs Wellcome Fund Investigator in Pathogenesis of Infectious Disease (2002 – 2007) ・ American Cancer Society Research Scholar (2002 – 2006) ・ The Welch Foundation Norman Hackerman Award in Chemical Research (2005) ・ The Edith and Peter O’Donnell Award in Science by The Academy of Medicine, Engineering and Science of Texas (2007) ・Robert McLemore Professor in Medical Science, UT Southwestern Medical Center (2008) ・ University of Buffalo Distinguished Biomedical Sciences Award (2012) ・ National Academy of Sciences Award in Molecular Biology (2012) ・ Fellow, American Association for the Advancement of Science (AAAS) (2013) ・ Member, National Academy of Sciences, USA (2014) ・ Merck Award, American Society of Biochemistry and Molecular Biology (ASBMB) (2015)	2016 June (3 days)	Lecture at IIIS seminar, discussion about the research project
5	Zheng Zhou		Department of Biochemistry &Molecular Biology, Baylor College of Medicine	Ph.D. Genetics, Biochemistry	・CUSBEA (China U.S. Biochemical Examination Association) Fellowship (1988) ・Predoctoral Fellowship of the Robert A. Welch Foundation (1990-1994) ・The V. C. Joshi Memorial Award, Verna & Marrs Mclean Department of Biochemistry, Baylor College of Medicine (1992) ・ Arnold O. Beckman Academic Achievement Award, Baylor College of Medicine (1993) ・ Postdoctoral Fellowship of the Damon Runyon-Walter Winchell Cancer Research Fund (1995-1998) ・Postdoctoral Fellowship of the Medical Foundation, Massachusetts Chapter ・ 1st Place Poster Presentation, Center for Cancer Research Annual Retreat, Massachusetts Institute of Technology, Cambridge, MA (2000) ・ Postdoctoral Fellowship of the Merck/MIT Collaboration Program (2000-2001) ・Investigator Award, Cancer Research Institute (2002) ・Basil O’Connor Starter Scholar Research Award, the March of Dimes Birth Defect Foundation (2003) ・Scholar’s Program Award, the Rita Allen Foundation (2005)	2016 June (1 day)	Lecture at IIIS seminar
6	Xiangwei He		Life Sciences Institute, Zhejiang University	Ph.D. Biochemistry	・ Postdoctoral Fellowship, NIH (NRSA) (1998-2001)	2016 June (1 day)	Lecture at IIIS seminar

