World Premier International Research Center Initiative (WPI)
FY 2017 WPI Project Progress Report

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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 2018.
* So as to base this fiscal year's follow-up review on the "last" center project, please prepare this report from the perspective of the latest project plan.
* Use yen (¥) when writing monetary amounts in the report. If an exchange rate is used to calculate the yen amount, give the rate.
* Please prepare this report within 10-20 pages (excluding the appendices, and including Summary of State of WPI Center Project Progress (within 2 pages)).

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. Domestic economic loss caused by sleep disorders in Japan was estimated by RAND Europe in 2016 as 138 billion USD/year, which corresponded to 2.92% of GDP and was ranked first in the world. 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 and verify treatment strategies for sleep disorders

To address the 1st objective, 9 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 and unexpected genes involved in the regulation of sleep/wake.

As for the 2nd objective, we study pathogenesis of various sleep disorders and related mental disorders including fear/anxiety disorders using genetically engineered mouse models.

To achieve the 3rd objective, we are discovering lead compounds of novel drugs modulating sleep/wake that are totally different from existing sleep-inducing agents or psychostimulants in their mechanisms of action. We are also developing new methods for prevention/early intervention and diagnosis of sleep disorders including the development of an EEG-measuring-wearable device and algorithms/software based on the artificial intelligence for fully-automated sleep staging.

Implementation of the translational research is the 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 filling the gaps between basic and human studies, we set the following strategic directions as countermeasures.

a. To establish a spin-out of IIIS, S'UIMIN Inc. as a business sector of IIIS.
b. To promote licensing of the lead compounds to pharmaceutical companies to implement non-clinical and clinical development.
c. To increase and expand collaboration/research alliances of translational researches with outside groups.

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. Collaborative research among laboratories in IIIS is thus crucial to fuse 3 research fields into "sleep science." The Nature paper published by Funato *et al.* in 2016 is a good example of the successful internal collaborations involving 4 laboratories. Joining of young PIs,

Dr. Honjoh and Dr. Abe, would accelerates generation of new collaborative research, and cross-sectional research activities are expected to further develop in the future.

3. Establishing international research environment

The PIs at overseas satellites visited IIIS quite often and actively participated in events such as the Site Visit, Annual IIIS Symposium, WPI-IIIS Seminar, etc. In FY2017 we hosted 20 WPI-IIIS Seminars, for which 7 foreign speakers (35%) were invited. The 6th IIIS Symposium was held on December 14, 2017 in Tokyo as a joint meeting with global pharmaceutical company, MSD, inviting 7 international and 6 domestic speakers and about 200 researchers and students participated in.

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 appointed the first female PI, Dr. Sakiko Honjoh in September 2017. We newly employed 15 researches including 4 foreign researchers and 4 Japanese researchers that had worked actively in foreign countries. On the other hand, we accepted 10 visiting foreign research fellows and 10 foreign students from overseas. After the completion of our new research building, requests to visit IIIS greatly increased.

4. Reforming the research organization

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 FY2017, we continued the efforts of system reforms in cooperation with University of Tsukuba as follows.

1. Extension of retirement age by special appointment by the President.
2. Delegating technology transfer function to the spin-out company
3. A new dispensation of distributing license revenues to research centers/departments

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

University of Tsukuba is making a plan of reorganization/restructuring/merger of all research centers and will 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. University of Tsukuba has provided IIIS with various resources as operational and financial supports

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 measures to sustain IIIS after the program funding ends have been consisted with 3 plans; 1) to offer a tenure position to qualified PIs, 2) to return licensing revenues to IIIS, 3) to implement the future expansion space in IIIS building. Fortunately R&D Center for Frontiers of MIRAI in Policy and Technology (F-MIRAI) supported by TOYOTA Motor Corporation decided to move into the future expansion space in October, 2017. We are trying to add another plan to sustain IIIS by contributing to a new Ph.D. program.

6. Others

IIIS put forth multiple and unconventional outreach activities in FY2017. Most notably, we hosted the 6th WPI Science Symposium as a major organizer. Challenging crowdfunding project is also another highlight in FY2017.

To avoid research misconduct, we have launched educational campaigns for research ethics since FY2015. In FY2017, we held two seminars in the series of Research Ethics Seminars.

7. Center’s response to the follow up results in last year

We agree to make the best efforts to recruit a foreign national to substitute a leaving administrative staff in future.

Agreeing to the advice not to focus on commercialization, we decided to limit the scope of our translational research and human studies within basic studies of pharmaceutical science and experimental medicine. We, instead, established a spin-out, S’UIMIN Inc. as IIIS business sector. S’UIMIN should be responsible for the social and industrial implementation of our business seeds created through basic studies in IIIS, including product development as well as technology transfer to industries.

* 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.

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.

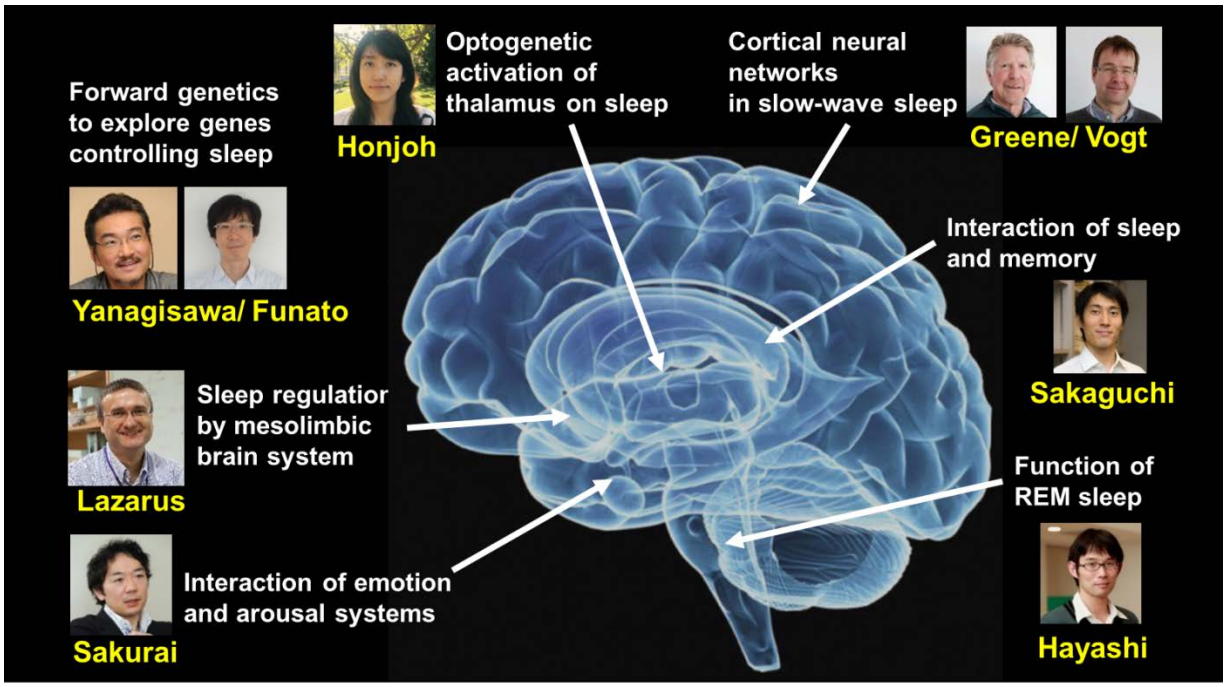
In developed countries, the prevalence rate of sleep disorders is around 15%, with the lifetime prevalence more than 30%. The underlying factors behind this problem include an increase of the elderly population and the increasingly nocturnal lifestyle of today's around-the-clock societies. The deficiencies 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 was estimated by RAND Europe in 2016 as 138 billion USD/year, which corresponded to 2.92% of GDP and was ranked first in the world. It is indeed 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 and verify treatment strategies 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)

In the previous fiscal year, we published our first report on the forward genetic analysis of sleep in mice (Funato *et al.*, **Nature** 2016), in which we showed *Sik3* and *Nalcn* genes are crucial for the regulation of NREM sleep and REM sleep, respectively. This achievement has proved that the forward genetics is really able to identify novel sleep-regulating genes in rodents. More importantly, we are convinced that how little we know about sleep and that there are many sleep-regulating genes to be identified. Thus, we decided to continue our EEG/EMG-based genetic research in a streamlined in-house workflow from the production of mutagenized mice to linkage analysis (Miyoshi, Kim *et al.* in preparation).

In addition to characterize another mutant pedigree, *Sleepy2* (Kim *et al.* in preparation), we are conducting a mechanistic research on SIK3 and NALCN. The exon 13 that is skipped in *Sleepy* mutant mice encodes a phylogenetically conserved PKA phosphorylation site (Ser551), suggesting a conserved role of Sik3 orthologues in sleep-like behaviors (Fig. 1a). In fact, our collaboration with Dr. Kazuhiko Kume at Nagoya City University showed that the alanine substitution of the PKA-phosphorylation site in the Sik3 orthologues increased sleep-like behavior in flies (Fig. 1b, Funato *et al.*, **Nature** 2016).

To prove that the Ser551 residue is crucial for sleep regulation by SIK3, we introduced the serine to alanine substitution using CRISPR/Cas9 technology to establish $Sik3^{S551A}$ mice. $Sik3^{S551A/+}$ mice showed an increased total NREM sleep time, a decreased total wake time and unaltered REM sleep time compared with wild-type littermates (Fig. 1c-e; Honda *et al.*, in submission). Furthermore, $Sik3^{S551A/+}$ mice showed increased delta density during NREM sleep, suggesting the persistent increase in sleep need in $Sik3^{S551A/+}$ mice. Actually, the sleep phenotype of $Sik3^{S551A/+}$ mice are indistinguishable from that of *Sleepy* mutant mice. We think that this is a striking finding that a single and heterozygous amino acid change alters sleep/wakefulness of mice.

Since the *Sleepy* mutant mouse is a unique genetic model of increased sleep need, we used them for the phosphoproteomics research to identify Sleep-Need-Index PhosphoProteins (Wang *et al.*, **Nature** 2018). Since there has been a total lack of knowledge

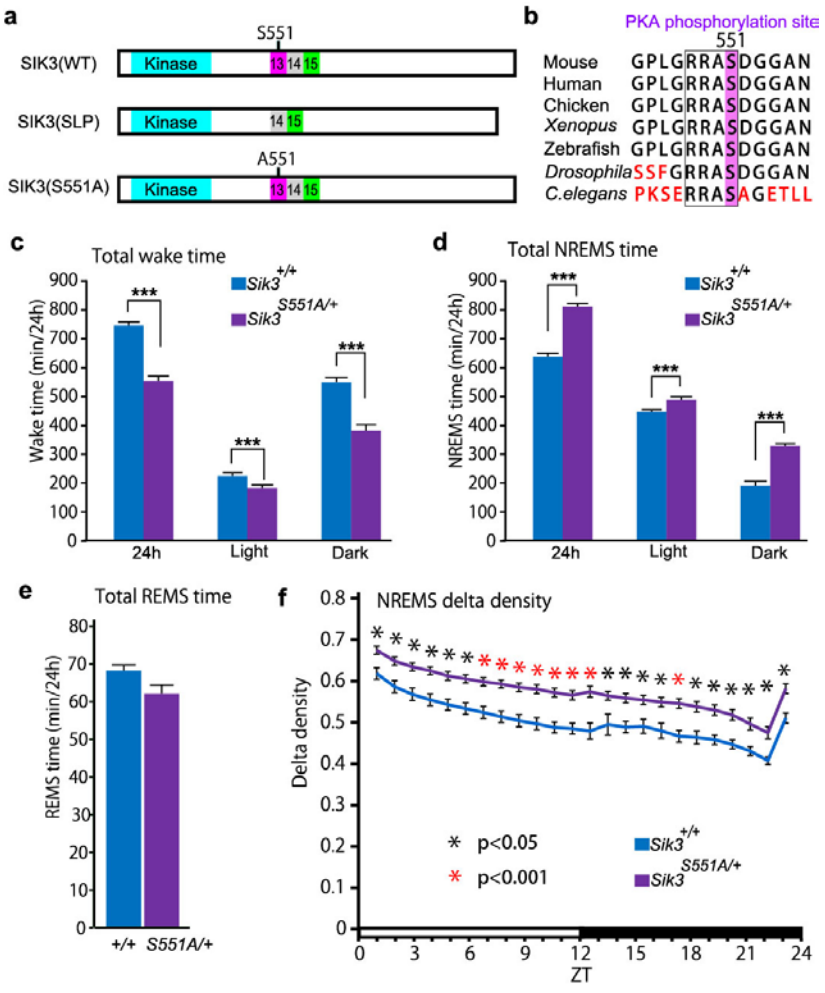


Fig. 1. Increased NREM sleep in Sik3 S551A heterozygous mice. (**a**) Structures of wild-type and mutant SIK3 proteins. Sleepy (SLP)-mutant SIK3 protein lacks the exon13-encoded region. SIK3 (S551A) has an amino acid substitution from serine to alanine within the exon13-encoded region. (**b**) The phylogenetic conservation of the PKA-phosphorylation site, R-R-A-S, within the exon 13-encoded region. The serine residue in the PKA-phosphorylation site is the 551th residue of the SIK3 protein. (**c**) $Sik3^{S551A/+}$ mice showed a shorter total wake time than wild-type littermates. (**d**) $Sik3^{S551A/+}$ mice showed a longer total NREM sleep time than wild-type littermates. (**e**) $Sik3^{S551A/+}$ mice spent a similar time in REM sleep time to wild-type littermates. * * * P < 0.001. One-way analysis of variance (ANOVA) followed by Tukey's test. Data are mean ± s.e.m. (**f**) NREMS delta density, an index for sleep need, of $Sik3^{S551A/+}$ mice was higher than that of wild-type littermates across the light and dark phases.

about the intracellular signaling and molecular substrates for “sleepiness,” the identification of SIK3 protein will open new frontiers in sleep research.

For a leak cation channel NALCN, we are conducting genetic research to narrow down the brain region responsible for REM sleep regulation by NALCN.

(2) Phosphoproteomic studies to understand the molecular basis of sleep need(Liu and Yanagisawa/Funato Lab)

Sleep and wake are two alternate states of the brain, which globally impact brain physiology, from molecular changes, neuronal activities to synaptic plasticity. The sleep-wake homeostasis is maintained by generation of a sleep need that accumulates during waking and dissipates through sleep. Homeostatic sleep regulation is a global, intrinsic and cumulative process ultimately involving most of brain cells/regions, which is distinct from executive switching between sleep and wake states controlled by specific neural circuits. We hypothesize that the molecular substrates of sleep need should satisfy four criteria: 1) globally and similarly regulated in most brain cells/regions; 2) accumulate gradually during waking and dissipate through sleep; 3) change in parallel with sleep need in different contexts; 4) gain/loss of functions of itself causes bidirectional changes of sleep need. To study the molecular basis of sleep need, we performed quantitative proteomic and phosphoproteomic analysis of whole mouse brain from two opposite (*Sleepy* and sleep-deprived) models of increased sleep need. Sleep deprivation induces cumulative phosphorylation of brain proteome, which dissipates during recovery sleep. Strikingly, *Sleepy* (*Sik3*$^{Slp/+}$) mutant brains, with constitutively high sleep need despite increased sleep amount, exhibit a hyper-phosphoproteome mimicking sleep-deprived brains, owing to a gain-of-function mutation of protein kinase SIK3[14]. Comparison of two models identified 80 mostly synaptic Sleep-Need-Index-PhosphoProteins (SNIPPs), whose phosphorylation states closely parallel changes of sleep need. Mutant SLEEPY/SIK3 kinase preferentially associated with and phosphorylated SNIPPs. Inhibition of SIK3 activity reduced phosphorylation state of SNIPPs and slow wave activity (SWA) during non-rapid-eye-movement sleep (NREMS), the best known measurable index of sleep need, in both *Sleepy* and sleep-deprived wild-type mice. Our results suggest that SNIPPs accumulate/dissipate phosphorylation as the molecular substrate of sleep need. While waking encodes memories by potentiating synapses, sleep consolidates memories and restores synaptic homeostasis by globally downscaling excitatory synapses. Thus, the phosphorylation/dephosphorylation cycle of SNIPPs may represent a major regulatory mechanism that underlies both synaptic homeostasis and sleep-wake homeostasis (Wang *et al.,* **Nature** 2018).

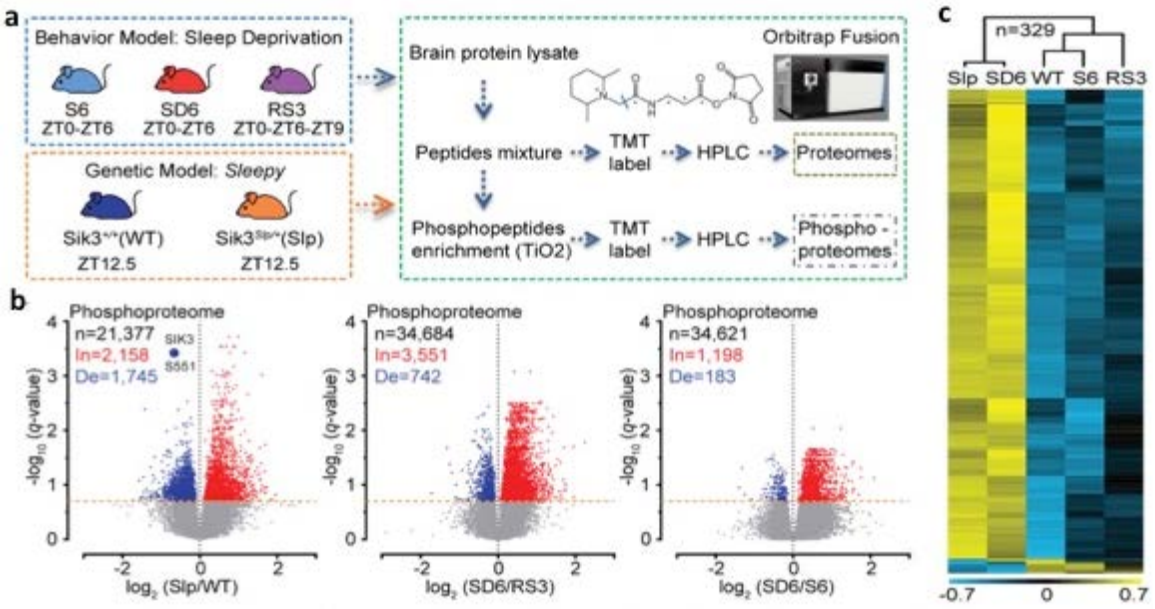


Fig. 2. *Sleepy* mutant brains exhibit a hyper-phosphoproteome mimicking sleep deprived brains.
a. An overview of quantitative mass spec analysis to two models.
b. Volcano plots showing Slp/WT, SD6/RS3 and SD6/S6 brain phosphoproteome comparison.
c. Unsupervised cluster analysis of Sleepy and sleep-deprived models.

(3) 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 nucleus of accumbens (NAc) and the bed nucleus of the stria terminalis (BST) (Saito *et al.*, submitted) (Fig. 3). VLPO neurons that make direct synaptic input to orexin neurons and histamine neurons were inhibited by noradrenalin (NA) and 5HT, suggesting that these input neurons have characteristics of sleep-active neurons.

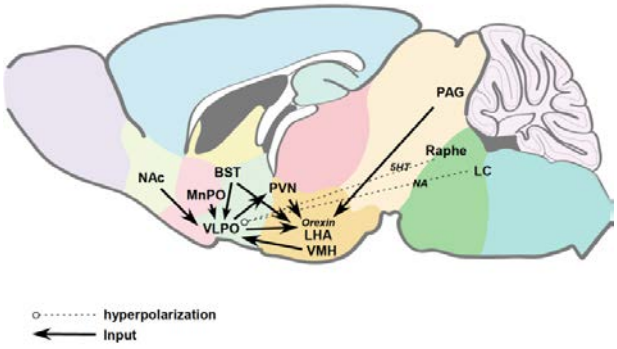


Fig. 3. Neuronal circuits that regulate hypothalamic arousal system.

We also found that optogenetic activation of GABAergic neurons in the BST during NREM sleep made immediate transition from NREM sleep to wakefulness, while stimulation during REM sleep did not show any effects (Kodani *et al.*, **J. Neurosci.**, 2017). This transition was not affected by dual orexin receptor antagonists DORA 22. Chemogenetic excitation of BNST GABA neurons evoked a sustained wakefulness state. This 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.

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 $OX_1R^{-/-}$;$OX_2R^{-/-}$ 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**, 2017). 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.*, **Nature Commun.**, 2017) (Fig. 4). 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, and arousal systems in turn influences amygdala function to modulate emotion-related behavior as well as arousal.

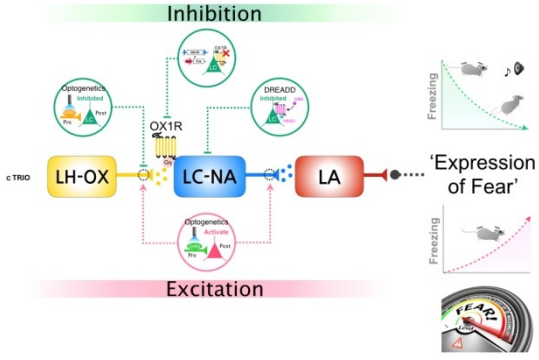


Fig. 4. The LH → LC → LA circuit that regulates fear expression.

(4) The gating of sleep by motivated behaviors (Lazarus Lab)

As humans, we often defy sleepiness and stay awake when attention is necessary, but also experience an inescapable desire to sleep in boring situations. The brain mechanisms governing the regulation of sleep by cognitive and emotional factors are not well understood. The Lazarus lab recently reported that a part of the brain that is associated with motivation and pleasure – the nucleus accumbens (NAc) – also can produce sleep (Oishi *et al.*, **Nature Commun.**, 2017). The new findings may explain why we have the tendency to fall asleep in the absence of motivating stimuli, *i.e.*, when bored. They used chemo-genetic and optical techniques to remotely control the activities of NAc neurons that express adenosine A_{2A} receptors ($A_{2A}R$), also known as indirect pathway neurons. As a result, they discovered that NAc $A_{2A}R$ neurons have an extremely strong ability to induce sleep (Fig. 5) that is indistinguishable from the major component of natural sleep, known as slow-wave sleep, as it is characterized by slow and high-voltage brain waves. The classic somnogen adenosine is a strong candidate for evoking the sleep effect in the NAc. Adenosine has long been known to represent a state of relative energy deficiency and to induce sleep via adenosine receptors. Caffeine, the most widely consumed psychostimulant in the world, produces its arousal effect also in the NAc by blocking $A_{2A}R$ (Lazarus *et al.*, **J Neurosci**, 2011). Compounds that promote $A_{2A}R$ signaling in the NAc may open therapeutic avenues for treating insomnia, which is a sleep disorder affecting millions of people around the world and it frequently co-occurs with a wide range of psychiatric disorders. Although $A_{2A}R$ agonists strongly induce sleep, classical $A_{2A}R$ agonists have adverse cardiovascular effects and cannot be used clinically to treat sleep disorders. Moreover, the development of adenosine analogs for treating disorders of the central nervous system, including insomnia, is hampered by the poor transport of these drugs across the blood-brain barrier (BBB). The lab hypothesized that selective physiologic $A_{2A}R$ responses may be evoked by a positive allosteric modulator, because its action, in contrast to an agonist, is limited to when and where adenosine is released (Fig. 6). In collaboration with the Nagase lab, they have recently identified a small BBB-permeable monocarboxylate that induces sleep by enhancing $A_{2A}R$ signaling in the brain, and surprisingly does not have the typical cardiovascular effects of $A_{2A}R$ agonists (Patent application 2017-202225, 'Novel slow-wave sleep-inducing agent' and Korkutata *et al.*, **Br J Pharmacol**, submitted). Their findings indicate that molecules that allosterically enhance $A_{2A}R$ signaling could help people with insomnia to fall asleep and perhaps also be a potential treatment for psychiatric illness.

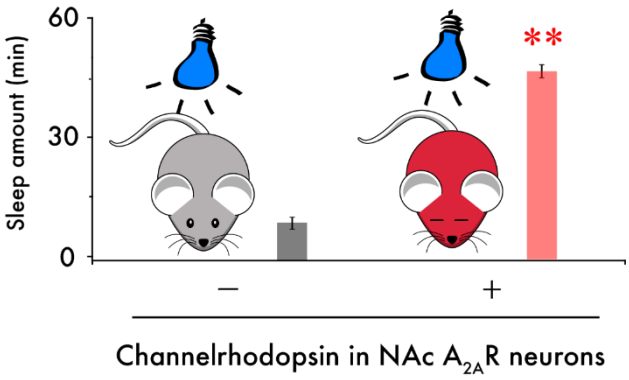


Fig. 5. Optogenetic excitation of NAc $A_{2A}R$ neurons drastically increases sleep amount.

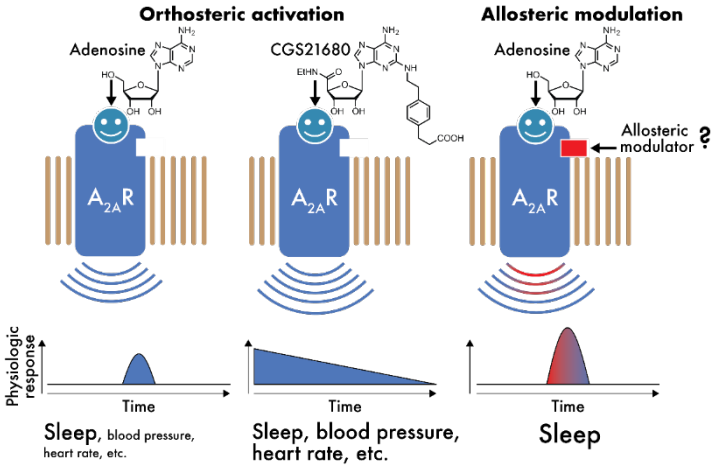


Fig. 6. Induction of selective physiologic $A_{2A}R$ responses by positive allosteric modulation.

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

Cortical networks show remarkable changes in their activity patterns in the transition from waking to slow wave sleep (SWS). Most prominently, neurons synchronously and rhythmically change between active ON and silent OFF periods at around 1 Hz. Due to their synchronicity these oscillations are visible in EEG and local field potential (LFP) recordings. The power of SWS slow wave activity (SWA) is the best indicator of sleep need and is gradually reduced during SWS as sleep need is resolved. We are investigating SWS SWA to understand the function of these oscillations in sleep need resolution and other aspects of SWS such as improved memory consolidation. Using in-vivo tetrode recordings, we can simultaneously record from multiple neurons in small cortical networks and determine their interactions and their relationship to SWA. We have found that individual neurons contributed more evenly to network activity in SWS and cortical networks show significant decreases in their functional organization. This indicates a shift away from network-dependent information processing to more cell-autonomous function in SWS. We also optogenetically activate specific inputs to the network to understand its reactivity during waking, and SWS ON and OFF phases. So far we have found an unexpected increase in cortical reactivity in SWS (Figs 7, 8 & 9).

Sleep need builds up during waking at different rates, depending on arousal and other circumstances. We are activating different wake-promoting centers and measuring the impact of this activation on sleep need buildup and later resolution.

We have evidence that increased neuronal calcium transients are linked to SWA and possibly sleep need resolution. We will study the effect of interfering with these signals on SWA and sleep need resolution.

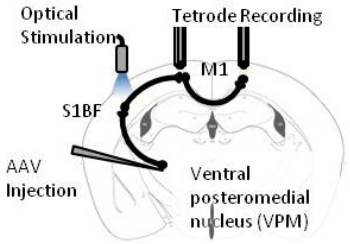


Fig. 7. Schematic of Optogenetic Experiments.

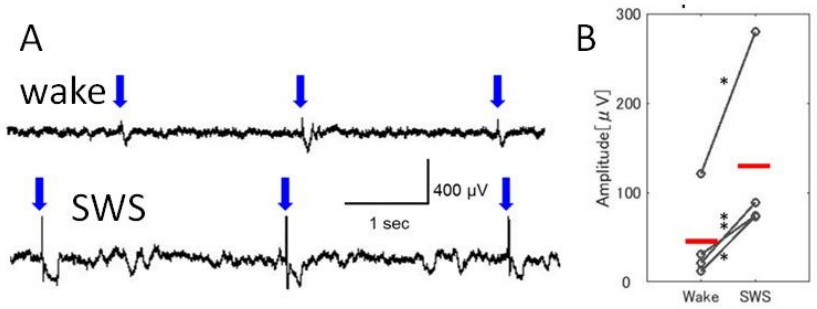


Fig. 8 A. Optogenetic activation (blue arrow) during wake (top) and slow wave sleep (SWS bottom). Effect on local field potentials (representing synaptic input into the recorded area). **B.** Summary of 4 animals shows clearly enhanced cortical reactivity.

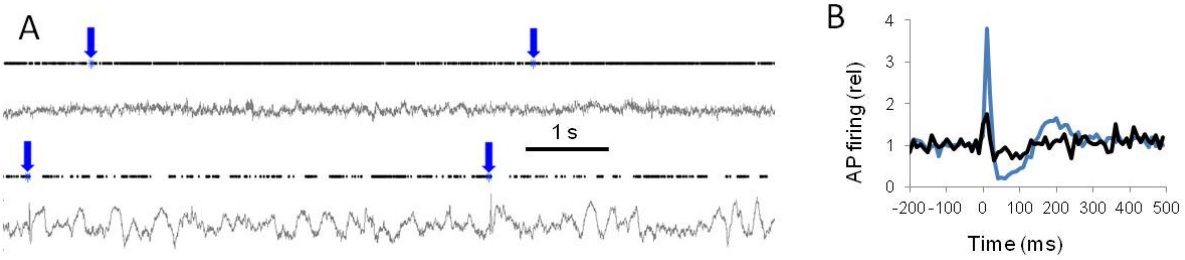


Fig. 9 A. Multi unit activity (dotted line top: output of recorded area) and LFP (solid line bottom) in waking (above) and slow wave sleep (below). Laser stimulus (blue arrow). Note the prominent pause in firing after laser stimuli in slow wave sleep.
B. Average response in waking (black) and slow wave sleep (blue) of action potential firing to the laser pulse. In slow wave sleep the pulse generates a large biphasic response with a silent period lasting more than 100 ms.

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

The necessity of sleep in memory consolidation has been revealed by variety of methods including manipulation of sleep architecture or exposing subjects to learning-related stimulation (*e.g.*, sound) during sleep (Akers & Sakaguchi *et al.*, **Stem Cells**, 2018; Purple & Sakaguchi *et al.*, **Sci. Rep**., 2017). More recently, manipulation of brain circuitries, which control neuronal oscillations characteristic to each stage of sleep, has revealed necessity of those oscillatory activities to memory consolidation. However, functional correlation of those neuronal activities during sleep to memory consolidation is still largely unknown. We have shown that the adult-born neurons (ABNs) are necessary for memory consolidation (Arruda-Carvalho & Sakaguchi *et al.*, **J. Neurosci.**, 2014). Here, we examined the function of the ABNs during a vulnerable period for fear memory consolidation (Fujinaka & Sakaguchi *et al.*, **Mol. Brain**, 2016) in naturally sleeping mice using miniaturized endoscope (Fig. 10A) and optogenetic silencing (Fig. 10B, Sakaguchi *et al.*, **PLoS One**, 2015), and its mechanisms by next-gen sequencing (Fig. 10C). We found that the ABNs show firing during sleep after learning and silencing their activities resulted in a latent deficit in fear memory retrieval. Interestingly, memory impairment is also observed when they are silenced sleep within but no later than the vulnerable time period. Moreover, the effect is limited to specific maturation stage of the ABNs and the type of memory. These results suggest that the activities of the ABNs are necessary in fear memory consolidation during sleep (Kumar & Sakaguchi *et al.*, in prep.).

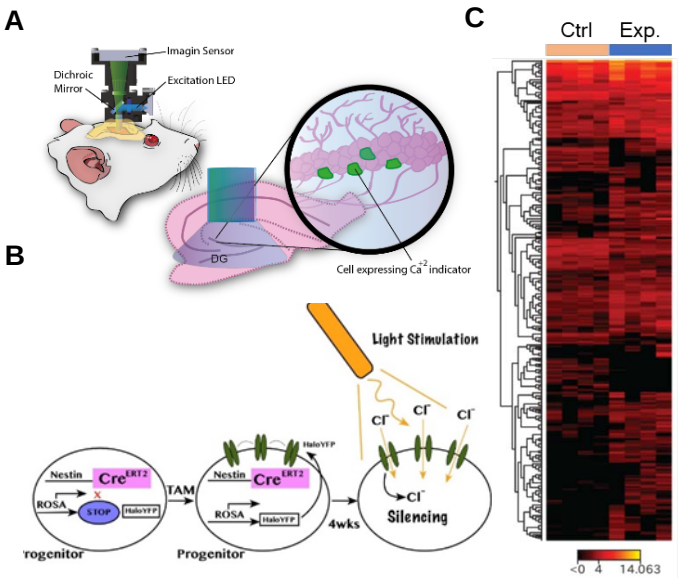


Fig. 10A. Imaging the adult-born neurons (ABNs) using genetically coded Ca-indicator in naturally sleep mice.
B. Optogenetic silencing of the ABNs at specific stage of sleep. Selective expression of Halorhodopsin (Halo) by transgenic mice allows to silence the activities.
C. Results of transcriptome analysis. RNA samples were retrieved and processed in next generation sequencer. The changed genes were shown in heat map.

(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. Previously, 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). Considering that there are many reports showing the importance of slow wave activity in neural plasticity, our findings support that REM sleep may contribute to various neural plasticity-related phenomena including brain maturation and learning. To further address this possibility, we aimed to establish mice in which REM sleep is chronically decreased, instead of only a few hours. We took advantage of our recent identification of a subpopulation of neurons in the pons that are essential for normal REM sleep. We expressed DTA, which causes cell death, selectively in these neurons using adeno-associated viral vectors (Fig. 11A). As a result, REM sleep was drastically reduced already on the first week after introducing the DTA gene. Moreover, the decrease in REM sleep was observed after several weeks (Fig. 11B). These mice are expected to be extremely useful for addressing the function of REM sleep. We are currently analyzing the behavioral outcome in these mice.

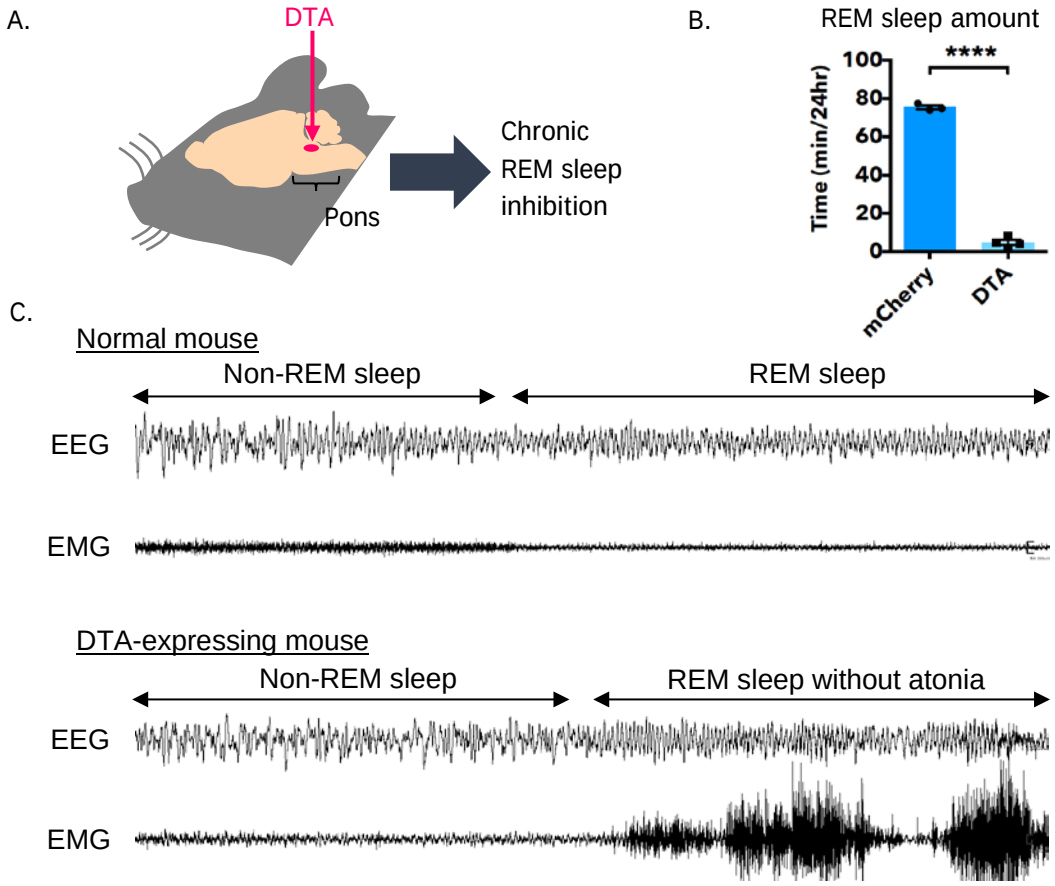


Fig. 11. Success in decreasing REM sleep for a long period by expression of DTA in identified REM sleep-inducing brain area (Liu et al., unpublished).
A. Adeno-associated viral vector expressing DTA was injected to the pons.
B. The DTA introduced mice exhibited drastic REM sleep reduction at 3 weeks after DTA expression.
C. The DTA introduced mice exhibited REM sleep without atonia resembling human RBD.

REM sleep behavior disorder (RBD) is a disorder in which the patient acts out of his or her dreams, resulting in violent behavior during REM sleep that causes injury of the patient or someone nearby. RBD is frequently observed in patients of Parkinson's disease or dementia with Lewy's bodies. While taking clonazepam is an effective treatment for patients that are in the early stage, for patients in a more advanced stage, currently there is no effective treatment for RBD. RBD patients suffer from daytime fatigue due to the low sleep quality. Thus, there are strong unmet medical needs concerning RBD, and a novel therapeutic target is desired. Notably, the DTA expressing mice that we established described above exhibited severe REM sleep without atonia which resembles the symptoms of patients with advanced RBD (Fig. 11C). Thus, these mice may also provide important clues to the neuronal mechanism of RBD.

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. RBD patients exhibit motor behaviors, such as kicking, punching, jumping, running, grabbing, talking, shouting, screaming, and inordinate jerking of body and limbs in relation to the dream content while they are in a REM sleep state. Recently, RBD has begun to attract increased attention because RBD patients have a high probability for later developing α-synuclein disorders. However, the precise cause of RBD is still largely unknown.

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 clonazepam, a benzodiazepine often used clinically to treat RBD symptoms. Surprisingly, the dual orexin receptor antagonist DORA22 was also highly effective. With our collaboration with one of major sleep clinics in Tokyo, we conducted a double-blind, randomized, placebo-controlled, and crossover trial with suvorexant in RBD patients. We found that suvorexant caused a significant reduction of motor activity during REM sleep in 86% of RBD patients. This is the first report showing that orexin blockade could be a potential treatment for RBD symptoms (Hondo *et al.*, in revision). Also, our data support the validity of this mouse model for examining the pathophysiology of RBD.

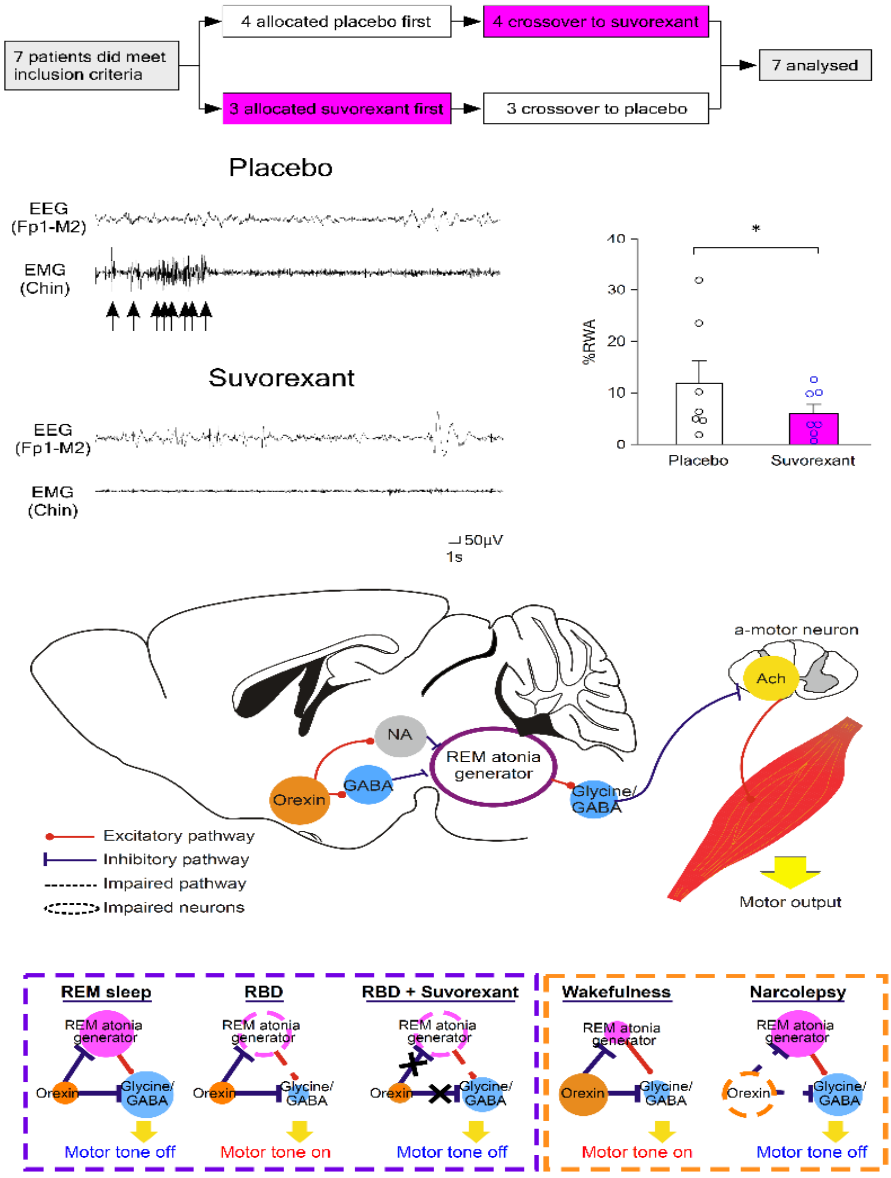


Fig. 12. Suvorexant decreases REM muscle activity in RBD patients. (Bottom) A schematic illustration of the pathophysiology of RBD in relation to orexin activity.