#	Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
7	Shien-Fong Lin		Institute of Biomedical Engineering National Chiao Tung University	Ph.D. Biomedical Engineering	・First Prize in Basic Research, NASPE Young Investigators Awards Competition (1998) ・Established Investigator, American Heart Association (2005) ・O. Hugo Schuck Award, American Automatic Control Council (2008) ・Fellow, Heart Rhythm Society (2014)	2016 June (1 day)	Lecture at IIIS seminar, discussion about the research project
8	Francis Szele		Department of Physiology Anatomy and Genetics, Medical Sciences Division, University of Oxford	Ph.D. Pharmacology	・Postdoctoral Fellow - Developmental Neurobiology. Harvard Medical School/Howard Hughes Medical Institute, Boston, MA, USA (1994 - 1999) ・Assistant Professor, Feinberg School of Medicine, Northwestern University, Chicago IL, USA (1999 - 2007) ・Adult Neurogenesis in Neuropsychiatric Disease.DANA Alliance for the Brain,(2012 - 2016) ・Schizophrenia models and the SVZ. Qatar Foundation, (2012 - 2016) ・Epigenetic mechanisms regulating pluripotency from embryonic to adult neurogeneisis. MRC (2014 - 2017) ・Molecular mechanisms regulating subependymal zone progenitor migration. BBSRC(2013 - 2016) ・Pharmacological activation of endogenous stem cell populations for neuroregeneration. Shionogi Science Program (2013 - 2016)	2016 September (1 day)	Lecture at IIIS seminar
9	Malia B. Potts		Department of Cell and Molecular Biology St. Jude Children's Research Hospital	Ph.D. Biology	・National Merit Scholarship, Duke University, (1997) ・Angier B. Duke Memorial Scholarship, Duke University, (1997) ・Phi Beta Kappa Scholarship, Duke University, (1997) ・First Prize in poster competition, International Worm Meeting, (2005) ・Dean's Discretionary Award for outstanding service, UT Southwestern,(2007) ・Ida M. Green Award for academics and service, UT ・Southwestern, (2008) ・F1000 Outstanding Poster Prize, Gordon Research Conference on Autophagy,(2016)	2016 November (3 days)	Lecture at IIIS seminar, discussion about the research project
10	P. Ryan Potts		Department of Cell and Molecular Biology St. Jude Children's Research Hospital	Ph.D. Biology	・American Cancer Society New Investigator Award/UTSW (2013) ・CPRIT Scholar in Cancer Research Award (2011) ・Michael L. Rosenberg Scholar in Medical Research (2011) ・Sara and Frank McKnight Independent Postdoctoral Fellowship Award (2008) ・Oral Presentation Award at AACR Telomere Meeting (2007) ・American Association for Cancer Research Scholar-in-Training Award (2007) ・UT Southwestern Dean's Discretionary Award (2007) ・Nominata Award – Highest honor bestowed by UT Southwestern to a graduate student (2007) ・Altrusa International, Martia Leita Pharmacology Award (2007) ・ASBMB Travel Award (2007) ・Keystone Symposia on Genomic Instability and Repair Travel Award (2005) ・Sigma Xi Abstract Award (2005)	2016 November (3 days)	Lecture at IIIS seminar, discussion about the research project
11	Antoine Adamantidis		Department of Neurology INSELSPITAL, University of Bern	Ph.D. Neuroscience	・Human Frontier Science Program Young Investigators' Grant(2012) ・Canada Foundation for Innovation (CFI) Award (2011)	2016 December (6 days)	Participation in symposium as a speaker, lecture at IIIS seminar
12	Patrick Nolan		Neurobehavioural Genetics, MRC Harwell	Ph.D. Neuroscience	・MRC Seminars-University of Oxford (2013) ・ActualHCA: Hot topic across IBANGS & Measuring Behaviour's Annual Conferences (2016) ・Editional Board in academia and not-for-profit institutions (2017) ・Collaborator of UCL-Institute of Neurology (2017)	2016 December (4 days)	Participation in symposium as a speaker, lecture at IIIS seminar
13	Chengyu Li	40	Institute of Neurosicence Shanghai Institutes for Biological Sciences Chinese Academy of Sciences	Ph.D. Neuroscience	・Di-Ao Award for Chinese Academy of Sciences (2002) ・CAS Mentor Award (2015)	2016 December (4 days)	Participation in symposium as a speaker, lecture at IIIS seminar
14	Christelle Anaclet		Department of Neurobiology University of Massachusetts Medical School	Ph.D. Neuroscience Sleep-Wake mechanisms	・Merit based travel award, SFRMS (Société Française de Recherche et de Médecine du Sommeil) (2006) ・Merit based travel award, European Histamine Research Society (2007) ・Merit based travel award, European Sleep Research Society (2010) ・Young Investigator Award, European Histamine Research Society (2010) ・Merit based travel award, Sleep Research Society (2013) ・Most Notable Publications in Sleep 2012, Sleep Research Society (2013) ・K99/R00 Award, NIMH (2014) ・Young Investigator Award, Sleep Research Society (2015)	2016 December (4 days)	Participation in symposium as a speaker, participation in IIIS seminar

#	Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
15	Jin-Hee Han		Department of Biological Sciences Korea Advanced Institute of Science and Technology	Ph.D. Neuroscience	・Bessemer Science Fellowship from POSCO TJ Park Foundation (2009) ・Andrew Sass-Kortsak Award from The Hospital for Sick Children (2009) ・Young Investigator Award from NARSAD, The World's Leading Charity Dedicated to Mental Health Research (2008) ・Brain Star Award from CIHR (Canadian Institutes of Health Research) (2008) ・Postdoctoral Fellow Travel Awards Supported by the Burroughs Wellcome Fund from Society for Neuroscience (2007) ・Exceptional Trainee Award from the Hospital for Sick Children Research Institute (2007) ・10 Outstanding Scientists Award from Korean Ministry of Science & Technology (2007) ・Restracomp Senior Fellowship from the Hospital for Sick Children Research Institute (2006) ・Trainee Travel Award from the Hospital for Sick Children Research Institute (2006) ・Postdoctoral Fellowship, BK21 Research Fellowship from the Korea Ministry of Education and Human Resources Development (2004) ・Best Poster presentation Award from The 3rd Congress of The Federation of Asian-Oceanian Neuroscience Societies (2002) ・Best Poster presentation Award from The Korean Society for Molecular and Cellular Biology (2001)	2016 December (3 days)	Participation in symposium as a speaker, participation in IIIS seminar

World Premier International Research Center Initiative (WPI)

Appendix 6 FY2016 State of Outreach Activities

Using the table below, show the achievements of the Center's outreach activities in FY2016(number of activities, times held).