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

Innate behaviors are genetically encoded, but their underlying molecular mechanisms remain largely unknown. Predator odor 2,4,5-trimethyl-3-thiazoline (TMT) and its potent analog 2-methyl-2-thiazoline (2MT) are believed to activate specific odorant receptors to elicit innate fear/defensive behaviors in naïve mice. Here, we conduct a large-scale recessive genetics screen of ethylnitrosourea (ENU)-mutagenized mice. We find that loss of Trpa1, a pungency/irritancy receptor, diminishes TMT/2MT and snake skin-evoked innate fear/defensive responses. Accordingly, *Trpa1*$^{-/-}$ mice fail to effectively activate known fear/stress brain centers upon 2MT exposure, despite their apparent ability to smell and learn to fear 2MT. Moreover, Trpa1 acts as a chemosensor for 2MT/TMT and Trpa1-expressing trigeminal ganglion neurons contribute critically to 2MT-evoked freezing. Our results indicate that Trpa1-mediated nociception plays a crucial role in predator odor-evoked innate fear/defensive behaviors. The work establishes the first forward genetics screen to uncover the molecular mechanism of innate fear, a basic emotion and evolutionarily conserved survival mechanism (Wang *et al.*, **Nature Commun.,** 2018).

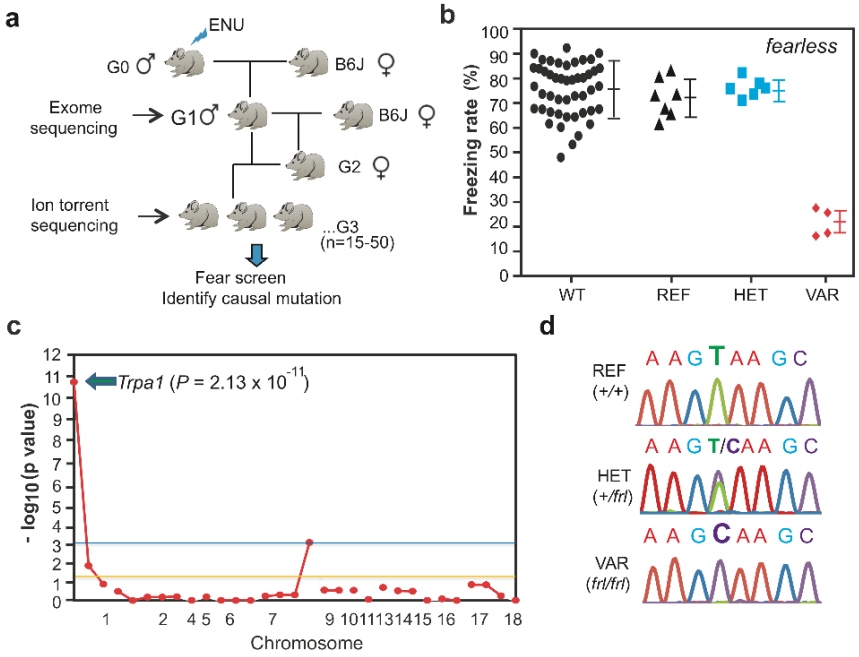


Fig. 13. Identification of *fearless (Trpa1)* mutant mice by forward genetics screening. **a.** A flowchart of the recessive fear screen. **b.** A graph of the *fearless* mutant pedigree consisting of 7 reference (REF), 6 heterozygous (HET), and 4 phenovariant (VAR) individuals. A separate group of wild-type (WT) mice were included as controls every week. **c.** A Manhattan plot showing a strong linkage (P = 2.13×10-11) between the *Trpa1* mutation and fearless phenotype. Horizontal yellow and blue lines represent the thresholds of P <0.05 without or with Bonferroni correction, respectively. **d.** The causative mutation was identified by sequencing the *Trpa1* gene of REF, HET and VAR mice.

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

We are discovering lead compounds of novel drugs modulating sleep/wake that are totally different from existing sleep-inducing agents or psychostimulants in their mechanisms of action. We are also developing new methods for prevention/early intervention and diagnosis of sleep disorders and related diseases. These studies include the development of an EEG-measuring-wearable device and algorithms/software based on the artificial intelligence for fully-automated sleep staging. It is likely that these new intervention programs will provide us with new treatment/diagnosis strategies not only for sleep disorders, but also for mood disorders and metabolic diseases.

(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 OX_2R, have been expected as a chemotherapeutic agent for narcolepsy. Nagase's group have discovered the potent OX_2R selective agonist YNT-185 (EC_{50} = 28 nM; selectivity ratio to OX_1R >100 times) and confirmed its anti-narcoleptic effects in the murine narcoleptic model. However, YNT-185 was required >1.0 g for oral administration due to the low absorbability, which leads us to improve the physicochemical and pharmacokinetic/dynamic properties. To obtain the preclinical candidates with improved these properties, we focused on the discovery of more potent agonist and the scaffold hopping for satisfactory physicochemical properties. And we finally identified the selective OX_2R agonist with an activity in the same order of magnitude as that of endogenous orexin.

(11) Relation between energy metabolism and sleep in human (Satoh/Tokuyama/Abe 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.

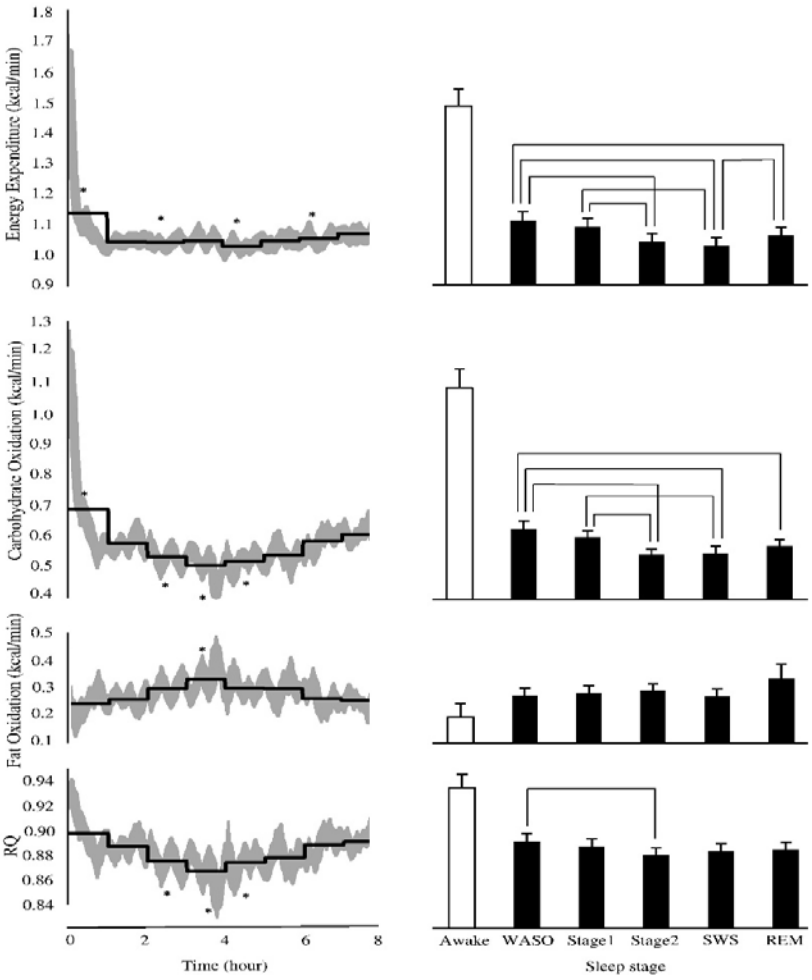


Fig. 14. Energy metabolism during sleep: summary of the raw data.The mean ± SE for the time course of energy metabolism during sleep at 1-min intervals is shown in gray, and the hourly averages are denoted by the black line. *Statistically significant difference of the hourly average compared to the final hour of sleep ($P < 0.05$) (left panel).
Means ± SE of the average energy metabolism during each sleep stage are shown, and values connected by a line were significantly different ($P < 0.05$) (right panel).
RQ, respiratory quotient; WASO, wake after sleep onset; REM, rapid eye movement; SWS, slow-wave sleep.

(12) Novel method of tracking vigilant attention (Satoh/Tokuyama/Abe Lab)

Although many systems have been developed to detect impairment of vigilant attention in order to prevent human-error-related accidents, a majority of them only measure severe vigilance impairment that typically involves eye closure while falling asleep. Therefore, we aimed to determine novel markers which can detect intermediate impairment of vigilance when eyes are open and to develop a new technique that could measure such impairment by integrating these novel markers. Eight participants performed the widely used assay of vigilance impairment (*i.e.*, the Psychomotor Vigilance Test (PVT)) with simultaneous recording of eye metrics every 2 hours during 38 hours of continuous wakefulness. According to the results, several novel markers were found which can measure vigilant attention when the eyes are open. In addition, a novel algorithm for detecting multilevel vigilant attention was developed, which estimated performance of the PVT by integrating these novel markers with other eye-related indices. The novel algorithm also tracked changes in intermediate vigilance impairment (specific reaction times in the PVT, *i.e.*, 300–500 ms) during prolonged time-on-task and sleep deprivation, which had not been tracked previously by conventional techniques. The implication of the findings is that this novel algorithm can be used to reduce human-error-related accidents caused by vigilance impairment even when the deficit level is intermediate.

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

Implementation of the translational research is the 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 filling the gaps between basic and human studies, internal resources available in IIIS are not sufficient, and we set the following strategic directions as countermeasures.

a. To establish a spin-out of IIIS, S’UIMIN Inc. as a business sector of IIIS
b. To promote licensing of the lead compounds to pharmaceutical companies to implement non-clinical and clinical development
c. To increase and expand collaboration/research alliances of translational researches with outside groups

1-2-1. Establishment of the spin-out of IIIS, S’UIMIN Inc.

S’UIMIN Inc. was established as a business sector of IIIS in October 2017, nominating Dr. M. Fujiwara, ex-CEO of Chiome Bioscience Inc., and the Center Director to the joint representatives. S’UIMIN means “sleep” in Japanese and stands for “Sleep is Ultimate Intelligent Mechanism In Nature” as well. Major missions of S’UIMIN are to implement translational researches such as the development of a sleep measuring system for diagnosis, as well as to facilitate licensing of research tools/lead compounds of novel drugs created in IIIS to pharmaceutical companies as a private TLO. S’UIMIN should take advantage of business seeds of IIIS to make profits, which should be fed back to IIIS to support future studies and reproduce new business seeds.

(1) Development of a sleep measuring system for diagnosis (Regional Innovation Ecosystem Program implemented by MEXT)

A proposal by Tsukuba Global Innovation Promotion Agency (TGI), which is the organization established by University of Tsukuba, Tsukuba City and Ibaraki Prefecture as the hub of alliances among research institutions in Tsukuba, was adopted for Regional Innovation Ecosystem Program implemented by MEXT in November 2016 to start 2 R&D projects aiming commercialization. One of the R&D projects is “development of a sleep measuring system for diagnosis,” in which 3 groups, *i.e.*, 1) IIIS, 2) Center for Computational Science, University of Tsukuba (CCS), and 3) Cyberdyne Inc., collaborate to develop an EEG-measuring-wearable device and algorithms/software based on the artificial intelligence for fully-automated sleep staging. CCS and Cyberdyne are responsible for development of the AI-based-software and the wearable device, respectively, while IIIS takes charge of their clinical tests/validation and collection of the training data for AI programming.

In the first half of FY2017, the team succeeded in developing the 1st prototypes of the wearable device with 3 channels of EEG and the AI-based-software for sleep staging of polysomnography (PSG) data. Based on this achievement, the spin-out of IIIS, S’UIMIN Inc. was established as mentioned above. S’UIMIN Inc. takes responsibility for development of an IT system integrating the wearable devices with a cloud server running the AI-based-software for data acquisition, analysis and reporting. S’UIMIN is also responsible for the medical device approval of the IT system, while Cyberdyne takes care of the approval of the wearable device.

In the second half of FY2017, the team finished the development of the 2nd prototypes of the wearable device and the AI-based-software with improved performances. The validation study of the wearable device was conducted at the end of FY2017 to compare it with PSG in the simultaneous measurement and to prove the equivalence.

(2) Licensing of research tools/lead compounds through S’UIMIN Inc.

To contribute research community, IIIS provides non-profit research organizations with its research tools including animal models free of charge. For commercial enterprises, however, the research tools are to be licensed through S’UIMIN Inc., which will negotiate a license fee with a licensee and obtain commission revenue adequate for its contribution as a private TLO. In addition to research tools, S’UIMIN Inc. is active to promote licensing of the lead compounds created in IIIS to pharmaceutical companies to implement non-clinical and clinical development. IIIS would not commit itself to the risky drug development but seek a pharmaceutical company accepting risks through licensing of lead compounds at the appropriate stage on R&D process.

In FY2017, S'UIMIN Inc. succeeded in the negotiations for licensing an animal model of narcolepsy to a pharmaceutical company and for transferring the IP right of an opioid δ agonist to another pharmaceutical company.

1-2-2. Collaboration/research alliances of translational researches with outside groups

Efforts have been continued to increase and expand collaboration/research alliances of translational researches with outside groups including groups in University of Tsukuba, the satellites, external research institutions, and even research groups in industries.

(1) Optimization of a CNS drug with 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 non-clinical and clinical development in collaboration with the company.

The progress of the collaboration is described at "(9) Design and synthesis of orexin agonists" in **1-1-3.**

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

The purpose of this study is to investigate adverse 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 adverse 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 (suborexant, brotizolam and a placebo) 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), agility and dynamic balance test (agility and dynamic balance) and Stroop color-word test (executive function) are conducted before the administration and immediately after awakening. We have already completed the intervention trial with 30 subjects, and the preliminary analysis revealed that static balance was impaired significantly ($p < 0.05$) with brotizolam (the positive control). In contrast, suvorexant showed no balance impairments. We are preparing for submission of an original paper.

(3) Exploratory research of RBD treatment by collaboration with Sumitomo Dainippon Pharma Co., Ltd.

Currently, the benzodiazepine clonazepam is often used as the initial therapy for REM sleep behavior disorder (RBD). Clonazepam is associated with significant adverse effects, which must be considered in RBD treatment, since most RBD patients are elderly and may have motor or cognitive deficits that make them more sensitive to adverse effects; in addition, many older patients receive polytherapy with other medications. The development of a safer and more effective treatment is thus highly anticipated. From FY2016, we started exploratory research of treatment for 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 clonazepam and 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 FY2016-2017, we investigated in detail one of them, which caused a significant reduction of motor activity during REM sleep (Fig. 15). 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 sleep parameters and EMG power in wildtype littermates (Ishibashi *et al.*, in prep.; patent application, in prep.). Our data support the validity of this mouse model for examining the new drug targets of RBD symptom.

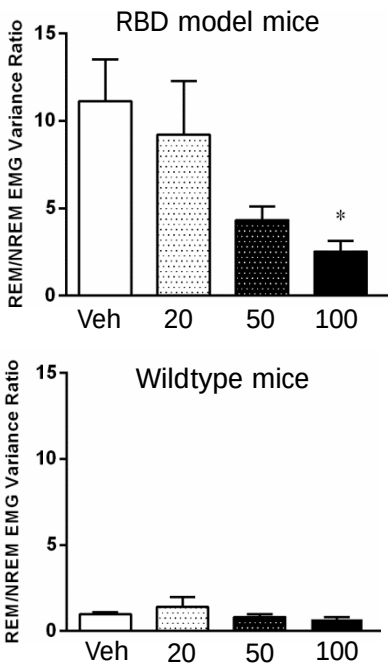


Fig. 15. The drug administration ameliorated the RBD phenotype in our RBD model mice.

(4) Optimization of κ opioid agonist in collaboration with Nippon Chemiphar Co., Ltd.

In FY2017, we have started collaboration with Nippon Chemiphar for optimization of morphinane derivatives YNT-1612, a kappa opioid agonist, obtained by modifying the structure of nalfurafine to remove the sedation of the kappa agonist. The only serious side effect of nalfurafine is sedation, which could not be separated from the analgesic effect. In rotor rod test of YNT-1612 we confirmed the separation of the sedation. As a result of this fruitful collaboration we have discovered more attractive compound than YNT-1612.

(5) Development of algorithms and software for fully-automated sleep staging from EEG and EMG data by collaboration with Center for Computational Sciences, University of Tsukuba

We developed a machine learning algorithm and software, named MASC, to automatically and accurately classify sleep/wakefulness stages of mice using EEG and EMG signals. MASC was based on the algorithm named exFASTER, which we developed by improving FASTER reported by Sunagawa *et al.* previously. By eliminating some drawbacks of exFASTER, MASC successfully achieved more than 95% accuracy, which is higher than any known methods, in the sleep staging based on mouse EEG and EMG datasets.

Besides, we have been developing a sleep staging model for humans, which is based on a convolutional neural network (CNN). CNN is an effective automated feature extraction model, and we used it for detecting characteristics waves of EEG, EOG, and EMG, which are unique to each sleep stage. This model achieved more than 85% accuracy, which is comparable to the results of manual inspections by experts.

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

Using a questionnaire, we recruited 13 candidates of short sleeper from 800 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 was 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 measured the real sleeping time by using 2 channel device for 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, while the father had a normal sleeping time and the younger sister had relatively long sleeping time. The father of another proband was also suspected to be short sleeper. Besides the investigated 800 students, one 47-year-old woman was identified as a short sleeper and her mother was suspected to be the same. We're now preparing for a study of human molecular genetics.

(7) A large-scale epidemiological survey for sleep on occupational fields and a local community by collaboration with Occupational and Aerospace Psychiatry Group, Graduate School of Comprehensive Human Sciences, University of Tsukuba

Objective sleep duration has been reported to associate with health condition. However, association between measured sleep durations and health conditions is still not clear. Genetic factors related with individual differences for sleep duration are also not clear. We, therefore, have planned a large-scale sleep epidemiological survey in collaboration with Sato and Matsuzaki labs. The aims of this study are (1) to examine association of measured sleep characteristics with health conditions including mental health, and (2) to seek genetic factors related to individual differences in sleep duration by identification of familial long sleepers and/or short sleepers thorough the epidemiological study. We collect the data of health checkup of subjects and estimate their sleep duration with not only a questionnaire but also the one week actigraphy records.

Since September 2016, more than 750 have participated in this survey in four occupational fields; a national university including the university hospital, two research institutes and a company. Further, in collaboration with Dr. H. Nakamura at Kanazawa University and Dr. T. Ikaga in Faculty of Science and Technology of Keio University, we have recruited more than 300 residents in a local community in Ishikawa Prefecture. Totally, more than 1,000 individuals have participated in this study.

(8) Study of the effect of body-pressure dispersion of a mattress on sleep in collaboration with Nishikawa Sangyo Co., Ltd.

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, there were significantly fewer SWS episodes with the functional mattress (10.3 ± 1.8) than with the control mattress (16.9 ± 1.2) and longer SWS episode duration (10.9 ± 1.7 min) with the functional mattress than with the control mattress (5.6 ± 0.5min). Delta power density increased (78.7% ± 1.3% vs. 77.5% ± 1.4%) along with improvement in the self-reported sleep quality with the functional mattress. The prolonged slow wave sleep induced by the higher body-pressure dispersion may contribute to the better recovery from the fatigue in the sleep.

Compared with younger people, the nocturnal sleep of elderly people is characterized by many changes from the sleep of younger adults; *i.e.,* decreased amount of sleep, increased number and length of arousals, early awakening, and decreased in slow wave sleep stages. There would be higher needs to improve the sleep problems of elderly people. Therefore, we started a new study of effects of body-pressure dispersion of a mattress on sleep in female adults aged > 64 years.

(9) Suntory Global Innovation Center Ltd.

In FY2017, we collaborated with Suntory Global Innovation Center Ltd. to screen for arousal-promoting food materials. They hope to use newly found natural psychostimulants for the development of functional beverages (drinks that are intended to convey a health benefit) for the Japanese and international markets. Moreover, they used the Lazarus Lab sleep bioassay system for the screening of food materials that promote sleep by antagonizing orexin receptors, similar to the orexin receptor antagonists suvorexant or alomorexant.

1-2-3. Patent applications in FY2017

As discussed above, to enforce the translational research filling the gaps between drug discovery and drug development, we promote licensing of the lead compounds to pharmaceutical companies to implement non-clinical and clinical development. To give sufficient motivation to the companies, intellectual property rights have to be secured for the lead compounds.

We filed 5 patent applications in FY2017. These inventions are all commensurate with developing new drugs of sleep and sleep-related disorders. Since the inauguration of IIIS in December 2012, 19 patent applications have been filed.

1-3. 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.

1-3-1. Number of citations of published papers, and contribution as reviewers and editors

WPI papers published by IIIS members are highly cited. The number of the citations in 2017 (calendar year) increased to 682, 6 times as many as that in 2014. Those published in high impact journals (with impact factors > 10) in 2017, such as *Nat Commun*, *Cell Metab*, *PNAS*, *Brain*, etc. will also be highly cited in the following years.

PIs in the core group of IIIS actively contribute to scientific community through serving as editors and/or reviewers of scientific journals. 8 PIs are appointed as editors of 12 journals and 12 PIs serve as reviewers of many journals including *Cell*, *Nature*, *Science*, *J Neuroscience*, *PNAS*, *PLoS One*, *Sleep*, etc. The average number of reviewing in FY2017 reaches more than 10.2.

1-3-2. Career tracks of ex-IIIS members (faculties, postdocs and students)

IIIS has produced an increasing number of alumni (about 50 people including students) for 5 years since the establishment.

Ex-IIIS members (faculties and postdocs) acquired various research positions: a professor, an assistant professor and a postdoc in the University of Tokyo, a tenured-assistant professor in University of Tsukuba, a professor in Daiichi University of Pharmacy, an assistant professor in Tokyo Medical University, a board member as the CTO of a venture company, a researcher in National Agriculture and Food Research Organization, an associate professor in Waseda University, etc. It is evident that achievements and experiences at IIIS positively contribute to the career paths as a researcher or an innovator from the acquired positions.

Many graduate students that joined the private companies after finishing Master courses in IIIS also engage in science-related jobs.

1-3-3. Securing competitive research funding

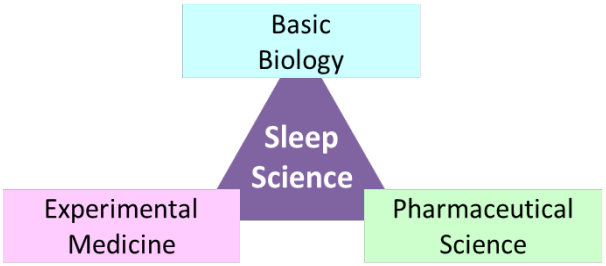
External funds acquired by the researchers in IIIS core team, except for Yanagisawa's grant of the Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST) project started before the establishment of IIIS, have drastically increased as ¥1,520,000 in FY2012, ¥63,840,000 in FY2013, ¥177,930,000 in FY2014, ¥282,070,000 in FY2015 and ¥610,920,000 in FY2016. In FY2017, the total amount of external funds acquired by IIIS core researchers reached ¥666,760,000. Particularly increases of acquired total amounts of Grants-in Aid for Scientific Research (JSPS) were remarkable (¥870,000 (FY2012), ¥23,470,000 (FY2013), ¥102,190,000 (FY2014), ¥115,540,000 (FY2015), ¥285,970,000 (FY2016), and ¥351,900,000 (FY2017)).

In University of Tsukuba, we have award system for the faculty who acquired large scale external funds. Six PIs, half of IIIS core PI, were honored for their achievements of acquiring external funds in FY2017, though there are only 126 award winners among total 2041 faculty members in University of Tsukuba. IIIS would be assessed as 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 FY2017 as described in **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 and verifying treatment strategies for sleep disorders, as shown in **1-1**. To achieve these objectives, we have to conduct 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 FY2017, to reinforce research capabilities of the team, especially in experimental medicine, T. Abe was invited from National Institute of Advanced Industrial Science and Technology and appointed as co-PI (Associate Professor) in Satoh Lab as of November 1, 2017. His appointment and installation of a human metabolic chamber to the clinical sleep lab improved our capability of human research significantly.

To strengthen pharmaceutical science in the team, we have commenced collaboration with a global pharmaceutical company since September 2015. We have appointed the leader of the collaboration on the company side as the Satellite PI. Since the first leader left the company in August 2016, his successor is now appointed to the Satellite PI. 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.

2-3. Collaborative research among laboratories

Collaborative research among laboratories in IIIS is thus crucial to fuse 3 research fields into "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. Holding Work In Progress (WIP) meetings and Dojo journal club, where all of IIIS member get together at the auditorium and introduce the research progress or published paper every week, facilitate communication among labs. As a result, the number of articles by collaborative research has drastically increased since FY2015. The Nature paper published by Funato *et al.* in 2016 is a good example of the successful internal collaborations involving 4 laboratories. Joining of young PIs, Dr. Honjoh and Dr. Abe, would accelerates generation of new collaborative research, and cross-sectional research activities are expected to further develop in the future.

#	Article information	Labs involved
1	Wang Z *et al.* (in press) *Nature*	Liu, Yanagisawa/Funato, Takahashi S
2	Wang Y *et al.* (in press) *Nature Commun.*	Liu, Yanagisawa/Funato, Sakurai, Nagase
3	Yamamoto N *et al.* (2017) *Bioorg. Med. Chem. Lett.* **27**(17): 4176-4179.	Yanagisawa/Funato, Nagase

4	Irukayama-Tomobe *et al*. (2017) *Proc. Natl. Acad. Sci. U.S.A.* **114**(22): 5731-5736.	Yanagisawa/Funato, Sakurai, Nagase, Vogt
5	Nagase H *et al*. (2017) *J. Med. Chem.* **60**(3): 1018-1040.	Nagase, Yanagisawa
6	Purple RJ *et al*. (2017) *Sci Rep* **7**: 46247.	Sakurai, Sakaguchi
7	Yoo SH *et al.* (2017) *Proc. Natl. Acad. Sci. U.S.A.* **114**(42): E8855-E8864.	Takahashi J, Green
8	Hughes ME *et al.* (2017) *J. Biol. Rhythms* **32**(5): 380-393.	Takahashi J, Green
9	Acosta-Rodriguez VA *et al.* (2017) *Cell Metab.* **26**(1): 267-277.e2.	Takahashi J, Green
10	Yagishita Y *et al.* (2017) *Cell Rep* **18**(8): 2030-2044.	Fukamizu, Takahashi S
11	Ogawa Y *et al.* (2017) *J. Comp. Neurol.* **525**(18): 3809-3820.	Vogt, Yanagisawa
12	Oishi Y *et al.* (2017) *Cell Metab.* **25**(2): 412-427.	Lazarus, Shimano
13	Oishi Y *et al*. (2017) *Brain Struct Funct* **222**(6):2907-2915.	Lazarus, Yanagisawa/Funato
14	Kaushik MK *et al*. (2017) *PLoS One* **12**: e0172508.	Urade, Yanagiswa/Funato
15	Zhang BJ *et al*. (2017) *Neuroscience* 340: 258-267.	Urade, Lazarus
16	Ogawa Y *et al*. (2016) *eLife* e21055.	Yanagisawa/Funato, Hayashi
17	McEown K *et al*. (2016) *eLife* e20269.	Urade, Lazarus
18	Funato *et al*. (2016) *Nature* **539**: 378-383.	Yanagisawa/Funato, Liu, Hayashi, Takahashi S, Takahashi J
19	Deguchi Y *et al*. (2016) *Cell Rep* **17**: 2405-2417.	Urade, Lazarus
20	Okamoto K *et al*. (2016) *PLoS One* **11**: e0164716.	Yanagisawa/Funato, Sakurai
21	Chen L *et al*. (2016) *Neuropsychopharmacology* **41**: 2133-2146.	Urade, Lazarus
22	Hossain MS *et al*. (2016) *Sci Rep* doi:10.1038/srep32453	Yanagisawa/Funato, Takahashi J
23	Tsuneki H *et al*. (2016) *Endocrinology* **157**: 4146-4157.	Yanagisawa/Funato, Sakurai
24	Motoike T *et al*. (2016) *Proc Natl Acad Sci* USA **113**: 6023-6028.	Yanagisawa/Funato, Sakurai
25	Bjorness TE *et al*. (2016) *J Neurosci* **36**: 3709-3721.	Yanagisawa/Funato, Greene/Vogt
26	Fujinaka A *et al*. (2016) *Mol Brain* doi: 10.1186/s13041-015-0184-0.	Sakurai, Sakaguchi, Lazarus
27	Tsuneki H *et al*. (2015) *Endocrinology* **157**: 195-206.	Yanagisawa/Funato, Sakurai
28	Oishi Y *et al*. (2016) *J Vis Exp* **107**: e53678.	Urade, Lazarus
29	Nagahara T *et al*. (2015) *J Med Chem* **58**: 7931-7937.	Nagase, Yanagisawa/Funato
30	Cherasse Y *et al*. (2015) *Mol Nutr Food Res* **59**: 2087-2093.	Urade, Lazarus
31	Lee IT *et al*. (2015) *Neuron* **85**: 1086-1102.	Yanagisawa/Funato, Takahashi J
32	Kaushik MK *et al*. (2014) *Exp Neurol* **253**: 82-90.	Urade, Lazarus
33	Wang Z *et al*. (2014) *J Biol Chem* **289**: 31950-31959.	Yanagisawa/Funato, Liu
34	Kaneko K *et al* (2014) *Am J Physiol Regul Integr Comp Physiol* **306**: R265-272.	Urade, Lazarus
35	Soya *et al*. (2013) *J Neurosci* **33**:14549-14557.	Yanagisawa/Funato, Sakurai
36	Lazarus *et al*. (2013) *Curr Opin Neurobiol* **23**: 780-785.	Urade, Lazarus
37	Suzuki A *et al*. (2013) *Proc Natl Acad Sci* USA **110**: 10288-10293.	Yanagisawa/Funato, Greene/Vogt

3. Establishing international research environment

* Describe what's been accomplished in the efforts to raise the center's recognition as a genuine globally visible 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

On matters of particular note, 7 outstanding foreign researchers were invited to WPI-IIIS Symposium (held on December 14, 2017 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 20 WPI-IIIS Seminars in FY2017, where we

invited domestic and international researchers in sleep/neuroscience fields almost every other week; 7 speakers from overseas gave us lectures and the ratio of foreign researchers were 35% of the total seminar speakers in FY2017. Consequently, 128 seminars have been conducted since the inauguration in December 2012.

While it is not explicitly described in the Appendix 5, besides foreign researchers, we also invited outstanding Japanese researchers working in foreign countries. Dr. Noboru Hiroi from Albert Einstein College of Medicine and Dr. Tsukasa Kamigaki from University of California, Berkeley, gave us a lecture at WPI-IIIS seminar on July 24th and on July 28th, respectively.

Another thing especially worth mentioning is close collaboration with a researcher in the global pharmaceutical company who has joined IIIS as a Satellite PI in FY2017. Regarding the progress and results of collaborative research, we have frequently exchanged e-mails and conducted meetings through WebEX to strengthen our relationship.

On the other hand, the PIs at overseas satellites actively participate in research activities at IIIS. Dr. Q. Liu stayed in IIIS for 87 days during 5 visits to Japan in FY2017, and initiatively attended to WPI-IIIS Symposium. Dr. R. Greene stayed at IIIS for 28 days in 3 visits to Japan in FY2017, and attended to the International Symposium as well. They actively contribute to the management of IIIS by participating in the PI meeting every month via Skype from UTSW. Dr. Yang Dan, another overseas satellite PI, had no opportunities to visit to IIIS but scheduled to join some IIIS events in the next fiscal year. (Refer to Appendix 5)

3-1-2. Hosting international meetings

IIIS hosts international meetings every year since the establishment in 2012. We held the international symposium "The 6th Annual IIIS Symposium" in Tokyo on December 14, 2017. Building on the experience of the past symposium collaborated with an industry, we co-hosted the symposium with the global pharmaceutical company, MSD. We invited 7 international and 6 domestic speakers, and about 200 researchers and students participated in and enjoyed active scientific discussion. Many invited speakers disclosed unpublished data of their studies, which inspired new ideas and expanded collaboration opportunities.

The joint meeting with the industry gathered people not only from academia but also from pharmaceutical/chemical companies, and largely contributed to create novel networks and improve domestic/international visibility of IIIS. The sponsorship also let us reduce the cost of holding the international meeting.

For the next annual symposium, we have been planning to involve the team of Grant-in-Aid for Scientific Research on Innovative Area, “Creation and Promotion of WILLDYNAMICS,” to boost interdisciplinary network and studies.

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

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

In FY2017, we newly employed 15 researchers including 4 foreign researchers and 4 Japanese researchers that had worked actively in foreign countries.

In the time series, in April, we employed 3 assistant professors and 3 postdocs including Dr. Arisa Hirano from University of California San Francisco to Sakurai Lab. She is a potential candidate of female PI in the next fiscal year. In July, we hired Dr. Katsuyasu Sakurai from Duke University Medical Center, as an assistant professor in Liu Lab, and Dr. Insung Park as a postdoc of Satoh Lab, who was a graduate student at the University of Tsukuba Graduate School of Comprehensive Human Sciences in the last fiscal year. In September, our unremitting effort finally brought us the female PI, Dr. Sakiko Honjoh from the University of Wisconsin-Madison. She started to set up a new laboratory with 2 postdocs recruited from Kyoto University by herself. In October, Dr. Deependra Kumar, who was a visiting foreign research fellow until September 30th, joined us as a postdoc of Sakaguchi Lab. We hired Dr. Takashi Abe as another Jr. PI in November. He studied as a postdoc at Pennsylvania University School of Medicine in the United States for three years and at JAXA and AIST in Tsukuba for another three years. He joined to Sato/Tokuyama Lab as Co-PI/Associate Professor. In January, Dr. Karim Fifel from Leiden University Medical Center, Netherland was hired through international open recruitment to Lazarus Lab. Lastly, Dr. Javier Antonio Diaz Cisternas from Facultad de Medicina, Universidad de Chile was recruited to Greene/Vogt Lab.

As mentioned above, IIIS actively engages in international open recruitment by placing job advertisements on websites such as the homepage of IIIS, jREC-IN jobsite and naturejobs.com,

etc. We renewed IIIS's Website completely in December 2017, and it became possible for foreign researchers to select and apply for the laboratory matching to their interests and expertise. The total number of applications for postdoctoral fellow positions in FY2017 was 45, where 100% of the applicants were foreign researchers. As for Jr. PI, we had 6 applicants, whose 67% were foreign researchers. In addition to posting job advertisements, we have employed some brilliant researchers through the continued efforts in international recruitment through networks of PIs. We regularly invite speakers from outside for the IIIS Seminar series and make use of these opportunities to look for Junior PI candidates in particular.

On the other hand, we accepted 10 visiting foreign research fellows from overseas in FY2017 as shown in the following table besides foreign students discussed in **3-2-2**. Most of them stayed at IIIS for sufficient time (4 months-2 years) to obtain skills and knowledge of sleep research, to advance their career paths.

Name of Visitors	Country	Instructor	Duration
Deependra Kumar	India	Sakaguchi	Oct 1, 2015～ Sep 30, 2017
Sunil Kumar Vimal	India	Lazarus	Jan 1, 2017～ Jan 1, 2018
Ying Liu	China	Liu	Mar 1, 2017～ Aug 31, 2017
Zhenkang Chen	China	Liu	Mar 1, 2017～ Aug 31, 2017
Sakthivel Srinivasan	India	Sakaguchi	Apr 1, 2017～ Mar 31, 2018
Xue Gao	China	Liu	Jul 1, 2017～ Mar 31, 2018
Chengyuan Ma	China	Liu	Jul 1, 2017～ Dec 31, 2017
Shuang Zhou	China	Liu	Jul 1, 2017～ Nov 17, 2017
Alessandra Matzeu	Italy	Sakurai	Oct 9, 2017～ Apr 2, 2018
Zhiyu Chen	China	Liu	Feb 1, 2018～ July 31, 2018

3-2-2. Admission of foreign students

We have accepted 10 international students in FY2017 through various systems to accept foreign students to University of Tsukuba, as shown in the following table. We accepted 2 students from Korea and Switzerland 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. The bylaw for TSSP was revised in March 2016, according to our request to extend a period of stay from 3 month to 1 year. We plan to accept more students as interns/trainees under this program to hold a workshop of skills/experimental methods of sleep research.

In addition, we invited 4 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.

IIIS accepted 3 graduate students through Japanese Government (MEXT) Scholarship Program which offers scholarships to international students that aim to get Master or Ph.D. degree at the Graduate School of Comprehensive Human Sciences (Master's Program in Medical Sciences and Doctoral Program in Biomedical Sciences/Clinical Sciences) of University of Tsukuba.

Concerning financial support for foreign students, 1 graduate student, I. Park was approved for a Research Assistant to obtain monthly wages in FY2017. As mentioned in **3-2-1,** he was employed as a postdoc after the RA period.

Taking advantage of these acceptance and supporting systems, we will broaden up opportunities for training of foreign students.

Name	Status	Country	Instructor	Duration	Remarks
Mujin Kim	Graduate	Korea	Sakaguchi	Sep 4, 2017～Sep 16, 2017	TSSP
Timothy Ecott	Graduate	Swiss	Hayashi	Oct 1, 2017～Dec 31, 2017	TSSP
Solal Chauquet	Graduate	France	Lazarus	Jan 9, 2017～Jun 9, 2017	CiC
Thibault Bittar	Graduate	France	Urade	Jan 9, 2017～Jun 9, 2017	CiC
Gabrielle Boix	Graduate	France	Sakurai	Feb 1, 2018～Jun 30, 2018	CiC
Juliette Torregrosa	Graduate	France	Sakaguchi	Feb 1, 2018～Jun 30, 2018	CiC
Pimpimon Nondhalee	Graduate	Thailand	Sakaguchi	Oct 1, 2016～Sep 30, 2018	MEXT
Vergara Garcia	Graduate	Chile	Sakaguchi	Oct 1, 2017～Sep 30, 2021	MEXT
Xuhao Zhou	Graduate	China	Lazarus	Oct 1, 2017～Aug 31, 2019	MEXT
Insung Park	Graduate	Korea	Satoh	Apr 1, 2017～Jun 30, 2017	RA

3-3. Other initiatives

After the completion of our new research building, requests to visit IIIS greatly increased. In FY2017, we accepted visits of 25 groups from overseas universities, research institutes, world organizations, media and high schools, and more than 200 visitors enjoyed the introduction/research presentation and lab 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.

The number of press releases in FY2017 on IIIS research achievements written in English became twice as many as that in FY2016. The increase improved the coverage by overseas media including newspapers and online media. A distinguished science writer, invited by Director Yanagisawa, visited IIIS and interviewed most of PIs, spending all day. The article was posted on a globally famous magazine “The Atlantic” and shared with people around the world via SNS. “National Geographic” also visited IIIS to cover our recent discoveries. International visibility of IIIS is rising sharply.

In response to growing reputation, we renewed IIIS official website which could be a major touch point with various people. PIs and their research activities are attractively introduced with the modern design to attract especially young researchers. Its contents such as sleep Q & A, in which IIIS researchers answer to questions from the general public, have been becoming popular. The more people visit the website, the more opportunities of collaboration with diverse sectors could arise in the future.

4. Reforming the research organization

* 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.
* Please describe the center’s operation and the host institution’s commitment to the system reforms.

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 24 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 five young PIs, appointed as either Associate Professor or Assistant Professor, in the core group of IIIS. 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 streamlined support organization that provides researchers with a cost-effective service to let them 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 two key positions in the administration, *i.e.*, Administrative Director, and the leader of Research Strategy and Management team 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. Further, a University Research Administrator (URA) has been assigned to the Research Strategy and Management team with a coalition of the Research Administration/Management Office in the university headquarters to support post- and pre-award research administration. The function of the Research Strategy and Management team has pre-empted the URA system, the development of which has been focused on recently by MEXT and which constitutes one of the IIIS characteristics.

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

We have made significant efforts to improve administration systems, rules and bylaws of the University to realize objectives/policies of IIIS and the WPI program as follows.

1) Establishment of IIIS's own personnel committee
2) Introduction of a simple appointment system comprised with 2 steps, *i.e.*, the intensive deliberation at the personnel committee and the approval at Administration Center Appointment Committee in the University headquarters
3) Introduction of a simple system of the achievement evaluation and the salary-raise based on the appraisal
4) Revision of the bylaw for Tsukuba Short-term Study Program (TSSP) to let foreign students as interns stay for training longer than 3 months (within a year)
5) Operation of IIIS's own animal facility, in collaboration with Laboratory Animal Resource Center of Faculty of Medicine, University of Tsukuba, as a pilot of new animal facility

In FY2017, we continued the efforts of system reforms in cooperation with University of Tsukuba as follows.

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 19 cases in the University now.

Starting as of April 1, 2018, IIIS will make another joint appointment. Dr. Emi Morita works for Forest Research and Management Organization (FRMO) in Tsukuba as PI and has served as a visiting associate professor in IIIS since FY2015, to enforce her research on sleep epidemiology. Since her efforts for the study in IIIS became much bigger recently, at FRMO's request, we concluded research collaboration agreement to start her joint appointment from April 1st, 2018.

4-2-2. Expansion of activities of the professor specially appointed by the President

One of PIs in IIIS, Dr. H. Nagase actively pursues the drug discoveries of orexin 2 receptor agonists and orexin 1 receptor antagonists, and leads the collaboration with the pharmaceutical companies, which is crucial to achieve the objective, the development of new treatments strategies for sleep disorders. He, however, became 70 years old in FY2017 and is supposed to retire as of March 31, 2018, according to the bylaw of mandatory retirement age. Since he is essential for the success of drug discovery in IIIS, we consulted the President and the Vice-president for personnel affairs for the extension of his appointment. The president decided to appoint him to "Tokumei-kyoju," the professor specially appointed by the President. Since research and education were not specified as activities/functions of "Tokumei-kyoju" in the internal regulations, the bylaw was revised to allow research and education under President's permission.

4-2-3. Delegating technology transfer function to the spin-out company

University of Tsukuba previously established a TLO, but it has been out of business due to unsuccessful business outcome. Headquarters for International Industry-University Collaboration takes care of technology transfer now, but its capacity is limited. To let the business sector of IIIS newly established in October 2017, S'UIMIN Inc., serve as private TLO, Headquarters for International Industry-University Collaboration concluded an agreement of outsourcing TLO function with S'UIMIN Inc. to make up the shortfall of its capacity (refer **5-3-2** for details).

4-2-4. A new dispensation of distributing license revenues to research centers/departments

To introduce an institutional dispensation of distributing a part of licensing revenues to research centers/departments having yielded the corresponding IP rights, we negotiated with the University management. It was agreed that, after deduction of the compensation for inventors and 10% of overhead expenses, licensing revenues received by the University should be distributed to the headquarters and IIIS in proportion to IP cost burdens (refer **5-3-2** for details).

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
- Host institution's organizational reforms carried out for the Center's autonomous administration simultaneously with the creation of the Center.

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 were reviewed and reconsidered in the course of advancing the research strategy based on the objectives outlined in **1-1**.