※Describe those activities that have yielded novel results or that warrant special mention in the "Special Achievements" space below.

※In appendix 7, list and describe media coverage (e.g., articles published, programs aired) in FY2016 resulting from press releases and reporting.

Activities	FY2016 (number of activities, times held)
PR brochure, pamphlet	1
Lectures, seminars for general public	20
Teaching, experiments, training for elementary, secondary and high school students	12
Science café	1
Open houses	0*
Participating, exhibiting in events	3
Press releases	8

<Special Achievements>

*There is no official 'Open house' but note that IIIS accepts visitors upon request. In FY2016, we accepted domestic and international visitors 25 times.

World Premier International Research Center Initiative (WPI)
Appendix 7 FY 2016 List of Project's Media Coverage

#	Date	Types of Media (e.g., newspaper, television)	Description	
1	2016.04.16	Television	NHK E-tele	"Why do animals sleep -Sleep Science-" (a program supervised by Sakurai)
2	2016.04.28	Television	NHK NEWS	Yanagisawa received the Medal with Purple Ribbon
3	2016.04.28	Newspaper	The Ibaraki Shimbun	Yanagisawa received the Medal with Purple Ribbon
4	2016.04.28	Newspaper	The Asahi Shimbun	Yanagisawa received the Medal with Purple Ribbon
5	2016.04.28	Newspaper	The Mainichi	Yanagisawa received the Medal with Purple Ribbon
6	2016.04.28	Newspaper	The Yomiuri Shimbun	Yanagisawa received the Medal with Purple Ribbon
7	2016.04.28	Newspaper	The Yomiuri Shimbun	Yanagisawa received the Medal with Purple Ribbon
8	2016.04.28	Newspaper	The Sankei Shimbun	Yanagisawa received the Medal with Purple Ribbon
9	2016.04.28	Newspaper	Tokyo Shimbun	Yanagisawa received the Medal with Purple Ribbon
10	2016.05.16	Newspaper	The Yomiuri Shimbun	Yanagisawa attended Symposium at G7 Summit
11	2016.05.27	Web article	Fuminners	"Any good way to have good dreams only?" (Yanagisawa's interview)
12	2016.06.16	Television	NHK NEWS	A new device to stop snoring (Satoh's interview)
13	2016.08.10	Newspaper	Nikkei Shimbun	Introduction of highly internationalized institute, IIIS (Interviews of Yanagisawa and Vogt)
14	2016.09.01	Newspaper	The Nikkan Kogyo Shimbun	Development of a new device to stop snoring (Satoh)
15	2016.09.05	Magazine	Weekly POST	Narcolepsy is caused by the lack of orexin (Yanagisawa's interview)
16	2016.09.06	Newspaper	The Yomiuri Shimbun	Hayashi received the 26th Tsukuba Encouragement Prize
17	2016.09.06	Newspaper	The Nikkan Kogyo Shimbun	Hayashi received the 26th Tsukuba Encouragement Prize
18	2016.09.06	Newspaper	Nikkei Sangyo Shimbun	Hayashi received the 26th Tsukuba Encouragement Prize
19	2016.09.08	Newspaper	The Asahi Shimbun	Hayashi received the 26th Tsukuba Encouragement Prize
20	2016.09.08	Magazine	Tarzan	Sakurai's interview about sleep associated with body and brain condition
21	2016.10.20	Radio	Radio NIKKEI	Yanagisawa's lecture "Mechanisms of sleep/wake regulation and the discovery of a novel neurotransmitter"
22	2016.10.23	Television	BS JAPAN	Mirai Eyes (Introduction of research activities in IIIS)
23	2016.10.27	Newspaper	Nikkei Sangyo Shimbun	Hayashi's interview
24	2016.10.9	Newspaper	The Joyo Shimbun	Hayashi's interview
25	2016.11.02	Web news	ResearchGate	Waking up to the mechanisms of sleep
26	2016.11.02	Web article	mental_floss	How You Sleep May Be Genetic