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 appointed the first female PI, Dr. Sakiko Honjoh in September 2017, as mentioned in **3-2-1**. She succeeded in recruiting 2 young postdocs from the lab in Kyoto University where she got Ph.D. As the next step to increase female PI in the core group of IIIS, we continue exploring possibilities of female appointment including the potential promotion of Dr. Arisa Hirano to co-PI in Sakurai/Sakaguchi Lab.

Organizational rejuvenation is another element of the consideration to keep productivity towards achieving the objectives. Especially, the reappointment of 2 elder PIs, Dr. Y. Urade (64 years old) and Dr. H. Nagase (70 years old) was carefully considered. As described in WPI Progress Report FY2016, we had carefully discussed for more than one year and decided to limit the extension of Dr. Urade's employment contract to March 2018. Dr. Nagase actively pursues the drug discoveries of orexin 2 receptor agonists and orexin 1 receptor antagonists, and leads the collaboration with the pharmaceutical companies, which is crucial to achieve the objective, the development of new treatment strategies for sleep disorders. 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.

We continue and even strengthen the collaborations with outside clinical/human research groups to translate the basic studies into human or to conduct studies of experimental medicine, as mentioned in **1-2-2**. As the collaborations increase, we expanded Satoh/Tokuyama Lab working on human sleep physiology as partners of the outside collaborators. In November 2017, we appointed Dr. Takashi Abe, a specialist of human sleep research, as co-PI/associate professor in Satoh/Tokuyama Lab. Dr. K. Tokuyama has served as co-PI/Professor collaborating with Dr. M. Satoh since FY2016 voluntary, while belonging to Faculty of Health and Sport Science, University of Tsukuba. To increase his efforts for the studies in IIIS, IIIS and Faculty of Health and Sport Science jointly appointed him by using the research fund from Nishikawa Sangyo Co. Ltd. The human sleep physiology lab, named as Satoh/Tokuyama/Abe Lab, is managed by 3 PIs and expanded to cover various aspects of translational/human studies.

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

In the revision of the Center Plan in FY2016, we reduced the target numbers of researchers including PIs and research support staffs from 115 to 62 and from 40 to 20, respectively. Since the personnel expenses occupied 70% of the WPI subsidy in FY2016, we judged that there was no much room to increase researchers and supporting staffs. On the other hand, we have tried to cover the personnel expenses, especially those of postdocs, by competitive external research funding, in order to decrease the ratio of personnel costs in the WPI subsidy budget. In the period from March 31, 2017 to March 31, 2018, researchers increased from 56 to 59 and the number of supporting staffs staid at 14, while we managed to reduce the ratio of personnel costs to 69% of the WPI subsidy budget. We will continue our efforts to cover the personnel expenses by external funding to attain the target numbers of researchers and research supporting staffs.

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 by the examination committees of the graduate schools and now accept 50 students from 4 graduate schools.

In FY2017, we introduced a mental care program for all the students studying in IIIS to provide them with a better environment in which they can concentrate on their studies. Face-to-face interviews by a counselor were conducted to find out various troubles or problems that a student confronts at early stage, and to take appropriate measures as needed. After the series of the interview completed, an anonymous survey with a questionnaire was conducted to get mostly good feedbacks on the counseling for mental healthcare from the students. We will continue the counseling in FY2018.

We would like to offer graduate students better financial support as well, to be a good model of research centers in University of Tsukuba. One of the support programs we established in FY2017 is IIIS Research Assistantship (IIIS RA) system characterized by the matching fund contributed by both of PI's external funding and WPI subsidy (¥120,000 month/person). We will also continue IIIS RA system in FY2018.

5-2. Future prospects of IIIS

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

The amount of competitive external research funding that the IIIS core group acquired in FY2017 reached ¥667 million by great efforts of all the researchers and the research strategy/management team.

We have acquired quite a few long-term research grants, *e.g.*, 1) JST CREST for FY2016-2021, 2) JSPS Grant-in-Aid for Scientific Research on Innovative Areas for FY2016-2020, 3) JSPS Grant-in-Aid for Specially Promoted Research for 2017-2021, 4) AMED Strategic Research Program for Brain Science for FY2016-2020, 5) MEXT Regional Innovation Ecosystem Support Program for FY2016-2020, 6) MMAF Model R&D Project in Alliance for Knowledge Integration/Application among Industry, Academia and Government for FY2017-2020, 7) AMED Cyclic Innovation for Clinical Empowerment FY2018-2021, which provide IIIS with a stable financial foundation.

We encourage all eligible researchers/technicians in IIIS to apply for Grant-in-Aid for Scientific Research every year. In FY2017, 60 applications were submitted to JSPS and 15 were adopted as of April 1, 2018. The acceptance rate decreased from 33% to 25% this year. To improve the acceptance rate, the research strategy/management team will provide young faculties and postdocs that failed to get the grant in spite of good appraisal with individual supports. In addition, young researchers, particularly junior PIs and young faculties diligently applied for research grants offered by various foundations for promotion of science. In FY2017 we obtained 18 grants amounting to ¥23,150,000 in total.

We will continue the efforts to secure the same or even higher levels of external research funds. R&D Center for Frontiers of MIRAI in Policy and Technology (F-MIRAI), established as the joint project between TOYOTA and University of Tsukuba in April 2017, decided to move into the future expansion space on 4th floor in IIIS building in June 2017. We are planning to start a long-term collaboration, and 130 m^2 of office was furnished in September 2017 as the first step.

We will continuously apply for other large-scale research grants, such as Cross-ministerial Strategic Innovation Promotion Program at Cabinet Office, Government of Japan, etc. We also seek opportunities of collaborations with pharmaceutical companies and other industries.

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 for the quest for truth and research for innovation contributing to society, in wide-ranging disciplines and research fields. To realize these objectives, the university is making a plan of reorganization/restructuring/merger of all research centers and will 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 follows.

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 external research funding.
3) The University supports most of the personnel cost of Vice Center Director, Dr. Sakurai.
4) The University delegates 3 university personnel to the administrative positions, including Vice-Administrative Director, in the key areas of general affairs and accounting. Since November, 2017, a URA having the career of a system engineer has been also assigned to the Research Strategy and Management team in IIIS with a coalition of the Research Administration/Management Office in the university headquarters, supporting post- and pre-award research administration as well as management of the IT infrastructure of IIIS building .
5) 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 FY2017.

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.

The measures to sustain IIIS after the program funding ends have been consisted with 3 plans; 1) to offer a tenure position to qualified PIs, 2) to return licensing revenues to IIIS, 3) to implement the future expansion space in IIIS building. We are trying to add another plan to sustain IIIS by contributing to a new Ph.D. program.

5-3-1. Tenure positions of PIs

In the third mid-term plan of University of Tsukuba, a strategic framework of research resources including tenure positions over the entire university will be set out and it will be planned to reallocate them based on evaluation of research activities/achievements of Faculties and research centers in the third mid-term plan of University of Tsukuba. According to results of the evaluation, some tenure positions could be allocated to IIIS.

On the other hand, University of Tsukuba has started restructuring and consolidation of research centers since FY2017, to classify them into 4 levels. The research centers at the top international level are ranked on the 1st level (R1). To support further the research centers with the highest reputation on R1, *e.g.*, IIIS, TARA Center, Center for Computational Sciences, the university management plan to propose a draft budget plan (gaisan-youkyu) to MEXT for the establishment of Global Research Center Initiatives (provisional name) which accommodates these research centers to be an independent department of the university. If the draft budget plan is accepted by MEXT and eventually by Ministry of Finance, additional tenure positions could be offered to PIs in IIIS.

The President, University of Tsukuba, Dr. Nagata has committed himself to offer a tenure position to qualified PIs in IIIS, and the Vice President for Research is planning specific measures in combination of the position reallocation and the establishment of new organization

The assistant professor in IIIS, Dr. Arisa Hirano at Sakurai/Sakaguchi Lab was recommended to the tenure track assistant professor at Faculty of Medicine, University of Tsukuba by the Head of Department of Biomedical Science, Dr. Satoshi Takahashi, due to her research achievements. If she is adopted to the tenure track position, we will offer her junior-PI position and she will be the second female PI in IIIS.

5-3-2. Return of licensing revenues to IIIS

We were 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. To implement this idea, we took 2 specific measures; 1) establishing a company to serves as a private TLO for the promotion of licensing the IP rights to industries, and 2) introducing an institutional dispensation for the distribution of license revenues to research centers/departments having yielded the IP rights.

(1) Establishment of the private TLO

University of Tsukuba previously established a TLO, but it is out of business now due to unsuccessful business outcome. Headquarters for International Industry-University Collaboration thus takes care of technology transfer, but its capacity is rather limited.

As discussed in **1-2-1**, we established S'UIMIN Inc. as the spin-out of IIIS on October 17, 2017 (CEO: Dr. M. Yanagisawa, and COO: Dr. M. Fujiwara, former president of Chiome Bioscience Inc.). S'UIMIN functions as IIIS Business Sector for social implementation of its business seeds, such as drug leads of sleep disorders, software programs of cognitive behavioral therapy, a sleep measuring system, a big database of sleep, software program of sleep disorder diagnosis, a vigilance measuring system, molecular targets for drug discovery, animal disease models and so on. S'UIMIN engages in three business models, 1) to develop a product until putting into practical use and carry out profit business by itself, 2) to carry out the development/improvement of seeds to attractive leads/technologies and license them to pharmaceutical or other industrial companies with higher values, and 3) to conduct just TLO activities to license out the IP rights IIIS created. Headquarters for International Industry-University Collaboration concluded an agreement of outsourcing TLO function to make up the shortfall of its capacity with S'UIMIN, accepting the same commission rate as those of TODAI TLO, Ltd. and Kansai TLO Co. Ltd., *i.e.*, 30%. S'UIMIN implements their third business model on the basis of this agreement, and had already succeeded in executing 1 material transfer agreement and 1 patent transfer agreement with pharmaceutical companies in FY2017. Thanks to Dr. Fujiwara's expertise in technology transfer activity, economical conditions of the both agreements were much higher than those of the agreements University of Tsukuba has made in the past.

(2) Distribution of license revenues to IIIS

In the "rules for office regulations and other regulations on inventions" of University of Tsukuba,

it is not specified whether licensing revenues received by the University should be distributed to research centers/departments having yielded the corresponding IP rights or not. Aiming to introduce an institutional dispensation for the distribution, we negotiated with the University management, including the President, and 3 Vice-presidents responsible for research, finance, and university-industry collaboration.

To realize licensing of a drug lead to a global pharmaceutical company, the IP right of the lead has to be secured in many countries. IIIS thus bears a lot of IP expenses especially to enter the PCT applications into the national phase in many countries. Considering the burden of the IP expenses, it was agreed that, after deduction of the compensation for inventors and 10% of overhead expenses, licensing revenues received by the University should be distributed to the headquarters and IIIS in proportion to IP cost burdens. The agreement let IIIS get a large portion of licensing revenues of promising drug leads such as orexin agonists/antagonists.

5-3-3. Implementation of the future expansion space by R&D Center for Frontiers of MIRAI in Policy and Technology (F-MIRAI)

We have aimed at implementation of the future expansion space in IIIS building, located on the south side of the 4th floor. We have searched several opportunities such as open-innovation drug discovery lab with a pharmaceutical company, or hosting a research group of the JST Strategic Basic Research Programs such as ERATO, as a part of our efforts to obtain major research funds or grants. As described in **5-2-1**, in June 2017, R&D Center for Frontiers of MIRAI in Policy and Technology (F-MIRAI) supported by TOYOTA Motor Corporation decided to move into the future expansion space. F-MIRAI led by Dr. Isamu Takahara is a 5-year joint project between TOYOTA and University of Tsukuba starting from April 2017 to develop fundamental technologies for regional communities to realize Society 5.0, to develop social measurements by applying Internet of Things (IoT), and to resolve the social engineering issues through the big data analysis by artificial intelligence.

We are planning a long-term collaboration with them and, as the first step, we are developing the Mobile Sleep Lab based on a fuel cell bus lent by TOYOTA at no charge, taking advantage of its characteristics. The fuel cell bus can supply bulk power for air conditioning and sleep measurement without noise and vibration, and access easily to subjects at living/working environment. A large funding to implement the collaboration with F-MIRAI would contribute to sustained operation of IIIS after the WPI program funding ends.

5-3-4. Contribution to establishment of a new Ph.D. Program

MEXT is inviting an application for a new graduate school program, Excellent Graduate School (Takuetsu-daigakuin) starting this year. Among a few groups in University of Tsukuba planning to apply for it, a team in Faculty of Medicine is proposing a new Ph.D. program, following to Human Biology Program, University of Tsukuba, which is the Ph.D. program established by Program for Leading Graduate Schools and assessed as “S” by the evaluation at the end of the funding period. In the draft proposal, the Center Director of IIIS, Dr. Yanagisawa is nominated to the Program Coordinator and IIIS is supposed to play a significant role as one of leading research centers/departments contributing to the program. The faculty members of IIIS will participate in this program if it is funded. This program will start from 2018 and continue for 7 years, offering a potential opportunity to fund personnel expenses of some young faculties in IIIS.

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

IIIS put forth multiple and unconventional outreach activities in FY2017. Most notably, we hosted the 6th WPI Science Symposium as a major organizer. Eight hundred onsite visitors, the largest number of guests for the WPI symposium, joined us and enjoyed diversity in science. Especially, a program named “Honki-Giron,” in which renowned researchers and CEOs from private companies gave talks and made discussion, gained glowing reviews.

As the first trial of open house of IIIS, a program via Internet broadcasting, named “IIIS x niconico,” were widely aired. About 20,000 viewers enjoyed the programs including talk-show,

lab-tour and sleep consulting by IIIS researchers as if they participated in onsite open house. Over 95% of them answered “satisfied” in the feedback by a questionnaire on the web. This result showed a potential of the new form of open house through the internet broadcasting.

Challenging a crowdfunding project is also another highlight in FY2017. This project started from March 14, 2018, intended to collect a research fund for the sleep epidemiological study on human in 84 days, and to communicate with public for better understanding of sleep science. To date, the project has made a good start because three major newspapers featured the launch.

In addition, we set up IIIS blog and hold a workshop targeting adults interested or suffered in sleep in collaboration with Hibiya Library in Tokyo.

6-2. Further facility development

We have been successfully operating and maintaining the ARC Satellite animal facility of IIIS without any serious problem/incident including microbiological contamination. Since our research activities are expanding, we installed additional 11 individually ventilated cage (IVC) racks for breeding. Current holding capacity of breeding rooms has grown up to 3,600 cages/18,000 mice. We plan further increase of IVC racks to respond to researcher’s requests. Moreover, at the common space in the Sleep Behavior Lab on the 5th floor, we also installed additional 24 sleep recording chambers with the simultaneous EEG/EMG/video recording system. We also rearranged an experimental area in the Sleep Behavior Lab including partition installation, to further improve efficiency of animal experiments.

We newly launched the Transgenic Core Facility in FY2017, which provides mouse embryo manipulation services, *e.g.*, generation of gene modified mice by CRISPR microinjection/electroportation, *in vitro* fertilization, embryo transfer and embryo/sperm freezing, for researchers of IIIS. Ms. Daniela Klewe-Nebenius was appointed to the manager of the facility, and a highly skilled technician was recruited to support her in the operation of the facility.

Another exciting collaboration project with the School of Art in the university is being planned. “Art Street-Satellite Gallery” for which we provide several spaces in the IIIS building to exhibit a part of the collection of prize-winning artworks created by the students of the School of Art will start from July, 2018.

6-3. Corresponding on the research ethics

To avoid research misconduct, we have launched educational campaigns for research ethics since FY2015. In FY2017, we held two seminars in the series of Research Ethics Seminars; the 3rd seminar entitled “Professional ethics for scientists and journalism” by Mr. Takao Fujiyoshi on September 25, 2017, and the 4th seminar entitled “Anti-Vax campaign using pseudoscience and lawsuits” by Dr. Riko Muranaka (awarded the 2017 John Maddox Prize) on February 13, 2018.

We are planning to introduce IIIS official laboratory notebook to formalize and let everyone use a common hard-covered laboratory notebook for better data management and prevention of research misconduct. We have prepared a standard operating protocol (SOP) on purchasing, distribution, weekly check by mentors, storage, return, archiving, etc.

7. Center’s response to the follow up results in last year

* Transcribe the item from the “Advice/ recommendations” section in the site visit report and “Actions required and recommendations” in the Follow-up report, then note how the center has responded to them.
* For the center launched in FY 2017, please describe the status of response to the pointed items in ″Major points that need to be improved″ of “The screening result for WPI centers launched in FY 2017.”
* However, if you have already provided this information, please indicate where in the report.

7-1. Center’s response to the site-visit report

1. *Identifying the substrates of SIK3 kinase is essential to understand the molecular functions of SIK3. After identifying substrates and their phosphorylation sites, the phosphorylation specific antibodies should be prepared to monitor the spatial and temporal activity of SIK3. The pathway analysis is also useful to understand the signaling pathways mediated by SIK3 and NALCN. This experimental approach is applicable to phospho-proteomic analysis in sleepy brains by Liu.*

   In collaboration with Yanagisawa/Funato Lab, Liu Lab found prospective substrates for SIK3 kinase. The achievement will be published in Nature soon. We will further explore the

signaling pathways underlying sleep/wake regulation and challenge to solve the entire neural network regulating sleep.

2. *Exome and whole genome sequences of DNA extracted from sleep disorder patients cost a lot. Focusing on more basic aspect of sleep science is recommended.*

   We have been implementing research environment for the experiment tied up with outside clinical/human research team. The project team plans to investigate on only sleep disorder patients who show extreme phenotype and expression.

3. *The strategy toward sustaining of IIIS after WPI funding ends does not appear to be promising. IIIS needs to seek more practical ways to ensure their sustainability in the future.*

   As discussed in 5-3, the strategy toward sustaining of IIIS is consisted with 3 measures, each of which has been further implemented to specific plans, as follows.

   1) To secure a sufficient number of tenure positions for qualified PIs, the university management moves ahead with tow specific plans, *i.e.*, a) reallocating tenure positions over the entire university in the third mid-term plan of the University and b) proposing a draft budget plan to establish a new organization accommodating IIIS and other research centers with the highest reputation.
   2) To distribute to IIIS a significant portion of licensing revenues of IP rights created by IIIS, a) the TLO function was outsourced to S'UIMIN Inc., which was originally established to implement translational researches such as the development of the sleep measuring system for diagnosis, in order to maximize the licensing opportunity, and b) it was agreed with the university management that, after deduction of the compensation for inventors and 10% of overhead expenses, licensing revenues received by the University should be distributed to the headquarters and IIIS in proportion to IP cost burdens.
   3) To implement the future expansion space in IIIS building and obtain a large funding for the collaboration, we invited R&D Center for Frontiers of MIRAI in Policy and Technology (F-MIRAI), which is a joint project with TOYOTA Motor Corporation, to the space to conduct a long-term collaboration.

   We are trying to add the 4th measure by applying for a new graduate school program announced by MEXT recently.

   4) To fund personnel expenses of young faculties in IIIS, we cooperate with a team in Faculty of Medicine, University of Tsukuba, to apply for the new graduate school program, Excellent Graduate School [Takuetsu-Daigakuin].

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

   We agree to make the best efforts to recruit a foreign national to substitute a leaving administrative staff in future.

5. *IIIS should create clearer mentorship programs, and delineate better exit or promotion pathways for various young investigators.*

   As discussed in 5-1-3., in University of Tsukuba, all PIs that would like to serve as official dissertation advisors (mentors) of graduate students have to be qualified by the examination committees of the graduate schools. In addition to this initial qualification, there are 2 ways to monitor PI's mentoring, *i.e.*, the "work in progress" meeting (WIP) and the mental care program for all students studying in IIIS. WIP is a review meeting held on the morning of every other Wednesday, in which a presenter nominated from a Lab reports progresses and plans of his/her study to share them with all faculties, postdocs and graduate students in IIIS. It is a good opportunity for the presenter as well as his/her mentor to get positive and negative feedbacks. Face-to-face interviews of students by a counselor are conducted for the sake of their mental care, but offer another way to monitor PI's mentoring.

Concerning mentorship for young investigators including Jr. PIs, interactions with the Center Director and the Vice-center Director are made on a daily basis. The open offices connected with the spiral staircase in the open celling facilitate physical interactions and thus informal communications on science, publication, grant application, etc.

7-2. Center's response to the Follow-up

1. Identifying the substrates of SIK3 kinase is essential to understanding its molecular functions. After identifying the substrates and their phosphorylation sites, phosphorylation specific antibodies should be prepared to monitor the spatial and temporal activity of SIK3. Pathway analysis is also useful to understanding the signaling pathways mediated by SIK3 and NALCN.

In collaboration with Yanagisawa/Funato Lab, Liu Lab found prospective substrates for SIK3 kinase. The achievement will be published in Nature soon. We will further explore the signaling pathways underlying sleep/wake regulation and challenge to solve the entire neural network regulating sleep.

2. Focusing on commercialization will detract from the center's ability to sustain its efforts toward solving more basic science problems, which would be a better way for the center to establish and maintain itself at a level of world prominence in its subject area.

Agreeing to the advice not to focus on commercialization, we decided to limit the scope of our translational research and human studies within basic studies of pharmaceutical science and experimental medicine. We, instead, established a spin-out, S'UIMIN Inc. as IIIS business sector, as we discussed in 1-2. and 5-3-2. S'UIMIN should be responsible for the social and industrial implementation of our business seeds created through basic studies in IIIS, including product development as well as technology transfer to industries. Especially, we promote licensing of the lead compounds of drugs to pharmaceutical companies to implement non-clinical and clinical development, taking advantage of its TLO activities.

3. A serious problem remains with funding after the WPI grant expires. One of the concerns is the budget for supporting the center's continuation. Tsukuba University should reconsider ways to support IIIS after the WPI grant ends.

As discussed in 5-3, the strategy toward sustaining of IIIS is consisted with 3 measures, each of which has been further implemented to specific plans, as follows.

1) To secure a sufficient number of tenure positions for qualified PIs, the university management moves ahead with tow specific plans, *i.e.*, a) reallocating tenure positions over the entire university in the third mid-term plan of the University and b) proposing a draft budget plan to establish a new organization accommodating IIIS and other research centers with the highest reputation.
2) To distribute to IIIS a significant portion of licensing revenues of IP rights created by IIIS, a) the TLO function was outsourced to S'UIMIN Inc., which was originally established to implement translational researches such as the development of the sleep measuring system for diagnosis, in order to maximize the licensing opportunity, and b) it was agreed with the university management that, after deduction of the compensation for inventors and 10% of overhead expenses, licensing revenues received by the University should be distributed to the headquarters and IIIS in proportion to IP cost burdens.
3) To implement the future expansion space in IIIS building and obtain a large funding for the collaboration, we invited R&D Center for Frontiers of MIRAI in Policy and Technology (F-MIRAI), which is a joint project with TOYOTA Motor Corporation, to the space to conduct a long-term collaboration.

We are trying to add the 4th measure by applying for a new graduate school program announced by MEXT recently.

4) To fund personnel expenses of young faculties in IIIS, we cooperate with a team in Faculty of Medicine, University of Tsukuba, to apply for the new graduate school program, Excellent Graduate School [Takuetsu-Daigakuin].

Appendix 1 FY2017 List of Center's Research Results and Main Awards

1. Refereed Papers

- List only the Center's papers published in 2017. (Note: The list should be for the calendar year, not the fiscal year.)

(1) Divide the papers into two categories, A and B.
   A. 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 in which the names of persons affiliated with the WPI program are contained only in acknowledgements.)
   B. WPI-related papers
      List papers related to the WPI program but whose authors are not noted in the institutional affiliations as WPI affiliated. (Including papers whose acknowledgements contain the names of researchers affiliated with the WPI program.)

      Note: On 14 December 2011, the Basic Research Promotion Division in MEXT's Research Promotion Bureau circulated an instruction requiring paper authors to include the name or abbreviation of their WPI center among their institutional affiliations. As some WPI-affiliated authors of papers published up to 2011 may not be aware of this requirement, their papers are treated as "WPI-related papers." From 2012, however, the authors' affiliations must be clearly noted and only category A papers will be basically listed.

(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 paper's categories when listing them.
   - Assign a serial number to each paper to be used to identify it throughout the system.
   - Order of Listing
      A. WPI papers
         1. Original articles
         2. Review articles
         3. Proceedings
         4. Other English articles
         5. Articles written in other than English

      B. WPI-related papers
         1. Original articles
         2. Review articles
         3. Proceedings
         4. Other English articles
         5. Articles written in other than English

(3) Submission of electronic data
   - In addition to the above, 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 2017.
   - They will be used as reference in analyzing the trends and whole states of research in the said WPI center, 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. Honjoh S, Ihara A, Kajiwara Y, Yamamoto T, Nishida E (2017) The Sexual Dimorphism of Dietary Restriction Responsiveness in Caenorhabditis elegans. *Cell Rep* **21**(13): 3646–3652. doi:10.1016/j.celrep.2017.11.108

2. Liu J, Zhang MQ, Wu X, Lazarus M, Cherasse Y, Yuan MY, Huang ZL, Li RX (2017) Activation of Parvalbumin Neurons in the Rostro-Dorsal Sector of the Thalamic Reticular Nucleus Promotes Sensitivity to Pain in Mice. *Neuroscience* **16**(366): 113-123. doi:10.1016/j.neuroscience.2017.10.013

3. Maeda S, Nakamura T, Harada H, Tachibana Y, Aritake K, Shimosawa T, Yatomi Y, Murata T (2017) Prostaglandin D-2 metabolite in urine is an index of food allergy. *Sci Rep* **7**(1): 17687. doi:10.1038/s41598-017-17798-w

4. Ogawa Y, Kanda T, Vogt K, Yanagisawa M (2017) Anatomical and electrophysiological development of the hypothalamic orexin neurons from embryos to neonates. *J. Comp. Neurol.* **525**(18): 3809-3820. doi:10.1002/cne.24261

5. Kaur S, Wang JL, Ferrari L, Thankachan S, Kroeger D, Venner A, Lazarus M, Wellman A, Arrigoni E, Fuller PM, Saper CB (2017) A Genetically Defined Circuit for Arousal from Sleep during Hypercapnia. *Neuron* **96**(5): 1153-1167. doi:10.1016/j.neuron.2017.10.009

6. Kobayashi M, Takeda K, Narita T, Nagai K, Okita N, Sudo Y, Miura Y, Tsumoto H, Nakagawa Y, Shimano H, Higami Y (2017) Mitochondrial intermediate peptidase is a novel regulator of sirtuin-3 activation by caloric restriction. *FEBS Lett.* **591**(24): 4067-4073. doi:10.1002/1873-3468.12914

7. Tran MTN, Hamada M, Jeon H, Shiraishi R, Asano K, Hattori M, Nakamura M, Imamura Y, Tsunakawa Y, Fujii R, Usui T, Kulathunga K, Andrea CS, Koshida R, Kamei R, Matsunaga Y, Kobayashi M, Oishi H, Kudo T, Takahashi S (2017) MafB is a critical regulator of complement component C1q. *Nat. Commun.* **8**(1): 1700. doi:10.1038/s41467-017-01711-0

8. Soya S, Takahashi TM, McHugh TJ, Maejima T, Herlitze S, Abe M, Sakimura K, Sakurai T (2017) Orexin modulates behavioral fear expression through the locus coeruleus. *Nat. Commun.* **8**(1): 1606. doi:10.1038/s41467-017-01782-z

9. Shinagawa S, Okazaki T, Ikeda M, Yudoh K, Kisanuki YY, Yanagisawa M, Kawahata K, Ozaki S (2017) T cells upon activation promote endothelin 1 production in monocytes via IFN-gamma and TNF-alpha. *Sci Rep* **7**(1): 14500. doi:10.1038/s41598-017-14202-5

10. Um MY, Kim S, Jin YH, Yoon M, Yang H, Lee J, Jung J, Urade Y, Huang ZL, Kwon S, Cho S (2017) A novel neurological function of rice bran: a standardized rice bran supplement promotes non-rapid eye movement sleep in mice through histamine H-1 receptors. *Mol. Nutr. Food. Res.* **61**(11). doi:10.1002/mnfr.201700316

11. Kutsumura N, Shibuya K, Yamaguchi H, Saito T (2017) *n*-Butyllithium-promoted regioselective elimination of vicinal bis-triflate having an adjacent ether oxygen. *Tetrahedron Lett.* **58**(43): 4099–4102. doi:10.1016/j.tetlet.2017.09.036

12. Azami T, Waku T, Matsumoto K, Jeon H, Muratani M, Kawashima A, Yanagisawa J, Manabe I, Nagai R, Kunath T, Nakamura T, Kurimoto K, Saitou M, Takahashi S, Ema M (2017) Klf5 maintains the balance of primitive endoderm versus epiblast specification during mouse embryonic development by suppression of Fgf4. *Development* **144**(20): 3706-3718. doi:10.1242/dev.150755

13. Yuan XS, Wang L, Dong H, Qu WM, Yang SR, Cherasse Y, Lazarus M, Schiffmann SN, d'Exaerde AD, Li RX, Huang ZL (2017) Striatal adenosine A(2A) receptor neurons control active-period sleep via parvalbumin neurons in external globus pallidus. *eLife* **6**: e29055. doi:10.7554/eLife.29055

14. Suda H, Kanbayashi T, Ito SU, Sagawa Y, Imanishi A, Tsutsui K, Takahashi J, Kikuchi Y, Takahashi Y, Shimizu T (2017) Residual effects of eszopiclone on daytime alertness, psychomotor, physical performance and subjective evaluations. *Sleep Biol Rhythms* **15**(4): 311–316. doi:10.1007/s41105-017-0112-z

15. Oishi Y, Xu Q, Wang L, Zhang BJ, Takahashi K, Takata Y, Luo YJ, Cherasse Y, Schiffmann SN, d'Exaerde AD, Urade Y, Qu WM, Huang ZL, Lazarus M (2017) Slow-wave sleep is controlled by a subset of nucleus accumbens core neurons in mice. *Nat. Commun.* **8**(1): 734. doi:10.1038/s41467-017-00781-4

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(2) Review articles

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152. Kodama S, Fujihara K, Ishiguro H, Horikawa C, Ohara N, Yachi Y, Tanaka S, Shimano H, Kato K, Hanyu O, Sone H (2018) Quantitative Relationship Between Cumulative Risk Alleles Based on Genome-Wide Association Studies and Type 2 Diabetes Mellitus. *J Epidemiol.* **28**(1): 3-18. doi:10.2188/jea.JE20160151

(3) Proceedings

153. Iizuka M, Takahashi S, Matsumoto I, Sumida T, Yoshimura A (2017) TCR analysis of infiltrated CD4(+) T cells in the salivary glands of Sjogren's syndrome mice model. *Cytokine*

(4) Other English articles

154. Kilduff TS, Dan Y (2017) Editorial overview: Neurobiology of sleep 2017. *Curr. Opin. Neurobiol.* **44**: A1-A3. doi:10.1016/j.conb.2017.05.020

155. Takahashi JS (2017) Enriching the Circadian Proteome. *Cell Metab.***25**(1): 1-2. doi:10.1016/j.cmet.2016.12.014

(5) Articles written in other than English

156. Abe, T (2017) EEG oscillations. *Physiological Psychology and Psychophysiology* **1**

157. Abe, T (2017) Evaluating sleepiness. *Physiological Psychology and Psychophysiology* **2**

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

- List up to 10 main presentations during FY2017 in order from most recent.
- For each, write the lecturer/presenter's name, presentation title, conference name and date(s)

1) Masanori Sakaguchi, Invited Speaker, "Memory consolidation during sleep and its mechanism for clinical insights", 2nd Congress of Asian Society of Sleep Medicine (Seoul, Korea), March 22-25, 2018

2) Takashi Kanbayashi, Invited Lecture, "Symptomatic Narcolepsy with Hypothlamic lesion and Orexin Deficiency", 2nd Congress of Asian Society of Sleep Medicine (Seoul, Korea), March 22-25, 2018

3) Qinghua Liu, Plenary Speaker, "Cumulative Phosphorylation of SNIPPs as a Function of Sleep Need" Gordon Research Conference on Sleep Regulation and Function (Galveston, USA), March 18-23, 2018

4) Carla Green, Symposium Speaker, “Molecular Biology of Circadian Clocks”, XIV Latin American Symposium on Chronobiology 2017(Valparaiso, Chile), November 14-18, 2017

5) Kumpei Tokyuyama, Invited Speaker, “Effects of timing of exercise or meals on energy metabolism”, 4th International Recent Advances and Controversies in Measurement of Energy Metabolism (RACMEM) Conference (Fribourg, Switzerland), October 20-22, 2017

6) Masashi Yanagisawa, Special Lecture, “Highlights of ET-15”, 15th International Conference on Endothelin (Prague, Czech), October 4-7, 2017

7) Hiroshi Nagase, Invited Speaker, “The science and the development of non-addictive opioid receptor agonists”, 26th French-Japanese Symposium on Medicinal & Fine Chemistry (Strasbourg, France), September 17-20, 2017

8) Masashi Yanagisawa, Lecture, “Towards the mystery of sleep and wakefulness: forward genetic analysis in mice”, The 38th IUPS World Congress (Rio de Janeiro, Brazil), August 1-5, 2017

9) Qinghua Liu, Plenary Speaker, “A quantitative phosphoproteome landscape of sleep-wake homeostasis” Asian Chronobiology Forum and 2nd Biennial conference of Chinese Society of Biological Rhythms (Hohhot, China), June 25-28, 2017

10) Takeshi Sakurai, Plenary Speaker, “The Mechanism of Narcolepsy: what it tells on clinical perspectives?”, The 2nd International Taiwanese Congress of Neurology (Taipei, Taiwan), May 19-21, 2017

3. Major Awards

- List up to 10 main awards received during FY2017 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, Asahi Prize, 2018

2) Emi Hasegawa, Inoue Research Award for Young Scientist, 2017

3) Masashi Yanagisawa/Hiromasa Funato, Bälz prize, 2017

4) Shingo Soya, Toshihiko Tokizane Memorial Award, 2017

5) Takeshi Sakurai, The 2nd Shiono Prize, 2017

6) Yu Hayashi, Encouragement Award for Young Faculty, University of Tsukuba, 2017

7) Yu Hayashi, The Young Scientists’ Prize, The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology (MEXT), 2017

Appendix 2　FY 2017 List of Principal Investigators

NOTE:

・Underline names of principal investigators who belong to an overseas research institution. Place an asterisk (*) by names of investigators considered to be ranked among world's top researchers

・In case of researchers not listed in the latest report, attach "Biographical Sketch of a New Principal Investigator".

<Results at the end of FY2017>　　**Principal Investigators Total: 24**

Name	Age	Affiliation (Position title, department, organization)	Academic degree specialty	Effort (%)*	Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
Center director Masashi Yanagisawa*	57	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Ph.D. Neuroscience, Pharmacology	95	December 2012	Usually stays at the center	
Takeshi Sakurai*	53	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Ph.D., Neuroscience	50	April 2013	Usually stays at the center	
Hiromasa Funato*	48	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba Associate Professor, Toho University	M.D., Ph.D. Neuroscience	45	December 2012	Usually stays at the center three times a week	
Yoshihiro Urade*	64	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D. Biochemistry Neuroscience	50	October 2013	Usually stays at the center	
Robert Greene*	67	Adjunct Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba Professor, Department of Psychiatry, University of Texas Southwestern Medical Center	M.D., Ph.D. Neuroscience	10	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*	46	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba Associate Professor, Department of Biochemistry, University of Texas Southwestern Medical Center	Ph.D. Genetics, Molecular Biology, Biochemistry	35	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	Accepted young scientists from abroad to the center. (6/period)
Hiroshi Nagase*	70	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D. Medicinal Chemistry, Organic Chemistry	65	April 2013	Usually stays at the center	
Makoto Satoh	62	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Ph.D. Sleep Medicine	75	April 2015	Usually stays at the center	
Ichiyo Matsuzaki*	58	Professor, Faculty of Medicine, University of Tsukuba	M.D., Ph.D. Occupational Psychiatric Medicine, Space	10	March 2013	About 10% of effort. The remaining is allocated for Faculty of Medicine.	
Hitoshi Shimano*	58	Professor, Faculty of Medicine, University of Tsukuba	M.D., Ph.D. Endocrinology, Metabolism	15	March 2013	Usually stays at Faculty of Medicine	
Kumpei Tokuyama	64	Professor, Faculty of Health and Sport Sciences, University of Tsukuba	Ph.D., Sports Medicine	20	April 2015	Stays at the center once a week Participates in the annual IIIS symposium Participates in annual Site Visit	
Akiyoshi Fukamizu*	58	Professor, Tsukuba Advanced Research Alliance, University of Tsukuba	Ph.D., Molecular Biology	2	March 2013	Usually stays at the satellite center Started the collaboration with Chika Miyoshi (Yanagisawa/Funato Lab.).	
Satoru Takahashi*	56	Professor, Laboratory Animal Resource Center, Department of Anatomy and Embryology, Faculty of Medicine, University of Tsukuba	M.D., Ph.D. Developmental biology	20	March 2013	Participates in generation of genetically modified mice by using CRISPR/Cas9 system at Laboratory Animal Resource Center	
Joseph Takahashi*	66	Professor, Department of Neuroscience, University of Texas Southwestern Medical Center	Ph.D. Neuroscience	5	December 2012	Usually stays at the satellite center	Collaboration. Available to accept young scientists from WPI for collaborative projects.

Carla Green*	55	Professor, Department of Neuroscience, University of Texas Southwestern Medical Center	Ph.D. Molecular Biology, Biochemistry, Circadian rhythms	5	March 2013	Usually stays at the satellite center	Collaboration. Available to accept young scientists from WPI for collaborative projects.
Yang Dan*	50	Professor, Department of Molecular and Cell Biology, University of California, Berkeley	Ph.D., Neurobiology	5	April 2014	Usually stays at the satellite center	
Tetsuo Shimizu*	65	Professor, Department of Neuropsychiatry, Akita University Graduate School of Medicine	M.D., Ph.D., Psychiatry	15	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*	65	Professor, Graduate School of Pharmaceutical Sciences, Kyoto University	M.D., Ph.D. Chronobiology	3	July 2015	Usually stays at the satellite center	
Kaspar Vogt	51	Associate Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Ph.D. Physiology, Pharmacology, Neurobiology	100	February 2014	Usually stays at the center	
Michael Lazarus	48	Associate Professor International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D. Neuroscience	100	April 2013	Usually stays at the center	
Masanori Sakaguchi	41	Associate Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	M.D., Ph.D. Neuroscience	100	January 2013	Usually stays at the center	
Yu Hayashi	37	Associate Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D. Neuroscience	80	April 2013	Usually stays at the center	
Takashi Abe	38	Associate Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D. Behavioral Science Psycho-physiology	100	November 2017	Usually stays at the center	
Sakiko Honjoh	37	Assistant Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	Ph.D. Molecular biology, Genetics, Neuroscience	100	September 2017	Usually stays at the center	

*Percentage of time that the principal Investigator will devote to his/her work for the center vis-à-vis his/her total working hours (total time for whole working activities including education, medical services, and others as well as research).

Researchers unable to participate in project in FY 2018

Name	Affiliation (Position title, department, organization)	Starting date of project participation	Reasons	Measures taken
Yoshihiro Urade	Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba	October 2013	No contract renewal for FY 2018	Recruited two young PIs
Tetsuo Shimizu	Professor, Department of Neuropsychiatry, Akita University Graduate School of Medicine	April 2013	Retirement at mandatory age	Planning to recruit a physician or appoint his successor as satellite PI.

Appendix 2a Biographical Sketch of Principal Investigator

(within 3 pages per person)

Name (Age)

* Place an asterisk (*) by the name of the principal investigators who are considered to be ranked among the world's top researchers.

Takashi Abe (38)

Affiliation and position (Position title, department, organization, etc.)

Associate Professor
International Institute for Integrative Sleep Medicine
University of Tsukuba

Academic degree and specialty

2008 Ph.D. (Philosophy) Hiroshima University Graduate School of Biosphere Science, Hiroshima, Japan
Behavioral Science, Psychophysiology

Effort **100 %**

* Percentage of time that the PI will devote to his/her work for the center vis-à-vis his/her total working hours (total time for whole working activities including education, medical services, and others as well as research).

Research and education history

2008	Ph.D. Department of Behavioral Sciences, Graduate School of Biosphere Science, Hiroshima University
2005-2008	Research fellow (DC1), Japan Society for the Promotion of Science
2008-2010	Postdoctoral Fellow, Japan Somnology Center, Neuropsychiatric Research Institute, Tokyo, Japan
2010-2013	Research Fellow, Japan Somnology Center, Neuropsychiatric Research Institute, Tokyo, Japan
2011-2013	Postdoctoral Fellow for Research Abroad, Japan Society for the Promotion of Science (Perelman School of Medicine University of Pennsylvania)
2013-2016	Aerospace Project Research Associate, Space Biomedical Research Office, Japan Aerospace Exploration Agency, Tsukuba, Japan
2016-2017	Senior researcher, Automotive Human Factors Research Center, National Institute of Advanced Industrial Science and Technology
2017-	Associate Professor, International Institute for Integrative Sleep Medicine, University of Tsukuba

Achievements and highlights of past research activities

***** Describe the PI's qualifications as a top-caliber researcher if s/he is considered to be ranked among the world's top researchers.

Achievements

(1) International influence * Describe the kind of attributes listed below.

a) Guest speaker or chair of related international conference and/or director or honorary chairman of a major international academic society in the subject field

Abe, T. (2010.11). Gamma band EEG activities before and after REM. 29 th international congress of clinical neurophysiology. (Kobe, Japan) (Invited speaker)

b) Member of a scholarly academy in a major country

N/A

c) Recipient of international awards

Abe, T. (2004.4) The 15th World Congress of the International Society of Brain Electromagnetic Topography, Young Scientist Award Creative Research Award.

d) Editor of an influential journal, etc.

N/A

(2) Receipt of large-scale competitive funds (over the past 5 years)

FY2013-2016: Development of a new vigilance monitoring system for space exploration, Management Expenses Grant from the Japan Aerospace Exploration Agency (19,684,000 yen) (Principle Investigator)

FY2017-2019: Neural mechanism of wake state instability, Grands-in-Aid for Scientific Research on Challenging Research (Exploratory) (4,700,000 yen) (Principle Investigator)

FY2015-2019: Comprehensive Understanding of Zero Gravity and Confinement Stress, Programmed Research in Grand-in-aid for Scientific Research on Innovative Area (98,000,000 yen) (Co-Investigator)

(3) Article citations (Titles of major publications, number of citations)

Total citations as of March 23, 2018: 487 (Google Scholar)

Abe, T., Inoue, Y., Komada, Y., Nakamura, M., Asaoka, S., Kanno, M., Shibui, K., Hayashida, K., Usui, A., Takahashi, K. Relation between morningness–eveningness score and depressive symptom among patients with delayed sleep phase syndrome. Sleep Medicine. 12, 680-684. 2011. (N of citations = 64)

Abe, T., Nonomura, T., Komada, Y., Asaoka, S., Sasai, T., Ueno, A., Inoue, Y. Detecting deteriorated vigilance using percentage of eyelid closure time during behavioral maintenance of wakefulness tests. International Journal of Psychophysiology. 82, 269-274. 2011. (N of citations = 43)

Abe, T., Komada, Y., Nishida, Y., Hayashida, K., Inoue, Y. Short sleep duration and long spells of driving are associated with the occurrence of Japanese drivers' rear-end collisions and single-car accidents. Journal of Sleep Research, 19, 310-316. 2010. (N of citations = 36)

Abe, T., Ogawa, K., Nittono, H., & Hori, T. Neural generators of brain potentials before rapid eye movements during human REM sleep: A study using sLORETA. Clinical Neurophysiology, 119, 2044-2053. 2008. (N of citations = 25)

Goel,N.,* Abe,T.,* Braun, M.E., Dinges,D.F. Cognitive Workload and Sleep Restriction Interact to Influence Sleep Homeostatic Responses. SLEEP. 37(11),1745-1756. 2014. (*Co-first authors. These authors contributed equally to this work.) (N of citations = 16)

(4) Others (Other achievements indicative of the PI's qualification as a top-world researcher, if any.)