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27	2016.11.02	Web news	Science Daily	Genetic analysis identifies proteins controlling sleep in mice
28	2016.11.02	Web news	Futurism	A New Genetic Discovery Could Help Us Regulate Sleep
29	2016.11.02	Web news	scimex	Two special genes balance your sleep routines
30	2016.11.02	Web news	Neuroscience News	Mouse Mutants May Shed Light on the Mysteries of Sleep
31	2016.11.02	Web news	Canarias7.es	Un análisis genético identifica las proteínas que controlan el sueño en ratones
32	2016.11.02	Web news	nrc.nl	Doorbraak in onderzoek naar slaap
33	2016.11.02	Web news	UTSW Newsroom	Researchers ID first two genes regulating sleep in mice using genetic screening
34	2016.11.03	Newspaper	The Ibaraki Shimbun	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
35	2016.11.03	Newspaper	Kyodo News **Distributed to 33 media webpages**	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
36	2016.11.03	Television	ANN News	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
37	2016.11.03	Web article	Biotrade	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
38	2016.11.03	Web news	Medical News Today	Genes for dreaming, deep sleep identified in new study
39	2016.11.03	Web news	Medical Daily	Identification Of Sleep Genes May Lead To Better Treatment For Sleeping Disorder And PTSD
40	2016.11.03	Web article	Genetic Engineering & Biotechnology News	GEN News Highlights: Two Essential Sleep and Dreaming Genes Identified
41	2016.11.03	Web news	Corriere Della Sera / Flash News 24	Due topi per studiare disturbi sonno
42	2016.11.03	Web news	infosalus.com	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
43	2016.11.04	Web news	Asahi Degital	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
44	2016.11.04	Web news	Mynavi News	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
45	2016.11.04	Newspaper	Tokyo shimbun	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
46	2016.11.04	Web news	The Asian Age (India)	How you sleep may be genetic
47	2016.11.05	Television	NHK NEWS	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
48	2016.11.06	Television	NBCDFW.com (NBC channel 5)	Study Could Reveal Secrets of Sleep Genes(Yanagisawa)
49	2016.11.06	Web news	goo News	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
50	2016.11.06	Web news	NIKKEI Online	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
51	2016.11.06	Web news	YOMIURI ONLINE	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
52	2016.11.06	Newspaper	The Yomiuri Shimbun	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
53	2016.11.07	Newspaper	Nihon Keizai Shimbun	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
54	2016.11.07	Web news	yomiDr.	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)

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55	2016.11.07	Web news	THE SANKEI SHIMBUN/ iza!	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
56	2016.11.08	Web article	Medial News QLifePro	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
57	2016.11.08	Web news	Brilio.net (Indonesia)	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
58	2016.11.09	Web article	UNIVERSITY JOURNAL ONLINE	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
59	2016.11.09	Web article	GIZMODO	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
60	2016.11.09	Web article	CIRCL	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
61	2016.11.20	Newspaper	The Asahi Shimbun	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
62	2016.11.X	Magazine	Rikejo Vol.42 p.60-63	Interview: "What is good sleep?" (Hayashi)
63	2016.12.05	Newspaper	Tsukuba University Shimbun	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
64	2016.12.22	Newspaper	Mainichi Syogakusei Shimbun	Hatsuyume(Yanagisawa)
65	2016.12.26	Magazine	AERA No.57 p.26-27	Sakurai's interview: mechnisms in the brain controlling appetite
66	2017.01.07	Magazine	JAPAN MEDICAL JOURNAL	Yanagisawa's story "Joy of scientific research"
67	2017.01.09	Magazine	JAPAN MEDICAL JOURNAL	Yanagisawa's interview
68	2017.01.10	Magazine	Tsukuba Style	Healthy lunch boxes of scientists (Vogt et al.)
69	2017.01.13	Web article	nippon.com	Discovery of novel genes involved in sleep/wake regulation (Yanagisawa/Funato)
70	2017.01.16	Web article	The Asahi Shimbun Degital	Direct link between REM sleep loss and the desire for sugary and fatty foods(Lazarus)
71	2017.01.18	Television	NHK NEWS	Direct link between REM sleep loss and the desire for sugary and fatty foods(Lazarus)
72	2017.02.02	Newspaper	The Asahi Shimbun	Direct link between REM sleep loss and the desire for sugary and fatty foods(Lazarus)
73	2017.02.16	Web news	The Asahi Shimbun Degital	Direct link between REM sleep loss and the desire for sugary and fatty foods(Lazarus)
74	2017.02.23	Web news	YOMIURI ONLINE	Direct link between REM sleep loss and the desire for sugary and fatty foods(Lazarus)
75	2017.02.23	Television	NHK Sogo TV	TV coverage of a IIIS faculty member
76	2017.02.28	Magazine	Weekly SPA!	Sakurai's interview: methods for the better sleep
77	2017.03.01	Newspaper	The Nikkan Kogyo Shimbun	Gene therapy for the Schizophrenia model mice (Hayashi)
78	2017.03.01	Newspaper	The Nikkey Sangyo Shimbun	Gene therapy for the Schizophrenia model mice (Hayashi)
79	2017.03.22	Web news	YOMIURI ONLINE	Gene therapy for the Schizophrenia model mice (Hayashi)