Following paper was selected as a cover figure for Clinical Neurophysiology, Volume 119, Issue 9.
Abe, T., Ogawa, K., Nittono, H., & Hori, T. Neural generators of brain potentials before rapid eye movements during human REM sleep: A study using sLORETA. Clinical Neurophysiology, 119, 2044-2053. 2008.

Recipient of domestic research awards
2009 14th Encouraging Prize of Japanese Society of Sleep Research
2011 Research Award of Mitsui Sumitomo Insurance Welfare Foundation
2012 17th Encouraging Prize of Japanese Society of Sleep Research

Appendix 2a Biographical Sketch of Principal Investigator

(within 3 pages per person)

Name (Age)

* Place an asterisk (*) by the name of the principal investigators who are considered to be ranked among the world's top researchers.

Sakiko Honjoh (37)

Affiliation and position (Position title, department, organization, etc.)

Assistant professor

The International Institute for Integrative Sleep Medicine

University of Tsukuba

Academic degree and specialty

2009 Ph.D. (Life Science) Kyoto University Graduate School of Biostudies, Kyoto, Japan

Molecular biology, genetics, neuroscience

Effort **100 %**

* Percentage of time that the PI will devote to his/her work for the center vis-à-vis his/her total working hours (total time for whole working activities including education, medical services, and others as well as research).

Research and education history

2004-2009 Ph.D. Kyoto University Graduate School of Biostudies, Nishida lab, Kyoto, Japan
Project; Molecular mechanisms underlying dietary restriction-induced longevity in *C. elegans*

2009-2012 Postdoctoral Training
Affiliation and Project; the same as above
Involved in teaching and training of graduate students

2012-2015 Postdoctoral Training
HFSP long term fellow, University of Wisconsin-Madison, Tononi lab, Madison, USA
Project; "The price for plasticity : Does learning make neurons tired?"

2015-2017 Postdoctoral Training
JSPS Overseas Research Fellowship, University of Wisconsin-Madison, Tononi lab, Madison, USA
Project; "Inverse synaptic tagging during sleep"

Achievements and highlights of past research activities

* Describe the PI's qualifications as a top-caliber researcher if s/he is considered to be ranked among the world's top researchers.

Not applicable

Achievements

(1) International influence * Describe the kind of attributes listed below.

a) Guest speaker or chair of related international conference and/or director or honorary chairman of a major international academic society in the subject field

Not applicable

b) Member of a scholarly academy in a major country

Not applicable

c) Recipient of international awards

2010 The GE & Science Prize for Young Life Scientists, Japanese regional winner

d) Editor of an influential journal, etc.

Not applicable

(2) Receipt of large-scale competitive funds (over the past 5 years)

Not applicable

(3) Article citations (Titles of major publications, number of citations)

Effects of chronic sleep restriction during early adolescence on the adult pattern of connectivity of mouse secondary motor cortex. eNeuro. 3, 0053-16 (2016) **Citation (1)**

Local slow waves in superficial layers of primary cortical areas during REM sleep. Curr. Biol. 26, 396-403 (2016) **Citation (10)**

A fasting-responsive signaling pathway that extends life span in *C. elegans*. Cell Rep. 3, 79-91 (2013) **Citation (23)**

Signalling through Rheb mediates intermittent fasting-induced longevity in *C. elegans*. Nature 457, 726-730 (2009) **Citation (90)**

ERK activation propagates in epithelial cell sheets and regulates their migration during wound healing. Curr. Biol. 14, 731-735 (2004) **Citation (61)**

***The citation numbers are based on Pubmed Central Articles**

(4) Others (Other achievements indicative of the PI's qualification as a top-world researcher, if any.)

Not applicable

Appendix 3-1 FY 2017 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

- Regarding the number of researchers at the Center, please fill in the table in Appendix 3-1a.

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 on the global circulation of 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, formerly a researcher of University of Wisconsin–Madison has joined the IIIS as a first female Junior PI since September, 2017. In addition, Dr. Takashi Abe, formerly a senior researcher of the National Institute of Advanced Industrial Science and Technology (AIST) has joined as a Junior PI since November 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		
The Jikei University		
Hiroshima University		Newly added in April, 2017
Faculty of Science & Technology, Keio University		Newly added in April, 2017
Daiichi University of Pharmacy		Newly added in July, 2016
The Kitasato Institute		Newly added in October, 2017

2. Securing external research funding*

External research funding secured in FY2017

Total: 666,759,832 yen

- Describe external funding warranting special mention. Include the name and total amount of each grant.
* External research funding includes "Grant-in-Aid for Scientific Research," funding for "commissioned research projects," and for "joint research projects" as listed under "Research projects" in Appendix 3-2, Project Expenditures.

Grants and Endowments: 41,150,000 yen
Joint research, etc.: 98,549,721 yen
Commissioned research projects, etc.: 174,060,820 yen
Grants-in-Aid for Scientific Research, etc.: 352,999,291 yen

The acquired large-scale research grants for FY2017
JST CREST: 67,600,000 yen
Grant-in-Aid for Scientific Research on Innovative Areas: 55,900,000 yen
Grant-in-Aid for Specially Promoted Research: 149,500,000 yen
AMED Strategic Research Program for Brain Science: 23,030,001 yen
Regional Innovation Ecosystem Program: 48,004,819 yen
Model R&D Project in Alliance for Knowledge Integration/Application among Industry, Academia and Government at MAFF: 24,000,000 yen

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

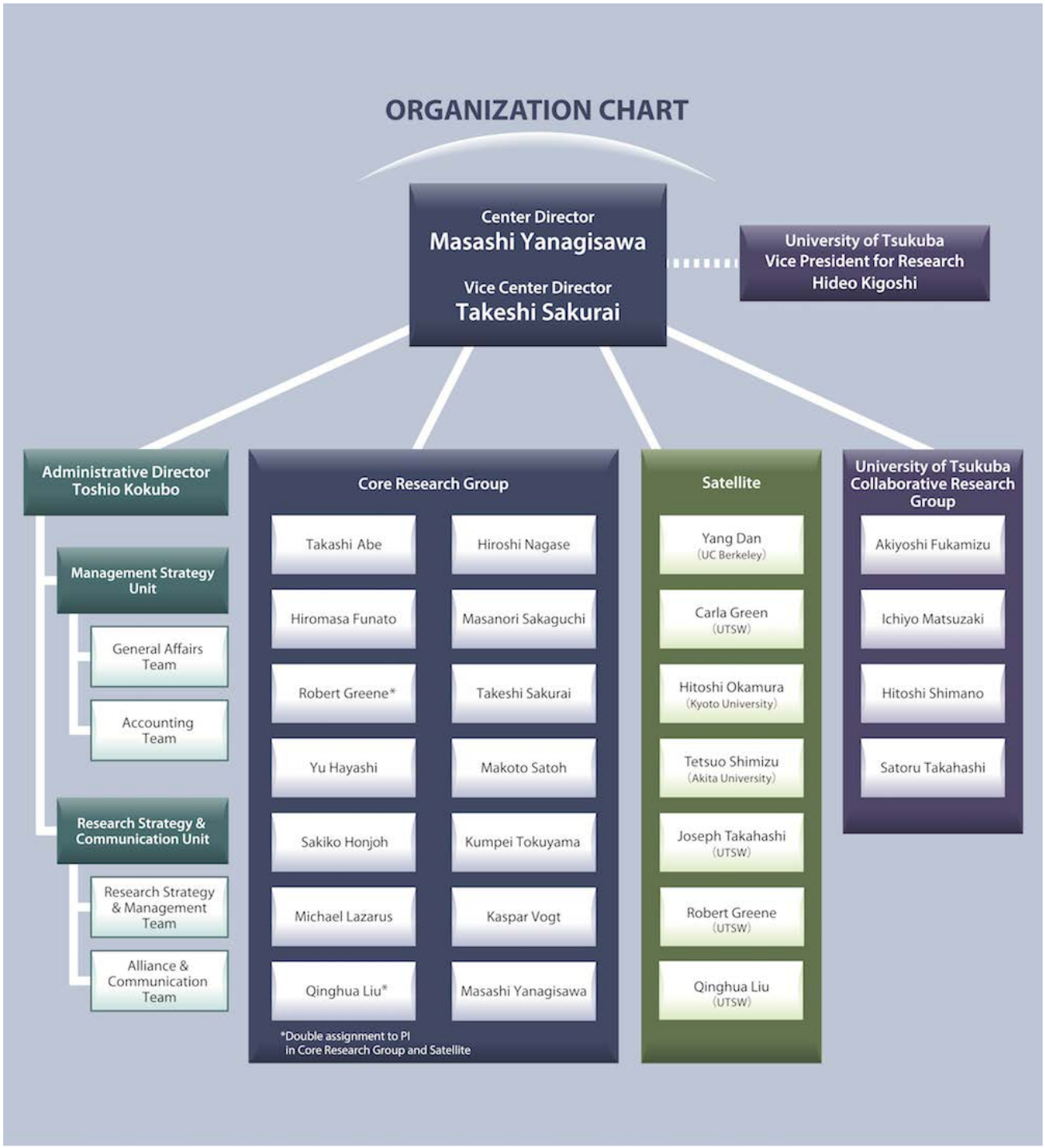
- Indicate the number of international research conferences or symposiums held in FY2017 and give up to three examples of the most representative ones using the table below.

FY 2017: 1 meetings

Major examples (meeting titles and places held)	Number of participants
The 6th Annual IIIS Symposium	From domestic institutions: 186 From overseas institutions: 8

4. Center's management system

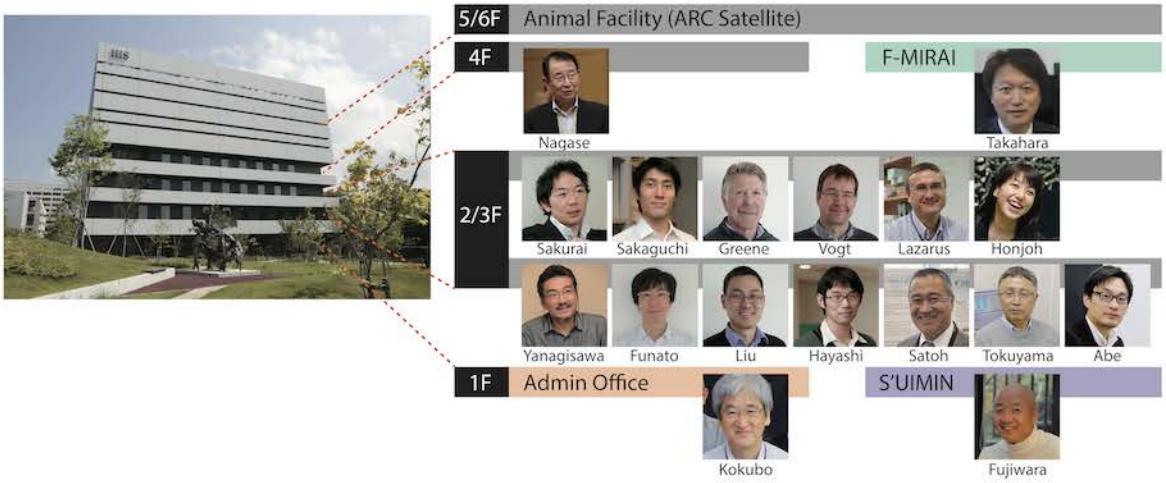
- Please diagram management system in an easily understood manner.
- If any changes have been made in the management system from that in the latest "center project," please describe them. Please describe any important changes made in such as the center director, administrative director, head of host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



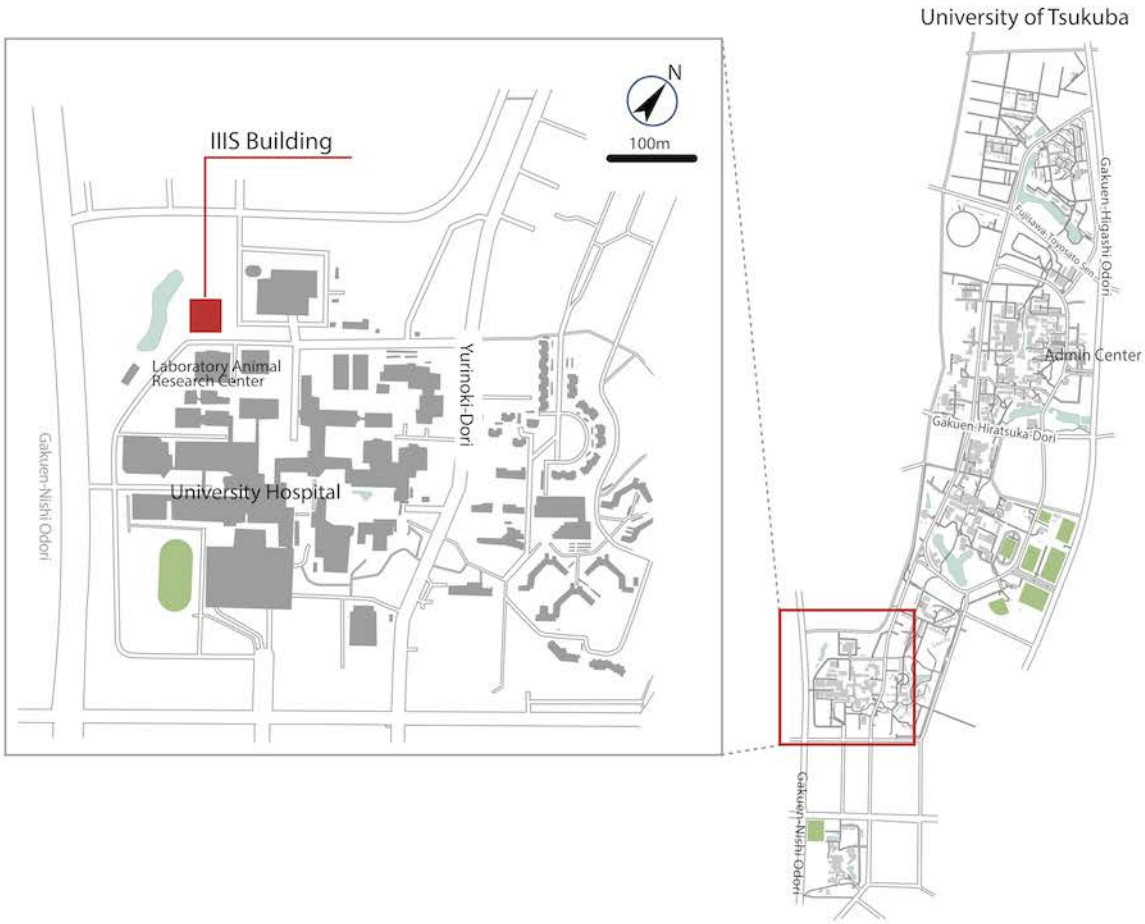
5. Campus Map

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

IIIS Building



Campus Map



Appendix 3-1a FY 2017 Records of Center Activities

1. Researchers and other center staffs, satellites, partner institutic

1-1. Number of researchers and other center staffs

* Please fill in the number of researchers and other center staffs in the table blow.
* Please describe the final goals for achieving these numbers and dates when they will be achieved.

a) Principal Investigators（full professors, associate professors or other researchers of comparable standing)

(persons)

	At beginning of project	At end of FY 2017	Final goal (March 31, 2022)
Researches from within the host institution	7	8	8
Foreign researchers invited from abroad	0	7	6
Researchers invited from other Japanese institutions	0	9	10
Total principal investigators	7	24	24

b) Total members

	At beginning of project		At end of FY2017		Final goal (March 31, 2022)	
	Number of persons	%	Number of persons	%	Number of persons	%
Researchers	41		65		62	
Overseas researchers	1	2	21	32	21	34
Female researchers	8	20	22	34	22	36
Principal investigators	7		24		24	
Overseas PIs	1	14	9	38	8	33
Female PIs	0	0	3	13	4	17
Other researchers	34		41		38	
Overseas researchers	0	0	12	29	13	34
Female researchers	8	24	19	46	18	47
Research support staffs	17		15		20	
Graduate students	4		49		68	
Administrative staffs	14		19		19	
Total number of people who form the "core" of the research center	76		148		169	

Appendix 3-2 Project Expenditures

1) Overall project funding

* In the “Total Cost” column, enter the total amount of funding required to implement the project, without dividing it into funding sources.
* In the “Amount covered by WPI funding” column, enter the amount covered by WPI within the total amount.
* In the “Personnel,” “Project activities,” “Travel,” and “Equipment” blocks, the items and details may be changed to coincide with the project’s actual content.

(Million yens)

Cost Items	Details (For Personnel - Equipment please fill in the breakdown of fiscal expenditure, and the income breakdown for Research projects.)	Total Costs	Amount covered by WPI funding
Personnel	Center director and Administrative director	39	39
	Principal investigators (no. of persons):6	63	37
	Other researchers (no. of persons):51	283	220
	Research support staffs (no. of persons):11	28	27
	Administrative staffs (no. of persons):16	76	52
	Subtotal	489	375
Project activities	Gratuities and honoraria paid to invited principal investigators (no. of persons):0	0	0
	Cost of dispatching scientists (no. of persons):1	1	1
	Research startup cost (no. of persons):11	21	21
	Cost of satellite organizations (no. of satellite organizations):2	22	22
	Cost of international symposiums (no. of symposiums):1	3	3
	Rental fees for facilities	70	70
	Cost of consumables	10	10
	Cost of utilities	82	0
	Other costs	34	34
	Subtotal	243	161
Travel	Domestic travel costs	2	1
	Overseas travel costs	4	4
	Travel and accommodations cost for invited scientists (no. of domestic scientists):0 (no. of overseas scientists):0	0	0
	Travel cost for scientists on secondment (no. of domestic scientists):4 (no. of overseas scientists):2	2	2
	Subtotal	8	7
Equipment	Depreciation of buildings	0	0
	Depreciation of equipment	659	240
	Subtotal	659	240
Research projects (Detail items must be fixed)			
	Grants-in-Aid for Scientific Research, etc.	0	0
	Commissioned research projects, etc.	126	0
	Joint research projects	152	0
	Ohers (donations, etc.)	0	0
	Subtotal	278	0
Total		1677	783

Costs (Million yens)

WPI grant in FY 2017	585
Costs of establishing and maintaining facilities	0
Establishing new facilities (Number of facilities: , OO m²)	0
Repairing facilities (Number of facilities: , OO m²)	0
Others	0
Cost of equipment procured	41
Clean isolator (Number of units:2)	13
Mice breeding equipment (Number of units:3)	13
Others	15

*1. Funding sources that include government subsidies (including Enhancements promotion expenses (機能強化促進経費), National university reform reinforcement promotion subsidy (国立大学改革強化推進補助金) etc.), indirect funding, and allocations from the university's own resources.
*2 When personnel, travel, equipment (etc.) expenses are covered by Grants-in-Aid or under commissioned research projects or joint research projects, the amounts should be entered in the “Research projects” block.

2) Costs of Satellites and Partner institutions

(Million yens)

Cost Items	Details	Total Costs	Amount covered by WPI funding
Personnel	Principal investigators (no. of persons):2	17	17
	Other researchers (no. of persons):3	5	5
	Research support staffs (no. of persons):0		
	Administrative staffs (no. of persons):0		
	Subtotal	22	22
Project activities	Subtotal		
Travel	Subtotal		
Equipment	Subtotal		
Research projects	Subtotal		
Total		22	22

Appendix 4 FY 2017 Status of Collaboration with Overseas Satellites

1. Coauthored Papers

- List the refereed papers published in FY 2017 that were coauthored between the center's researcher(s) in domestic institution(s) (include satellite institutions) 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. 2018 and not described in Appendix 1.

Overseas Satellite 1 (Total: 1 papers)

1) Greene RW, Bjorness TE, Suzuki A (2017) The adenosine-mediated, neuronal-glial, homeostatic sleep response. *Curr. Opin. Neurobiol.* **44**:236-242. doi: 10.1016/j.conb.2017.05.015

Overseas Satellite 2 (Total: 0 papers)

2. Status of Researcher Exchanges

- Using the below tables, indicate the number and length of researcher exchanges in FY 2017. 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
FY2017	1	0	0	0	1
	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
FY2017	0	8	0	0	8
	1	0	0	0	1

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
FY2017	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
FY2017	0	0	0	0	0
	0	0	0	0	0

Overseas Satellite 3: Merck Sharp and Dohme (MSD)

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2017	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
FY2017	0	0	0	0	0
	0	0	0	0	0

Appendix 5　FY 2017 Visit Records of World Top World-level Researchers from Abroad

* If top world-level researchers have visited/ stayed at the Center, please provide information on them in the below table.
* To determine whether the researcher is a "top world-level researcher," please see the standard stipulated in the Application Guideline.

Total: 12

	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	46	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)	2017 April (7 days) 2017 May (8 days) 2017 July (12 days) 2017 September (6 days) 2017 October (10 days) 2017 December (28 days) 2018 January (2 days) 2018 February (14 days)	Participation in symposium as a principal investigator and short-term stay for joint research
2	Robert W. Greene	67	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)	2017 April (8 days) 2017 August (2 days) 2017 September (7 days) 2017 December (11 days)	Participation in symposium as a principal investigator and short-term stay for joint research
3	Junhua Li		Deputy Director of Metagenomic Institute BGI Research	Ph.D. Microbiology	・Principal Investigator of Human Microbiome BGI Research (2015-2016) ・Speaker, Microbiome/Microbiota R&D and Business Collaboration Forum, Asia (2016) ・Speaker, The International Human Microbiome Standards 4th Workshop, France (2014)	2017 June (1 day)	Lecture at IIIS seminar
4	Juan Carlos Letelier Parga		Professor, Universidad de Chile	Ph.D. Biological Sciences	・Canonical cortical circuits in birds? The avian visual DVR as a study case (2017- Present) ・Organization of the visual pallium in the pigeon (Columba Livia): Layers and columms in the avian telecephalon (2012-2015) ・Neural mechanisms of magnetopreception in birds. A study in the pigeon "Columba Livia" (2011-2015)	2017 September (1 day)	Discussion about the research project
5	Liangyi Chen		Principal Investigator Laboratory of Cell Secretion & Metabolism Peking University	Ph.D. Neuroscience	・Member of the American Society for Biochemistry and Molecular Biology (USA) ・Member of the Biophysical Society (USA) ・Professional Member of the American Diabetes Association (USA)	2017 December (4 days)	Participation in symposium as a speaker, Participation in IIIS seminar
6	Shu-min Duan		Professor and Dean, Zhejiang University School of Medicine	Ph.D. Neuroscience	・Member, International Affairs Committee, Society for Neuroscience (2012-) ・Member, The Governing Council, International Brain Research Organization (2011) ・Editor in Chief, Neuroscience Bulletin (Official Journal of Chinese Society for Neuroscience (2010-) ・Academician, Academy of Sciences for the Developing World (TWAS), (2008) ・Prize for Scientific and Technological Achievements of Ho Leung Ho Lee Foundation (2008) ・Academician, Chinese Academy of Sciences (2007)	2017 December (2 days)	Participation in symposium as a speaker
7	Minmin Luo		Investigator, National Institute of Biological Sciences (NIBS), Beijing Professor, Tsinghua University School Life Sciences	Ph.D. Neuroscience	・Paul Jansen & Wu Jieping Prize in Medicine (2016) ・Beijing Scholar (2016- Present) ・Wuxi Pharma Award for Biomedical Researches (2011) ・China Youth Science and Technology Award (2011) ・H-T Chiang Award for Outstanding Young Neuroscientists, Hsiang Tung Chang Foundation and Chinese Neuroscience Society, China (2009) ・Outstanding Young Investigator Award National Natural Sciences Foundation of China (2006 -2009） ・Human Frontier Science Program Young Investigator Grant (2006 -2009) ・Career Awards in the Biomedical Sciences, Burroughs Wellcome Fund (2002-2007) ・University of Pennsylvania Fellowship for Biomedical Graduate Studies (1995-1999)	2017 December (4 days)	Participation in symposium as a speaker, lecture at IIIS seminar
8	Joshua J. Gooley		Associate Professor Neuroscience & Behavioural Disorders Programme Duke-NUS Medical School Adjunct Senior Lecturer, School of Psychological Sciences, Monash University	Ph.D. Neurobiology	・Scientific Review Committee Members, Sleep Research Society (2005-2017) ・Harold M Weintraub Graduate Student Award, Fred Hutch (2015) ・Outstanding Faculty for Learning (Brain & Behavior Award, Duke-NUS Medical School (2014) ・Trainee, Harvard Medical School (2005)	2017 December (4 days)	Participation in symposium as a speaker, lecture at IIIS seminar

9	Francesca Siclari	37	Principal Investigator Center for Research and Investigation in Sleep, Lausanne University Hospital	Ph.D. Neurology	・Ad Hoc reviewer for Nature Scientific Reports, Journal of Cognitive Neuroscience, Sleep Medicine, BioMed Research, Brain Topography Frontiers in Psychology and Archives Italiennes de Biologie ・Ad Hoc reviewer for grants of the French National Research Agency ・External expert and member of the evaluation committee of a PhD thesis; PhD program in Automation, Robotics and Bioengineering, University of Pisa, Italy ・Member of the organizing committee, Swiss Meeting of the Swiss Society for Sleep Research, Sleep Medicine and Chronobiology and the Swiss Society of Epileptology, Basel, Switzerland, April 28-29 2016 ・Member of the organizing committee of the exhibition for the general public 'Open Mind' at the Science Museum 'Musée de la Main', Lausanne	2017 December (4 days)	Participation in symposium as a speaker, lecture at IIIS seminar
10	Vladuslav Vyazovskiy		Associate Professor of Neuroscience Department of Physiology, Anatomy and Genetics, University of Oxford	Ph.D. Neuroscience	・Keynote speaker, 1st International Conference on Sleep Spindles, Budapest, Hungary;(2016) ・Keynote speaker, 12th Annual Symposium of Korean Sleep Research Society (KSSR);(2015) ・Member, European Biological Rhythms Society (2015) ・Travel Awardee for the 2014 American College of Neuropsychopharmacology meeting;(2014) ・Keynote speaker, XIV Brazilian Sleep Meeting, Rio de Janeiro, Brazil;(2013) ・"Year in Review", Invited speaker, 25th Meeting of British Sleep Society, UK;(2013) ・Member, British Neuroscience Association (2012) ・"Notable Publication in Sleep", Sleep Research Society, 2011;(2011) ・Sleep Research Society Young Investigator Award;(2008) ・Two-years Research Fellowship, Swiss National Science Foundation;(2005-2006) ・Travel Awardee for the 2002 FENS meeting, Paris (2002) ・Member, European Sleep Research Society (2001) ・Member, Sleep Research Society (2005)	2017 December (5 days)	Participation in symposium as a speaker, lecture at IIIS seminar
11	Jamie Zeitzer		Associate Professor Department of Psychiatry and Behavioral Sciences, Stanford University	Ph.D. Neurobiology	・Faculty Fellow in Human Biology, Stanford University (2014) ・National Alliance for Research on Schizophrenia and Depression (NARSAD) Young Investigator Award (2006) ・Young Investigator Award, Honorable Mention, American Academy of Sleep Medicine (2005) ・Sleep Research Society Trainee Research Merit Award (2003) ・National Alliance for Research on Schizophrenia and Depression (NARSAD) Young Investigator Award (2003) ・Pickwick Fellowship in Sleep Medicine, National Sleep Foundation (2002) ・C.F. Aaron Dean's Fellowship, Stanford University School of Medicine (2002) ・Travel Fellowship, SRBR Annual meeting (2002) ・Travel Fellowship, APSS Annual meeting (2001) ・Travel Fellowship, American Paraplegia Society Annual Meeting (2000) ・Travel Fellowship, American Paraplegia Society Annual Meeting (1999) ・Travel Fellowship, Gordon Conference on Pineal Cell Biology (1998) ・Travel Fellowship, Northeast Sleep Society Annual Meeting (1996) ・Certificate of Distinction in Teaching, Harvard University (1995) ・Honorable Mention, National Science Foundation Fellowship (1994) ・Phi Beta Kappa, Vassar College (1993) ・Kate Roberts Prize in Biology, Vassar College (1993) ・Council on Undergraduate Research Academic-Industrial Undergraduate Research Partnership Fellowship, Vassar College/Merck Sharpe & Dohme Research Laboratories (1992) ・Harriet Gurnee Van Allen Prize, Vassar College (1991)	2017 December (4 days)	Participation in symposium as a speaker, lecture at IIIS seminar
12	Francis Szele		Department of Physiology Anatomy and Genetics, Medical Sciences Division, University of Oxford	Ph.D. Pharmacology	・Epigenetic mechanisms regulating pluripotency from embryonic to adult neurogeneisis. MRC (2014 - 2017) ・Pharmacological activation of endogenous stem cell populations for neuroregeneration. Shionogi Science Program (2013 - 2016) ・Molecular mechanisms regulating subependymal zone progenitor migration. BBSRC(2013 - 2016) ・Schizophrenia models and the SVZ. Qatar Foundation, (2012 - 2016) ・Adult Neurogenesis in Neuropsychiatric Disease.DANA Alliance for the Brain,(2012 - 2016) ・Assistant Professor, Feinberg School of Medicine, Northwestern University, Chicago IL, USA (1999 - 2007) ・Postdoctoral Fellow - Developmental Neurobiology. Harvard Medical School/Howard Hughes Medical Institute, Boston, MA, USA (1994 - 1999)	2018 January (1 day)	Discussion about the research project

Appendix 6 FY2017 State of Outreach Activities

* Using the table below, show the achievements of the Center's outreach activities in FY2017(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 FY2017 resulting from press releases and reporting.

Activities	FY2017 (number of activities, times held)
PR brochure, pamphlet	1*[1]
Lectures, seminars for general public	24
Teaching, experiments, training for elementary, secondary and high school students	15
Science café	2
Open houses	1*[2]
Participating, exhibiting in events	3
Press releases	25

<Special Achievements>

*1 We renewed IIIS official website instead of PR brochure and pamphlet.

*2 As the first trial of open house of IIIS, a program via Internet broadcasting, named "IIIS x niconico," were widely aired. About 20,000 viewers enjoyed the programs.

Appendix 7 FY 2017 List of Project's Media Coverage

#	Date	Types of Media (e.g., newspaper, television)	Description	
1	2017.04.06	Web media	IoTNEWS	TOYOTA and University of Tsukuba co-established "F-MIRAI"
2	2017.04.07	Magazine	CREA Bungeishunju	Interview (Sakurai)
3	2017.04.10	Magazine	Life Science	The function of orexin in sleep/wake regulation (Sakurai)
4	2017.04.10	Magazine	Weekly SPA!	Interview (Sakurai)
5	2017.04.11	Web media	Mynavi News	Does loss of sleep cause obesity? (Lazarus)
6	2017.04.12	Web media	Mynavi News	Neural circuit which can prevent cataplexy, the major symptom of narcolepsy, was discovered (Sakurai)
7	2017.04.14	Web media	Hazard Lab	Memory can be manipulated using auditory stimuli during sleep (Sakaguchi)
8	2017.04.14	Newspaper	The Ibaraki Shimbun	Memory can be manipulated using auditory stimuli during sleep (Sakaguchi)
9	2017.04.17	Web media	NEWS SALT	Memory can be manipulated using auditory stimuli during sleep (Sakaguchi)
10	2017.04.19	Television	NHK WORLD TV	Sleep Science (Yanagisawa)
11	2017.04.19	Web media	Yomiuri Online	Interview: "How to stop habitual mouth-breathing" (Satoh)
12	2017.04.20	Web media	University Journal Online	Memory can be manipulated using auditory stimuli during sleep (Sakaguchi)
13	2017.04.21	Magazine	NHK Publishing	Interview: "Today's health"(Yanagisawa)
14	2017.04.27	Newspaper	The Mainichi Shimbun	Memory can be manipulated using auditory stimuli during sleep (Sakaguchi)
15	2017.05.16	Newspaper	The Nihon Keizai Shimbun	Wake-promoting compound validated—the first step to deliver a magic bullet for curing narcolepsy(Yanagisawa)
16	2017.05.16	Newspaper	The Ibaraki Shimbun	Wake-promoting compound validated—the first step to deliver a magic bullet for curing narcolepsy(Yanagisawa)
17	2017.05.16	Newspaper	The Mainichi Shimbun	Wake-promoting compound validated—the first step to deliver a magic bullet for curing narcolepsy(Yanagisawa)
18	2017.05.16	Newspaper	The Nihon Keizai Shimbun	Wake-promoting compound validated—the first step to deliver a magic bullet for curing narcolepsy(Yanagisawa)
19	2017.05.17	Web media	Asian Scientist Magazine	Wake-promoting compound validated—the first step to deliver a magic bullet for curing narcolepsy(Yanagisawa)
20	2017.05.18	Web media	Medial News QLifePro	Wake-promoting compound validated—the first step to deliver a magic bullet for curing narcolepsy(Yanagisawa)
21	2017.05.25	Newspaper	The Asahi Shimbun	Wake-promoting compound validated—the first step to deliver a magic bullet for curing narcolepsy(Yanagisawa)
22	2017.05.30	Web media	Medical Xpress	Wake-promoting compound validated—the first step to deliver a magic bullet for curing narcolepsy(Yanagisawa)
23	2017.06.07	Web media	Daily Ameba News	Interview: "Sleep when you get sleepy"(Sakurai)
24	2017.06.12	Radio	CBC RADIO	Wake-promoting compound validated—the first step to deliver a magic bullet for curing narcolepsy(Yanagisawa)
25	2017.06.15	Magazine	Shuukanbunshun	Interview: "Old people and sleep disorders" (Sakurai)
26	2017.06.19	Newspaper	The Nikkan Kogyo Shimbun	Wake-promoting compound validated—the first step to deliver a magic bullet for curing narcolepsy(Yanagisawa)
27	2017.07.01	Magazine	Diamond weekly	Interview: "Good sleep makes difference" (Yanagisawa)
28	2017.07.03	Web media	Mynavi News	Elucidation of energy metabolism in sleep(Satoh)
29	2017.07.01	Web media	Science Daily	The secret connection between anxiety and sleep(Sakurai)
30	2017.07.02	Web media	Medial News QLifePro	The secret connection between anxiety and sleep(Sakurai)

31	2017.07.06	Web media	astavision	Interview: "Our brain require 7 hours sleep on average" (Yanagisawa)
32	2017.07.06	Web media	Asian Scientist Magazine	The secret connection between anxiety and sleep(Sakurai)
33	2017.07.07	Web media	Sleep Review	The secret connection between anxiety and sleep(Sakurai)
34	2017.07.12	Web media	PRTIMES	Evaluate effects of mattress on sleep(Satoh)
35	2017.07.20	Web media	JIJI PRESS	Brain wave pattern in sleep(Hayashi)
36	2017.07.20	Web media	Medical Tribune	Interview: "Narcolepsy" (Yanagisawa)
37	2017.07.25	Magazine	Weekly SPA!	Ranking of bad habits in summer (Sakurai)
38	2017.07.26	Web media	academist Journal	Memory can be manipulated using auditory stimuli during sleep (Sakaguchi)
39	2017.08.18	Web media	Newswitch	Lack of sleep makes you more offensive and less sympathetic (Tokuyama)
40	2017.08.22	Magazine	Fujinkoron	Interview: The cause of insomnia and ways to deal with the disease (Sakurai)
41	2017.09.05	Web media	Science Daily	Cannot sleep due to stress? Here is the cure (Urade)
42	2017.09.05	Web media	Sleep Review	Sugarcane Active Component Restores Stress-affected Sleep (Urade)
43	2017.09.10	Web media	Gendai Business	Interview: "Does loss of sleep make you crazy?" (Sakurai)
44	2017.09.10	Web media	Medical News Today	Sugarcane extract may relieve stress-induced insomnia(Urade)
45	2017.09.15	Magazine	junior AERA	Interview: "Direct link between REM sleep loss and the desire for sugary and fatty foods discovered" (Lazarus)
46	2017.09.20	Web media	Newswitch	Interview: " Do people who often dream have higher brain structure?" (Hayashi)
47	2017.09.21	Web media	Science Daily	Cannabis, 'spice' – better think twice(Urade)
48	2017.09.27	Web media	Mynavi News	Cannabis, “Spice” – better think twice(Urade)
49	2017.09.29	Web media	Aging Style	Lecture Report on Aging Style×GOOD DESIGN panel session (Urade)
50	2017.09.29	Web media	Science Daily	Why do we fall asleep when bored? (Lazarus)
51	2017.09.30	Web media	Financial Express	Why do we fall asleep when bored? (Lazarus)
52	2017.10.01	Web media	TOKYO Web	Nobel prize will be announced from tomorrow (Yanagisawa)
53	2017.10.02	Television	Asaichi	Interview: "Possible to gain beauty and health?" (Sakurai)
54	2017.10.03	Newspaper	Zaikei Shimbun	Cannabis, 'spice' – better think twice(Urade)
55	2017.10.04	Web media	Seeker	Why do we fall asleep when bored?(Lazarus)
56	2017.10.10	Web media	IBM Japan "Mugendai"	Interview (Yanagisawa)
57	2017.10.18	Web media	Fuminners	Interview: "Why do people in Ibaraki Pref. sleep less ? The relationship between the consumption of Natto and insomnia" (Yanagisawa)
58	2017.10.19	Web media	University Journal Online	Why do we fall asleep when bored?(Lazarus)
59	2017.10.19	Web media	AERA dot.	Interview: "Direct link between REM sleep loss and the desire for sugary and fatty foods discovered"(Lazarus)
60	2017.10.19	Web media	University Journal Online	Why do we fall asleep when bored?(Lazarus)
61	2017.10.24	Web media	ReliaWire	Why We Still Don't Understand Sleep, And Why It Matters (Yanagisawa)
62	2017.10.31	Newspaper	The Nikkan Kogyo Shimbun	Why do we fall asleep when bored?(Lazarus)
63	2017.11.06	Web media	Diamond online	Interview: "Sleep cycles is wrong: there are lots of myth" (Sakurai)

64	2017.11.10	Magazine	SEIBUNDO SHINKOSHA "kodomonokagaku"	Super science - Sleep method -(Sakurai)
65	2017.11.21	Web media	academist Journal	Why do we fall asleep when bored?(Lazarus)
66	2017.11.22	Web media	anannews	Interview: "No worries if you are a night person! A professional advices you suitable ways for sleep" (Sakurai)
67	2017.11.23	Magazine	Tarzan	Interview: "7 keys to improve your sleep"(Sakurai)
68	2017.11.23	Web media	anannews	Interview: "Can we talk to a sleep-talker? Sleep Q&A" (Sakurai)
69	2017.11.24	Web media	Medial News QLifePro	A neuropeptide that regulates behavior: a key to ease excessive fear (Sakurai)
70	2017.11.25	Web media	GIZMODO JAPAN	Interview: A mastermind of sleep/awake? Secret power of Orexin which controls sleep (Yanagisawa)
71	2017.11.25	Web media	ananweb	Interview: "Prime time" is a lie!? New common sense of sleep you should know (Sakurai)
72	2017.11.28	Magazine	anan	Interview: "Have a best sleep with the very latest science"(Sakurai)
73	2017.11.30	Web media	University Journal Online	A neuropeptide that regulates behavior: a key to ease excessive fear (Sakurai)
74	2017.12.01	Web media	Medical Tribune	Prof. Yanagisawa and Visiting Prof. Funato won Baelz Prize (Yanagisawa/Funato)
75	2017.12.02	Web media	Nikkei Health	Interview: Recommendation of mouth tape for better sleep (Satoh)
76	2017.12.03	Television	Mainichi Broadcasting System	Interview: Behavior while sleeping(Sakurai)
77	2017.12.06	Web media	asahi.com	Interview: "Why do we sleep? " (Sakurai)
78	2017.12.11	Web media	Genetic Literacy Project	Chasing a cure for narcolepsy—and why it should be a priority (Yanagisawa)
79	2017.12.18	Web media	Nature Asia	Slow-wave sleep is controlled by a subset of nucleus accumbens core neurons in mice(Lazarus)
80	2017.12.19	Web media	BCN RETAIL	Interview: "Sleepless country, Japan"(Yanagisawa)
81	2018.01.01	Web media	JIJI PRESS	The Asahi Prize 2017 (Yanagisawa)
82	2018.01.01	Newspaper	The Asahi Shimbun	The Asahi Prize 2017 (Yanagisawa)
83	2018.01.03	Web media	The Atlantic	Why do we need to sleep?(Yanagisawa)
84	2018.01.22	Web media	Sankei News	The Asahi Prize 2017 (Yanagisawa)
85	2018.02.06	Web media	Top Researchers	Interview: "Challenge to elucidate definition of sleep"(Hayashi)
86	2018.02.12	Web media	Science and Technology in Japan	WPI Science Symposium
87	2018.03.07	Web media	Medial News QLifePro	Sleep disorder risk factors among student athletes(Tokuyama/Satoh)
88	2018.03.09	Web media	University Journal Online	Sleep disorder risk factors among student athletes(Tokuyama/Satoh)
89	2018.03.11	Television	Mainichi Broadcasting System	Interview: "Behavior while sleeping" (Sakurai)
90	2018.03.13	Newspaper	The Yomiuri Shimbun	Crowdfunding project of sleep study on human (Yanagisawa)
91	2018.03.15	Newspaper	The Mainichi Shimbun	WPI Science Symposium
92	2018.03.17	Web media	Healthy Living	Crowdfunding project of sleep study on human (Yanagisawa)
93	20180.3.24	Web media	Sankei News	Interview:" Discovery of Orexin to regulate sleep/wake mechanism" (Yanagisawa)
94	2018.03.25	Web media	The Asahi Shimbun (English)	Crowdfunding project of sleep study on human (Yanagisawa)
95	2018.03.26	Newspaper	The Asahi Shimbun	Crowdfunding project of sleep study on human (Yanagisawa)
96	2018.03.28	Newspaper	The Daily Engineering & Construction News	IIIS building

97	2018.03.29	Newspaper	The Mainichi Shimbun	Crowdfunding project of sleep study on human (Yanagisawa)